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STUDY TITLE

Report

DHDPS

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley rats
Oral Administration (Gavage)

TEST GUIDELINES

OECD 443

AUTHORS

[REDACTED]

STUDY COMPLETION DATE

04 Jul 2019

TEST FACILITY

BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen, Germany

TEST FACILITY PROJECT IDENTIFICATION

Project No.: 90R0066/05R034

SPONSOR

BASF SE
67056 Ludwigshafen, Germany

PART I OF III (REPORT SECTION AND SUMMARY TABLES)

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No claim of confidentiality, on any basis whatsoever, is made for any information contained in this document. I acknowledge that information not designated as within the scope of FIFRA sec.10(d)(1)(A), (B) or (C) and which pertains to a registered or previous registered pesticide is not entitled to confidential treatment and may be released to the public, subject to the provisions regarding disclosure to multinational entities under FIFRA 10(g).

Submitter: Date:

Typed Name of Signer:

Typed Name of Company:

GLP COMPLIANCE STATEMENT

This study was conducted in accordance with the OECD Principles of Good Laboratory Practice and the GLP Principles of the German "Chemikaliengesetz" (Chemicals Act), which meet the United States Environmental Protection Agency Good Laboratory Practice Standards [40 CFR Part 160 (FIFRA) and Part 792 (TSCA)], with the exception that recognized differences exist between the GLP Principles/Standards of OECD and the Principles/Standards of FIFRA and TSCA.

However, there was the following deviation from the requirements of the principles mentioned above:

Because of a technical defect of the FACS Calibur flow cytometer in the clinical pathology lab of the test site on 15 Feb 2018, analysis of the splenic lymphocyte subpopulations for the scheduled samples could not be performed on this instrument in the test facility. To obtain comparable results with samples of the same cohort (F1A) analysed the day before, this analysis had to be performed on the same instrument type, with high urgency due to limited stability of the samples. Therefore, the samples were immediately transported to the instrument and reagent supplier, Becton Dickinson, Tullastr. 8-12, Heidelberg, Germany (without GLP status), where the measurements of the samples were conducted using the same FACS Calibur instrument type (without GLP status).

The validity of the data and of the overall results of the present study is not considered to be adversely affected by the above-mentioned deviation.

Study Director

Typed name of Study Director:

Typed name of Laboratory:

BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen
Germany

Date:

04 July, 2019

To be filled for USA EPA submission only:

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FLAGGING CRITERIA

I have applied the criteria of 40 CFR 158.34/40 CFR161.34 for flagging studies for potential adverse effects to the results of the attached study. This study meets or exceeds the criteria numbered 5.

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SIGNATURE PAGE

Study Director:

[Redacted Signature]

04 Jul, 2019

Clinical Pathology / Spermatology /
Developmental Immunotoxicity:

[Redacted Signature]

04 Jul 2019

Pathology:

[Redacted Signature]

04 Jul 2019

Neuropathology:

[Redacted Signature]

04 July 2019

Analytical Chemistry:

[Redacted Signature]

04 Jul 2019

Test Facility Management:

[Redacted Signature]

04.07.2019

CONTRIBUTORS TO THE STUDY / SUPERVISORY LABORATORY PERSONNEL

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Pathology:

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Neuropathology:

[REDACTED]

Analytical Chemistry:

[REDACTED]

Data Processing:

[REDACTED]

Statistics:

[REDACTED]

Quality Assurance Unit (QAU):

[REDACTED]

Coordination QAU:

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Reproduction Toxicology:

[REDACTED]

Clinical Pathology/Hematology:

[REDACTED]

Pathology:

[REDACTED]

Neuropathology:

[REDACTED]

STATEMENT OF THE QUALITY ASSURANCE UNIT

The Quality Assurance Unit (QAU) inspected the study and reported any inspection results to the Study Director and to Test Facility Management.

The final report reflects the raw data.

Phase of study:	Date of inspection (mm-dd-yyyy)	Reported to Study Director and to Test Facility Management (mm-dd-yyyy)
Study Plan:	08-08-2017	08-08-2017
Conduct of study:	08-31-2017	08-31-2017
	09-06-2017	09-06-2017
	11-15-2017	11-15-2017
	12-08-2017	12-08-2017
	01-23-2018	01-23-2018
	01-31-2018	01-31-2018
	02-01-2018	02-01-2018
	02-07-2018	02-07-2018
	02-15-2018	02-15-2018
	02-21-2018	02-21-2018
	03-19-2018	03-19-2018
	03-23-2018	03-23-2018
	04-04-2018	04-04-2018
	04-09-2018	04-09-2018
	05-15-2018	05-15-2018
	05-28-2018	05-28-2018
Report:	05-29-2019	05-29-2019

Ludwigshafen,

04 July 2019

GLP CERTIFICATE (FROM THE COMPETENT AUTHORITY)



Rheinland-Pfalz

LANDESAMT FÜR UMWELT

GUTE LABORPRAXIS – GOOD LABORATORY PRACTICE
GLP-BESCHEINIGUNG
STATEMENT OF GLP COMPLIANCE
gemäß/according to § 19b Abs. 1 Chemikaliengesetz

Eine GLP-Inspektion zur Überwachung der Einhaltung der GLP-Grundsätze gemäß Chemikaliengesetz und Richtlinie 2004/9/EG wurde durchgeführt in: Assessment of conformity with GLP according to Chemikaliengesetz and Directive 2004/9/EC at:

Prüfeinrichtung / Test facility

BASF SE
Experimentelle Toxikologie und Ökologie
67056 Ludwigshafen

BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen, Germany

Prüfung nach Kategorien / Areas of Expertise

(gemäß / according ChemVwV-GLP Nr. 5.3/OECD guidance)

1,2,3,4,5,8,9

Kat. 9 – Biochemische und pathologische Untersuchungen zu Wirkmechanismen /
Biochemical and pathological examinations concerning mode of action

Datum der Inspektion / Date of Inspection

(Tag/Monat/Jahr / day.month.year)

12. bis 14.09.2016

Die genannte Prüfeinrichtung befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.

Eine erneute behördliche Überprüfung der Einhaltung der GLP-Grundsätze durch die Prüfeinrichtung ist spätestens drei Jahre nach der letzten Inspektion zu beantragen. Ohne diesen Antrag wird die Prüfeinrichtung nach Ablauf der Frist aus dem deutschen GLP-Überwachungsprogramm genommen und diese GLP-Bescheinigung verliert ihre Gültigkeit.

The above mentioned test facility is included in the national GLP Compliance Programme and is inspected on a regular basis.

Based on the inspection report it can be confirmed, that the test facility is able to conduct the aforementioned studies in compliance with the Principles of GLP.

Verification of the compliance of the test facility with the Principles of the GLP has to be applied for not later than three years after the last inspection. Elapsing this term, the test facility will be taken out of the German GLP-Monitoring Programme and this GLP Certificate becomes invalid.

Unterschrift, Datum / Signature, Date



Dr.-Ing. Stefan Hill - Präsident -

(Name und Funktion der verantwortlichen Person /
name and function of responsible person)

MESSEN
BEWERTEN
BERATEN



Landesamt für Umwelt, Wasserwirtschaft und Gewerbeaufsicht
Kaiser-Friedrich-Straße 7, 55116 Mainz
(Name und Adresse der GLP-Überwachungsbehörde /
Name and address of the GLP Monitoring Authority)

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F0 GENERATION PARENTAL ANIMALS (05R034M0/F0/L1)

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Clinical observations (including mortality)

- Males	IA-001 + IA-009 - IA-010
- Females (except gestation and lactation periods)	IA-002 + IA-011 - IA-012
- Gestation (F1)	IA-013 - IA-014
- Lactation (F1)	IA-015

Clinical Observations (pre- and/or post-dosing)

- Males	IA-003 - IA-005
- Females	IA-006 - IA-008

Water consumption (g/animal/day)

- Males	IA-016 - IA-017
- Females	
- Premating	IA-018 - IA-019
- Gestation and lactation (F1)	IA-020 - IA-021

Food consumption (g/animal/day)

- Males	IA-022 - IA-024
- Females	
- Premating	IA-025 - IA-027
- Gestation and lactation (F1)	IA-028 - IA-029

Body weight (g)

- Males	IA-030 - IA-031 + IA-034
- Females	
- Premating	IA-032 - IA-033
- Gestation (F1)	IA-035
- Lactation (F1)	IA-036

Body weight change (g)

- Males	IA-037 - IA-038 + IA-041
- Females	
- Premating	IA-039 - IA-040
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- Lactation (F1)	IA-043

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- Data concerning F1 litter IA-047

Female reproduction and delivery data

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F1 GENERATION PUPS (05R034L1)

Litter data

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Pup clinical observations

- F1 pups IA-015

Presence of areolae/nipples

- F1 pups IA-053 - IA-054

Pup body weight/body weight change (g)

- F1 pups IA-055 - IA-058

Pup anogenital distance / index

- F1 pups IA-059 - IA-062

Pup necropsy observations

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Sexual maturation data

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- Females IA-070

Clinical Observations (pre- and/or post-dosing)

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- Males IA-089 - IA-090
- Females IA-091 - IA-092

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- Males IA-093
- Females IA-094

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- Data concerning F0F females IA-095

F1 GENERATION PARENTAL ANIMALS, COHORT 1B (05R034M1/F1/L2)

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- Females (except gestation and lactation periods)	IA-097 + IA-105 - IA-106
- Gestation (F2)	IA-107
- Lactation (F2)	IA-108

Clinical Observations (pre- and/or post-dosing)

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- Females	IA-101 - IA-103

Water consumption (g/animal/day)

- Males	IA-109 - IA-110
- Females	
- Premating	IA-111 - IA-112
- Gestation and lactation (F2)	IA-113 - IA-114

Food consumption (g/animal/day)

- Males	IA-115 - IA-117
- Females	
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Body weight (g)

- Males	IA-123 - IA-125 + IA-129
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- Females	
- Premating	IA-134 - IA-135
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- F2 pups

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Presence of areolae/nipples

- F2 pups

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- Females

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Water consumption (g/animal/day)

- Males
- Females

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Food consumption (g/animal/day)

- Males
- Females

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Body weight (g)

- Males
- Females

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Body weight change (g)

- Males
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Body weight (g)

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- Males IIA-957 - IIA-960
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Food consumption (g/animal/day)

- Males IIA-965 - IIA-968
- Females IIA-969 - IIA-972

Body weight (g)

- Males IIA-973 - IIA-976
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- Males IIA-1001 - IIA-1007 + IIA-1457 - IIA-1472
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- Gestation (F2) IIA-1492 - IIA-1503
- Lactation (F2) IIA-1504 - IIA-1515

Clinical Observations (pre- and/or post-dosing)

- Males IIA-1015 - IIA-1248
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Water consumption (g/animal/day)

- Males IIA-1516 - IIA-1519
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- Females
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Body weight change (g)

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Delivery and postimplantation loss data

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F2 GENERATION PUPS, COHORT 1B (05R034L2)
Pup sex and status post partum

- F2 litter IIA-1654 - IIA-1657

Pup clinical observations

- F2 pups
 - for all groups IIA-1504 - IIA-1515
 - more detailed tables only for litters/pups with clinical observations not applicable²

Presence of areolas/nipples

- F2 pups IIA-1658 - IIA-1665

Pup body weights (g)

- F2 pups IIA-1666 - IIA-1685

Pup anogenital distance / index

- F2 pups IIA-1686 - IIA-1693

Pup organ weights / to body weight ratio

- Selected F2 pups IIA-1694 - IIA-1701

Pup necropsy observations

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² None of the F2 pups/litter showed any abnormal clinical observation up to weaning

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Tables

Clinical observations (including mortality)

- Males IIA-1737 - IIA-1741
- Females IIA-1742 - IIA-1746

Clinical Observations (pre- and/or post-dosing)

- Males IIA-1747 - IIA-1814
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Water consumption (g/animal/day)

- Males IIA-1883 - IIA-1886
- Females IIA-1887 - IIA-1890

Food consumption (g/animal/day)

- Males IIA-1891 - IIA-1894
- Females IIA-1895 - IIA-1898

Body weight (g)

- Males IIA-1899 - IIA-1902
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Body weight change (g)

- Males IIA-1907 - IIA-1910
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Clinical Observations (DCO)

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Auditory Startle Response

- Males IIA-1923 - IIA-1926
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Functional Observational Battery (FOB)

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Water consumption (g/animal/day)

- Males IIA-2119 - IIA-2122
- Females IIA-2123 - IIA-2126

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- Females IIA-2131 - IIA-2134

Body weight (g)

- Males IIA-2135 - IIA-2138
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PART B
CLINICAL PATHOLOGY (INDIVIDUAL VALUES)

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F0 parental animals

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Substrates	IIB 25 – IIB 32
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Urinalysis	IIB 49 – IIB 64
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F1 animals

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PATHOLOGY (INDIVIDUAL VALUES)

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F0 generation, parental animals

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Single animal sheet
F0 generation, parental animals

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F1 generation, rearing animals, cohort 1A

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- Certificate of Analysis **Cyclophosphamide Monohydrate**

2. Analyses of the test substance preparations

- Stability Analysis of **DHDPS** in 1% Carboxymethylcellulose in Drinking Water
- Stability Analysis of **Cyclophosphamide Monohydrate** in drinking water
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3. Nipple/areola anlagen

- Nipple count

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- Individual estrous stages of F0 females on the day of sacrifice
- Individual estrous stages of cohort 1A females on the day of sacrifice
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- Individual estrous stages of cohort 1A females from vaginal opening to first estrous

5. Selection of animals

- Selection for all cohorts

6. Historical control data

- Historical control data

7. Functional Observation Battery

- Detailed description of examinations, ranking and documentation procedures

**8. Positive Control (Cyclophosphamide monohydrate)
(Mean values and Individual values)****Clinical observations (including mortality)**

- Males
 - Females

Food consumption (g/animal/day)

- Males
- Females

Body weight (g)

- Males
- Females

Body weight change (g)

- Males
- Females

THIS REPORT CONSISTS OF PART I, II AND III

1. SUMMARY

1.1. METHODS

DHDPS was administered to groups of 24 male and 24 female healthy young Sprague-Dawley rats for test groups 00 - 03 as an aqueous preparation by stomach tube at different dosages (0, 20, 60 and 180 mg/kg body weight/day [mg/kg bw/d]). F0 animals were treated at least for 10 weeks prior to mating to produce a litter (F1 generation). Mating pairs were from the same dose group. Pups of the F1 litter were selected (F1 rearing animals) and assigned to 5 different cohorts which were subjected to specific postweaning examinations. Cohort 1B (=F1 generation parental animals) were selected to produce F2 pups. F1 animals selected for breeding were continued in the same dose group as their parents. Groups of 24 males and 24 females, selected from F1 pups to become F1 parental generation, were offered an aqueous preparation by stomach tube at different dosages (0, 20, 60 and 180 mg/kg bw/d) of the test substance post weaning, and the breeding program was repeated to produce a F2 litter. The study was terminated with the terminal sacrifice of the F2 weanlings and F1 parental animals. Control animals were dosed daily with the vehicle (0.5% Sodium carboxymethyl cellulose [CMC] suspension in drinking water).

1.2. OBSERVATIONS

The parents' and the pups' state of health was checked each day, and parental animals were examined for their mating and reproductive performances.

Water consumption of the F0 and F1 parents and F1 rearing animals was determined regularly once weekly and weekly during gestation days (GD) 0-1, 3-4, 7-8, 10-11, 14-15, 17-18, 19-20 and lactation days (PND) 1-2, 4-5, 7-8, 10-11, 14-15, 17-18 and 20-21.

Food consumption of the F0 and F1 parents and F1 rearing animals was determined regularly once weekly and weekly during GD 0-7, 7-14, 14-20 and PND 1-4, 4-7, 7-10, 10-14, 14-17, 17-19 and 19-21.

In general, body weights of F0 and F1 parents and F1 rearing animals were determined once weekly. However, during gestation and lactation F0/F1 females were weighed on GD 0, 7, 14 and 20 and on PND 1, 4, 7, 10, 14, 17, 19 and 21.

A detailed clinical observation (DCO) was performed in all F0 parents and F1 animals in cohorts 1A, 1B, 2A and 3 at weekly intervals.

Estrous cycle data were evaluated for F0 and cohort 1B (=F1 generation) females over a three weeks period prior to mating until evidence of mating occurred. In all cohort 1A females, vaginal smears were collected after vaginal opening until the first cornified smear (estrous) was recorded. The estrous cycle also was evaluated in cohort 1A females for 2 weeks around PND 75. Moreover, the estrous stage of each female was determined on the day of scheduled sacrifice.

An auditory startle response test was carried out in all animals of cohort 2A on PND 24.

Learning and memory was tested using a Morris water maze in all animals of cohort 2A from PND 60 onwards.

A functional observational battery (FOB) was performed in all animals of cohort 2A on PND 75.

Motor activity was measured in all animals of cohort 2A on PND 75.

The F1 and F2 pups were sexed on the day of birth (PND 0) and were weighed on the first day after birth (PND 1) as well as on PND 4, 7, 14 and 21. Their viability was recorded. At necropsy, all pups were examined macroscopically (including weight determinations of brain, spleen and thymus in one pup/sex/litter).

Date of sexual maturation, i.e. day of vaginal opening (females) or balanopreputial separation (males), of all F1 pups selected to become F1 parental generation was recorded.

All surviving pups were examined for the presence or absence of nipple/areola anlagen on PND 13. If nipple/areola anlagen were recorded, all surviving male pups were carefully re-examined one PND 20 (F1) or PND 21 (F2).

Anogenital distance (defined as the distance from the anus [center of the anal opening] to the base of the genital tubercle) measurements were conducted in a blind randomized fashion, using a measuring ocular on all live F1 and F2 pups on PND 1.

Blood samples for clinical pathological investigations were withdrawn from 10 selected F0 and cohort 1A animals per sex and group.

Further blood samples were taken from 10 surplus (culled) PND 4 pups per sex and group as well as from 10 surplus PND 22 pups per sex and group.

Various sperm parameters (motility, sperm head count, morphology) were assessed in the F0 and 1A males at scheduled sacrifice or after appropriate staining.

All F0 and F1 parental animals were assessed by gross pathology (including weight determinations of several organs) and subjected to an extensive histopathological examination; special attention being paid to the organs of the reproductive system. A quantitative assessment of primordial and growing follicles in the ovaries was performed for all control and high-dose F1 parental females.

All F1 rearing animals were assessed by different pathological, neuro- and histopathological examinations.

1.3. RESULTS

1.3.1. Analytics

The various analyses:

- Demonstrated the stability of the test substance preparations over a period of 4 days at ambient temperature and over a period of 7 days in a refrigerator.
- Confirmed the homogeneous distribution of the test substance in 0.5% CMC suspension in drinking water.
- Verified correct concentrations of the test substance in 0.5% CMC suspension in drinking water.

1.3.2. Effects

The following test substance-related adverse effects/findings were noted:

180 mg/kg bw/d

F0 PARENTAL ANIMALS (05R034M0/F0/L1)

CLINICAL EXAMINATIONS/ REPRODUCTIVE PERFORMANCE/ CLINICAL PATHOLOGY/ PATHOLOGY

- Increased water consumption in females during major parts of the premating and gestation period (up to 25% and 28% above control, respectively)
- Increased food consumption in females during major parts of the premating period and during GD 14 - 20 (up to 36% and 8% above control, respectively)
- Increased postimplantation loss (10.5% vs. 3.1% in control)
- Increased absolute (+16%) and relative (+20%) weights of the kidneys in males
- Macroscopically enlarged kidneys in 6/24 males
- Increased mineralization in the kidneys in the transition from medulla to cortex in 21/24 male animals (minimal to severe)
- Nuclear crowding in the kidneys in 22/24 male animals (minimal to moderate)
- Tubular dilation in the kidneys in 13/24 male animals (minimal to slight)

F1 PUPS (05R034L1)

CLINICAL EXAMINATIONS/ SEXUAL MATURATION/ GROSS FINDINGS

- Decreased number of liveborn pups subsequent to higher postimplantation loss

F1 REARING ANIMALS, COHORT 1A (05R0341A)

CLINICAL EXAMINATIONS/ CLINICAL PATHOLOGY/ PATHOLOGY

- Increased water consumption in females during major parts of the study period (up to 25% above control)
- Increased food consumption in females during major parts of the study period (up to 21% above control)

- Increased body weights in females on study days 14 and 28 (up to 7% above control, respectively)
- Increased body weight change in females during study days 7 - 14 (about 19% above control, respectively)
- Prolonged prothrombin time in males
- Increased total protein, albumin and calcium values in females
- Increased absolute (+12%) and relative (+17%) weights of the kidneys in males
- Increased mineralization in the kidneys in the transition from medulla to cortex in 7/20 male animals (minimal to moderate)
- Nuclear crowding in the kidneys in 6/20 male animals (minimal to slight)
- Tubular dilation in the kidneys in 7/20 male animals (minimal to slight)
- Increased incidence of atrophy in the mammary gland and mammary fat pad

F1 PARENTAL ANIMALS, COHORT 1B (05R034M1/F1/L2)

CLINICAL EXAMINATIONS/ REPRODUCTIVE PERFORMANCE/ CLINICAL PATHOLOGY/ PATHOLOGY

- Increased water consumption in females during major parts of the premating period (up to 26% above control)
- Increased food consumption in females during premating days 28 - 49 and 0 - 70 (up to 22% and 13% above control, respectively)
- Increased body weights in females during major parts of the premating period (up to 10% above control)
- Increased body weight change in females during premating days 0 - 21 and 0 - 70 (up to 18% and 10% above control, respectively)
- Increased postimplantation loss (24.6% vs. 6.4% in control)
- Increased absolute (+26%) and relative (+32%) weights of the kidneys in males.
- Macroscopically enlarged kidneys in 10/24 males

F2 PUPS (05R034L2)

CLINICAL EXAMINATIONS/ PUP ORGAN WEIGHTS/ GROSS FINDINGS

- Decreased mean pups delivered subsequent to higher postimplantation loss

F1 REARING ANIMALS, COHORT 2A (05R0342A)

CLINICAL EXAMINATIONS/ CLINICAL PATHOLOGY/ PATHOLOGY

- No test substance-related adverse findings

F1 REARING ANIMALS, COHORT 3 (05R0343)

CLINICAL EXAMINATIONS/ CLINICAL PATHOLOGY/ PATHOLOGY

- No test substance-related adverse findings

60 mg/kg bw/d**F0 PARENTAL ANIMALS (05R034M0/F0/L1)**

CLINICAL EXAMINATIONS/ REPRODUCTIVE PERFORMANCE/ CLINICAL PATHOLOGY/ PATHOLOGY

- Increased water consumption in females during GD 17 - 20 (up to 22% above control)
- Increased food consumption in females during premating days 0 - 7, 28 - 35 and during GD 14 - 20 (up to 9%, 14% and 6% above control, respectively)
- Increased postimplantation loss (9.4% vs. 3.1% in control)

F1 PUPS (05R034L1)

CLINICAL EXAMINATIONS/ SEXUAL MATURATION/ GROSS FINDINGS

- No test substance-related adverse findings

F1 REARING ANIMALS, COHORT 1A (05R0341A)

CLINICAL EXAMINATIONS/ CLINICAL PATHOLOGY/ PATHOLOGY

- Increased water consumption in females during study days 7 - 17 (up to 20% above control)
- Increased body weights in females on study days 14 and 28 (up to 7% above control, respectively)
- Increased body weight change in females during study days 0 - 7 (about 9% above control, respectively)

F1 PARENTAL ANIMALS, COHORT 1B (05R034M1/F1/L2)

CLINICAL EXAMINATIONS/ REPRODUCTIVE PERFORMANCE/ CLINICAL PATHOLOGY/ PATHOLOGY

- Increased water consumption in females during premating days 14 - 17 and 42 - 45 (about 14% and 15% above control, respectively)
- Increased food consumption in females during premating days 7 - 14 (about 13% above control)
- Increased body weights in females during major parts of the premating period and on PND 14 (up to 9% and 6% above control, respectively)
- Increased body weight change in females during premating days 0 - 21 (up to 20% above control)
- Increased absolute (+13%) and relative (+10%) weights of the kidneys in males

F2 PUPS (05R034L2)

CLINICAL EXAMINATIONS/ PUP ORGAN WEIGHTS/ GROSS FINDINGS

- No test substance-related adverse findings

F1 REARING ANIMALS, COHORT 2A (05R0342A)

CLINICAL EXAMINATIONS/ CLINICAL PATHOLOGY/ PATHOLOGY

- No test substance-related adverse findings

F1 REARING ANIMALS, COHORT 3 (05R0343)

CLINICAL EXAMINATIONS/ CLINICAL PATHOLOGY/ PATHOLOGY

- No test substance-related adverse findings

20 mg/kg bw/d**F0 PARENTAL ANIMALS (09R123M0/F0/L1)**

CLINICAL EXAMINATIONS/ REPRODUCTIVE PERFORMANCE/ CLINICAL PATHOLOGY/ PATHOLOGY

- No test substance-related adverse findings

F1 PUPS (05R034L1)

CLINICAL EXAMINATIONS/ SEXUAL MATURATION/ GROSS FINDINGS

- No test substance-related adverse findings

F1 REARING ANIMALS, COHORT 1A (05R0341A)

CLINICAL EXAMINATIONS/ CLINICAL PATHOLOGY/ PATHOLOGY

- No test substance-related adverse findings

F1 PARENTAL ANIMALS, COHORT 1B (05R034M1/F1/L2)

CLINICAL EXAMINATIONS/ REPRODUCTIVE PERFORMANCE/ CLINICAL PATHOLOGY/ PATHOLOGY

- No test substance-related adverse findings

F2 PUPS (05R034L2)

CLINICAL EXAMINATIONS/ PUP ORGAN WEIGHTS/ GROSS FINDINGS

- No test substance-related adverse findings

F1 REARING ANIMALS, COHORT 2A (05R0342A)

CLINICAL EXAMINATIONS/ CLINICAL PATHOLOGY/ PATHOLOGY

- No test substance-related adverse findings

F1 REARING ANIMALS, COHORT 3 (05R0343)

CLINICAL EXAMINATIONS/ CLINICAL PATHOLOGY/ PATHOLOGY

- No test substance-related adverse findings

1.4. CONCLUSION

Under the conditions of the present modified extended 1-generation reproduction toxicity study the **NOAEL** (no observed adverse effect level) for **general, systemic toxicity** is 60 mg/kg bw/d for the F0 and F1 parental as well as adolescent animals, based on evidence for kidney toxicity, as well as corresponding effects on clinical-pathological parameters, which were observed at the LOAEL (Lowest Observed Adverse Effect Level) of 180 mg/kg bw/d.

The **NOAEL** for **fertility** and **reproductive performance** for the F0 and F1 parental rats is 180 mg/kg bw/d, the highest dose tested.

The **NOAEL** for **developmental toxicity** in the F1 and F2 progeny is 20 mg/kg bw/d, based on increased postimplantation loss in the F1 progeny, which was observed at the LOAEL (Lowest Observed Adverse Effect Level) of 60 mg/kg bw/d.

The **NOAEL** for **developmental neurotoxicity** for the F1 progeny is 180 mg/kg bw/d, the highest dose tested.

The **NOAEL** for **developmental immunotoxicity** for the F1 progeny is 180 mg/kg bw/d, the highest dose tested. Lower mean and median anti-SRBC IgM antibody titers of the positive control group (4.5 mg/kg bw/d cyclophosphamide, oral) demonstrated that the test system worked properly.

2. INTRODUCTION

2.1. OBJECTIVES

The objective of this study was to obtain general information on the possible effects of **DHDPS** on the integrity and performance of the male and female reproductive systems, including gonadal function, estrous cyclicity, mating behavior, conception, gestation, parturition, lactation and weaning, as well as on growth and development of the offspring. The study should also provide information about the effects on neonatal morbidity, mortality, target organs of the pups and preliminary data on prenatal and postnatal developmental toxicity. As part of this assessment, offspring were investigated for effects on the embryonic, fetal and preadult development of the nervous and immune systems as well as alterations in endocrine function (including thyroid perturbations).

2.2. SELECTION OF DOSES

The following doses levels were selected:

20 mg/kg bw/d	as low dose level
60 mg/kg bw/d	as mid dose level
180 mg/kg bw/d	as high dose level

2.2.1. Dose rationale

The doses were selected based on signs of toxicity noted at dose levels of 100 and 300 mg/kg bw/d in a previously conducted dose range-finding reproduction/developmental toxicity study in Sprague Dawley Rats (BASF project 80R0066/05R033) which preceded this definitive extended one-generation reproduction toxicity study.

In the dose range-finding reproduction/developmental toxicity study, clinical signs of parental toxicity were observed in the high-dose F0 animals (300 mg/kg bw/d), such as mildly reduced food consumption and body weight gain during several sections of the study. Males were more affected than females. In addition, dilated cecum, enlarged and discolored kidneys, enlarged livers, reduced terminal body weights and distinctly increased absolute/relative kidney weights were noted in the 300 mg/kg bw/d F0 males at necropsy. Kidney weights were still significantly increased in F0 males at 100 mg/kg bw/d. Histopathology revealed dose-dependently increased incidences of findings in the cecum (thickening of wall, increased apoptosis), kidneys (tubular degeneration/regeneration, tubular dilation, medulla mineralization, lymphoid infiltration) and liver (lymphoid infiltration) in F0 males and females at 100 and 300 mg/kg bw/d.

F0 parental females (300 mg/kg bw/d) had a prolonged estrous cycle. All 8 pregnant females had a significantly lower average number of implants compared to the concurrent control (10.4 vs. 15.8). In addition, post-implantation loss was significantly increased (34.6 vs 3.6%) and 2 of the 8 pregnant females had complete intrauterine litter losses. These effects resulted in a significantly lower live litter size (10.3 vs. 15.0). Newborn pups developed normally.

The selected high dose for the present study was expected to evoke moderate systemic toxic effects in the parental animals. The present dose selection, however, also considered the need of generating a sufficient number of F1 offspring to serve the purpose of an extended one-generation study which included the full set of reproductive (extended to F2), neurotoxicity and immunotoxicity investigations along with additional learning/memory testing and histopathological investigations of the mammary gland. Thus, excessive impairment of reproductive performance in the F0/F1 parental animals was avoided. This procedure to select the high dose in a regulatory study meets the principles of guideline OECD 443 (adopted 2011), as well as ECHA practical guide 10 ("how to avoid unnecessary testing on animals"; chapter 4 "animal welfare"; ECHA-10-B-17-EN, 2010) which is in compliance with EU Directive 86/609/EEC on animal protection.

2.3. TEST GUIDELINES

This study was conducted according to or exceeded the requirements of the following test guideline:

- OECD Guidelines for Testing of Chemicals; No. 443 (28 Jul 2011, incl. correction of 2 Oct 2012)

2.4. STUDY DATES

Phase of study/examination	F0 generation parental animals and progeny	F1 generation parental animals and progeny (Cohort 1B)	F1 rearing animals (cohort 1A, 2A, 2B and 3)
Study initiation date:	09 Aug 2017		
Experimental starting date (Arrival of the animals):	09 Aug 2017		
Randomization date	12 Aug 2017	not relevant	not relevant
Acclimatization period	09 - 14 Aug 2017	not relevant	not relevant
Administration period	14 Aug - 13 Dec 2017	11 Dec 2017 - 18 Apr 2018	1A: 12 Dec 2017 - 14 Feb 2018 2A: 14 Dec 2017 - 01 Feb 2018 3: 14 Dec 2017 - 18 Jan 2018
Blood sampling of parental/ rearing animals*	F0M: 27 + 28 Nov 2017 F0F: 14 Dec 2017	not relevant	1A: 14 + 15 Feb 2018
Urinanalysis:	F0M: 23 Nov 2017 F0F: 12 Dec 2017	not relevant	1A: 07 Feb 2018
AST (Auditory startle response test)	not relevant	not relevant	2A: 08 - 11 Dec 2017
Morris water maze	not relevant	not relevant	2A: 14 - 23 Jan 2018
FOB (Functional observational battery)	not relevant	not relevant	2A: 28 - 31 Jan 2018
MA (Motor activity measurement)	not relevant	not relevant	2A: 28 - 31 Jan 2018
Mating period	F1: 22 Oct - 25 Oct 2017	F2: 25 Feb - 11 Mar 2018	not relevant
Gestation period	F1: 23 Oct - 16 Nov 2017	F2: 26 Feb - 24 Mar 2018	not relevant
Parturition	F1: 13 - 17 Nov 2017	F2: 19 - 25 Mar 2018	not relevant
Lactation period	F1: 13 Nov - 08 Dec 2017	F2: 19 - 15 Apr 2018	not relevant
Sacrifice of litters after weaning	F1: 04 - 08 Dec 2017	F2: 09 - 15 Apr 2018	not relevant
Sacrifice of parental/ rearing animals*	F0M: 27 - 29 Nov 2017 F0F: 16 Oct and 13 - 14 Dec 2017	F1M: 03 - 05 Apr 2018 F1F: 18 - 19 Apr 2018	1A: 12 - 15 Feb 2018 2A: 30 Jan - 02 Feb 2018 2B: 05 - 09 Dec 2017 3: 16 - 19 Jan 2018
Experimental completion date (Draft report to QAU**):			

* Before blood sampling and necropsy food was withdrawn for about 16-20 hours.

** QAU = Quality Assurance Unit

FOB = Functional observational battery

MA = Measurement of motor activity

2.5. RETENTION OF RECORDS

GLP-relevant records and materials are archived at BASF SE for at least the period of time specified in the GLP principles. This includes the study plan, any amendments, raw data, test/ positive/ reference item samples (if applicable in this study), specimens (according to test facility SOPs and as appropriate for this study type) and the study report.

Details concerning responsibilities or locations of archiving can be seen from the respective SOPs as well as from the raw data.

2.6. ANIMAL WELFARE

This study was performed in an AAALAC-approved laboratory in accordance with the German Animal Welfare Act and the effective European Council Directive.

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3. MATERIAL AND METHODS

3.1. TEST ITEM

The analyses of the test item (= test substance) have been carried out at Competence Center Analytics, BASF SE, 67056 Ludwigshafen, Germany.

3.1.1. DHDPS

Name of test substance: DHDPS

Test substance No.: 05/0066-8

Batch identification: 03508136W0

CAS No.: 80-09-1

Content: 99,9 g/100 g

Identity: Confirmed

Homogeneity: Given

Storage stability: Expiry date: 13 Mar 2021

The stability of the test substance under storage conditions over the test period was guaranteed by the sponsor, and the sponsor holds this responsibility.

The test facility is organizationally independent from the BASF SE sponsor division

ADDITIONAL TEST SUBSTANCE INFORMATION

Chemical name: 4,4'-Dihydroxydiphenylsulfon; 4,4'-Sulfonyldiphenol;
4,4'-Dihydroxyphenylsulfon

Synonym: 4,4'-dihydroxydiphenylsulfone

Physical state/Appearance: Solid / white

Storage conditions: Room temperature

The positive control substance was used with the given specifications of the producer (Sigma-Aldrich Chemie GmbH, 89555 Steinheim, Germany). No further analyses were conducted.

3.1.2. Cyclophosphamide monohydrate (Positive control substance)

Name of positive control substance: Cyclophosphamide monohydrate

Positive control substance No.: 05/0012-10

Batch identification: MKBX1822V

CAS No.: 6055-19-2

Purity: 100.0%

Identity: Confirmed

Homogeneity: Given

Storage stability: Expiry date: 19 Dec 2018

The stability of the positive control substance under storage conditions over the test period was guaranteed by the manufacturer and the manufacturer hold this responsibility.

ADDITIONAL REFERENCE ITEM INFORMATION

Physical state/Appearance: Solid / white

Storage conditions: Refrigerator

3.2. TEST ANIMALS

3.2.1. Species and strain

Male and female Sprague-Dawley rats, strain Crl:CD(SD), supplied by Charles River Laboratories, Research Models and Services, Germany GmbH, which were free from any clinical signs of disease, were used for the investigations. The females were nulliparous and non-pregnant at the beginning of the study. According to a written statement from the breeder, male and female animals were derived from different litters. This was necessary to rule out the possibility of sibling mating.

These animals were used as F0 generation parental animals. All other animals used in this study (F1 and F2 generation pups and F1 rearing animals) were derived from the supplier-provided animals.

3.2.2. Animal identification

The rats of the F0 generation parental animals were uniquely identified by ear tattoo.

The animals of cohorts 1A, 1B, 2A and 3 were identified by cage labels and tail markings (Edding) postweaning and as soon as possible after weaning by ear tattoo. The animals of cohorts 2B were identified by cage labels postweaning.

All live pups were identified by skin tattoo on postnatal day (PND) 1 and with picric acid markings between days 10 and 15 after birth.

3.2.3. Reason for species selection

The rat is the preferred animal species for reproduction studies according to test guidelines. The Sprague-Dawley strain was selected on request of the sponsor.

3.3. HOUSING AND DIET

During the study period, the rats were housed together in Polysulfonate cages supplied by TECHNIPLAST, Hohenpeißenberg, Germany and Becker & Co., Castrop-Rauxel, Germany, with the following exceptions:

- During overnight matings, male and female mating partners were housed together in Polycarbonate cages type III (supplied by TECHNIPLAST, Hohenpeißenberg, Germany and Becker & Co., Castrop-Rauxel, Germany).
- Dams and their litters were housed together until PND 21 in Polycarbonate cages type III.
- Females after weaning were housed individually in Polycarbonate cages type III.

Pregnant females were provided with nesting material (cellulose wadding) towards the end of gestation.

For enrichment wooden gnawing blocks (Typ Lignocel® block large, J. Rettenmaier & Söhne GmbH + Co KG, Rosenberg, Germany) were added. In addition, in Polysulfonate cages large play tunnels (Art. 14153; supplied by PLEXX B.V., Elst, Netherlands) were added.

The cages with the test animals were arranged on the racks in such a way that uniform experimental conditions (ventilation and light) were ensured.

The animals were housed in fully air-conditioned rooms in which central air conditioning guaranteed a range of temperature of 20-24°C and a range of relative humidity of 30-70% (till 09.11.2017) and from 10.11.2017 a range of relative humidity of 45-65%. The air change rate was 15 times per hour. There were no or only minimal deviations from these limits.

The day/night cycle was generally 12 hours (12 hours light from 6.00 h to 18.00 h and 12 hours darkness from 18.00 h to 6.00 h).

The animal room was completely disinfected using a disinfector ("AUTEX" fully automatic, formalin-ammonia-based terminal disinfection) before use. Walls and floor were cleaned once a week with water containing an appropriate disinfectant.

The food used was ground Kliba maintenance diet mouse/rat "GLP" meal, supplied by Provimi Kliba SA (new name Garanovit AG), Kaiseraugst, Switzerland, which was available to the animals ad libitum throughout the study (from the day of supply to the day of or the day before necropsy). Drinking water was supplied from water bottles (ad libitum).

Dust-free wooden bedding was used in this study (the present supplier is documented in the raw data).

3.4. TEST GROUPS AND DOSES

F0 generation parental animals

Premating and males during postmating

Test group	Dose (mg/kg bw/d)	Concentration (g/100 mL)	Volume (mL/kg bw/d)	Number of animals		Animal No.		Cage No.***	
				Male	Female	Male	Female	Male	Female
00	0	0	10*	24	24	1 - 24	101 - 124	1 - 8	101 - 108
01	20	0.2	10**	24	24	25 - 48	125 - 148	9 - 16	109 - 116
02	60	0.6	10**	24	24	49 - 72	149 - 172	17 - 24	117 - 124
03	180	1.8	10**	24	24	73 - 96	173 - 196	25 - 32	125 - 132

* = 0.5% CMC suspension in drinking water

** = Test substance preparations in 0.5% CMC suspension in drinking water

*** = Polysulfonate cages Typ 2000P (H-Temp), 3 animals per cage

Mating, gestation, lactation and females after weaning

Test group	Dose (mg/kg bw/d)	Concentration (g/100 mL)	Volume (mL/kg bw/d)	Number of animals		Animal No. (=Cage No.****)	
				Male	Female	Male	Female
00	0	0	10*	24	24	1 - 24	101 - 124
01	20	0.2	10**	24	24	25 - 48	125 - 148
02	60	0.6	10**	24	24	49 - 72	149 - 172
03	180	1.8	10**	24	24	73 - 96	173 - 196

* = 0.5% CMC suspension in drinking water

** = Test substance preparations in 0.5% CMC suspension in drinking water

**** = Polycarbonate cages type III, 1 animal per cage

Before weaning of the F1 generation pups (PND 21), 74 males and 74 females per group were selected by lot as F1 rearing animals. The pups were assigned to the different cohorts (details see below). The assignment of more than one male or female littermate to one individual cohort was avoided unless unavoidable in order to complete the number of rearing animals. Another 10 male and 10 female surplus offspring derived from test group 00 were selected at weaning to become a positive control group in this study.

F1 rearing animals, cohort 1A (Reproductive PND 90)

(1 male and 1 female pup/litter)

Test group	Dose (mg/kg bw/d)	Concentration (g/100 mL)	Volume (mL/kg bw/d)	Number of animals		Animal No.		Cage No.***	
				Male	Female	Male	Female	Male	Female
10	0	0	10*	20	20	201 - 220	301 - 320	201 - 210	301 - 310
11	20	0.2	10**	20	20	221 - 240	321 - 340	211 - 220	311 - 320
12	60	0.6	10**	20	20	241 - 260	341 - 360	221 - 230	321 - 330
13	180	1.8	10**	20	20	261 - 280	361 - 380	231 - 240	331 - 340

* = 0.5% CMC suspension in drinking water

** = Test substance preparations in 0.5% CMC suspension in drinking water

*** = Polysulfonate cages Typ 2000P (H-Temp), 2 animals per cage

F1 rearing animals, cohort 1B (=F1 generation parental animals)

(1 male and 1 female pup/litter)

Premating and males during postmating

Test group	Dose (mg/kg bw/d)	Concentration (g/100 mL)	Volume (mL/kg bw/d)	Number of animals		Animal No.		Cage No.***	
				Male	Female	Male	Female	Male	Female
10	0	0	10*	24	24	401 - 424	501 - 524	401 - 408	501 - 508
11	20	0.2	10**	24	24	425 - 448	525 - 548	409 - 416	509 - 516
12	60	0.6	10**	24	24	449 - 472	549 - 572	417 - 424	517 - 524
13	180	1.8	10**	24	24	473 - 496	573 - 596	425 - 432	525 - 532

* = 0.5% CMC suspension in drinking water

** = Test substance preparations in 0.5% CMC suspension in drinking water

*** = Polysulfonate cages Typ 2000P (H-Temp), 3 animals per cage

Mating, gestation, lactation and females after weaning

Test group	Dose (mg/kg bw/d)	Concentration (g/100 mL)	Volume (mL/kg bw/d)	Number of animals		Animal No. (=Cage No.****)	
				Male	Female	Male	Female
10	0	0	10*	24	24	401 - 424	501 - 524
11	20	0.2	10**	24	24	425 - 448	525 - 548
12	60	0.6	10**	24	24	449 - 472	549 - 572
13	180	1.8	10**	24	24	473 - 496	573 - 596

* = 0.5% CMC suspension in drinking water

** = Test substance preparations in 0.5% CMC suspension in drinking water

**** = Polycarbonate cages type III, 1 animal per cage

F1 rearing animals, cohort 2A (Neurotoxicity PND 75-90) (1 male or 1 female pup/litter)

Test group	Dose (mg/kg bw/d)	Concentration (g/100 mL)	Volume (mL/kg bw/d)	Number of animals		Animal No. (= animal No. in the ToxLIMS system)		Cage No.***		Tattoo No.*****	
				Male	Female	Male	Female	Male	Female	Male	Female
10	0	0	10*	10	10	601 - 610	701 - 710	601 - 605	701 - 705	2001 - 2040	2101 - 2140
11	20	0.2	10**	10	10	611 - 620	711 - 720	606 - 610	706 - 710		
12	60	0.6	10**	10	10	621 - 630	721 - 730	611 - 615	711 - 715		
13	180	1.8	10**	10	10	631 - 640	731 - 740	616 - 620	716 - 720		

* = 0.5% CMC suspension in drinking water

** = Test substance preparations in 0.5% CMC suspension in drinking water

*** = Polysulfonate cages Typ 2000P (H-Temp), 2 animals per cage

***** = To guarantee the impartiality of the investigator assessing the Functional observational battery (FOB), the ear tattoos will be allocated in a randomized sequence.

F1 rearing animals, cohort 2B (Neurotoxicity PND 22)

(1 male or 1 female pup/litter)

Test group	Dose (mg/kg bw/d)	Number of animals		Animal No.	
		Male	Female	Male	Female
10	0	10	10	801 - 810	901 - 910
11	20	10	10	811 - 820	911 - 920
12	60	10	10	821 - 830	921 - 930
13	180	10	10	831 - 840	931 - 940

F1 rearing animals, cohort 3 (Immunotoxicity)

(1 male or 1 female pup/litter)

Test group	Dose (mg/kg bw/d)	Concentration (g/100 mL)	Volume (mL/kg bw/d)	Number of animals		Animal No.		Cage No.***	
				Male	Female	Male	Female	Male	Female
10	0	0	10*	10	10	1001 - 1010	1101 - 1110	1001 - 1005	1101 - 1105
11	20	0.2	10**	10	10	1011 - 1020	1111 - 1120	1006 - 1010	1106 - 1110
12	60	0.6	10**	10	10	1021 - 1030	1121 - 1130	1011 - 1015	1111 - 1115
13	180	1.8	10**	10	10	1031 - 1040	1131 - 1140	1016 - 1020	1116 - 1120

* = 0.5% CMC suspension in drinking water

** = Test substance preparations in 0.5% CMC suspension in drinking water

*** = Polysulfonate cages Typ 2000P (H-Temp), 2 animals per cage

F1 rearing animals, positive control animals

(1 male or 1 female pup/litter from test group 00)

Test group (color of cage cards)	Dose of Cyclophosphamide monohydrate (mg/kg bw/d) [#]	Concentration (mg/100 mL)	Volume (mL/kg bw/d)	Number of animals		Animal No.		Cage No.**	
				Male	Female	Male	Female	Male	Female
14 (orange)	4.5	45	10*	10	10	1041 - 1050	1141 - 1150	1021 - 1025	1121 - 1125

* = Positive control substance preparations in drinking water

** = Polysulfonate cages Typ 2000P (H-Temp), 2 animals per cage

= The dose refers to the body weight of the individual animals determined most recently.

Numbering of samples for thyroid hormones (PND 4)

(from surplus pups PND 4)

Test group	Number of samples		Sample No.	
	Male	Female	Male	Female
00	10	10	1401 - 1410	1501 - 1510
01	10	10	1411 - 1420	1511 - 1520
02	10	10	1421 - 1430	1521 - 1530
03	10	10	1431 - 1440	1531 - 1540

Numbering of samples for thyroid hormones and pathology (PND 22)

(from surplus pups PND 22)

Test group	Number of samples		Sample No.	
	Male	Female	Male	Female
10	10	10	1601 - 1610	1701 - 1710
11	10	10	1611 - 1620	1711 - 1720
12	10	10	1621 - 1630	1721 - 1730
13	10	10	1631 - 1640	1731 - 1740

3.5. TEST SUBSTANCE PREPARATION

3.5.1. DHDPS

The test substance preparations were prepared in intervals, which took into account the analytical results of the stability verification.

For the test substance preparations, the specific amount of test substance were weighed in a calibrated beaker, topped up with 0.5% CMC suspension in drinking water and intensely mixed with a homogenizer

Before and during administration, the preparations were kept homogeneous with a magnetic stirrer.

3.5.2. Cyclophosphamide monohydrate

The positive control substance solution in drinking water was prepared at the beginning of the administration period.

For the preparation of the administration solution the positive control substance was weighed in a weighing boat depending on the dose group and transferred quantitatively in a graduated flask, topped up with drinking water and subsequently thoroughly mixed by a magnetic stirrer until it was completely dissolved. Thereafter the positive control preparation was split in "Nalgene Dosen" (40 ml each) and frozen by -18°C.

3.6. ANALYSES

3.6.1. Analyses of the test substance preparations

The analyses of the test substance preparations were carried out at the Analytical Chemistry Laboratory of Experimental Toxicology and Ecology of BASF SE, Ludwigshafen, Germany, as a part of this study.

Analytical verifications of the stability of the test substance in 1% CMC suspension in drinking water over a period of 4 days at room temperature and over a period of 7 days in a refrigerator has been verified prior to the start of the study in a comparable batch.

Samples of the test substance preparations were sent to the analytical laboratory during the study period (at the beginning, towards the middle and towards the end) for verification of the concentrations.

The samples, which were taken for the concentration control analyses at the beginning of the administration period, were also used to verify the homogeneity for the samples of the low and the high concentrations (20 and 180 mg/kg bw/d). Three samples (one from the top, middle and bottom in each case) were taken for each of these concentrations from the beaker with a magnetic stirrer running.

The samples of the middle of the study were not analyzed because no imprecision occurs during the analysis of the samples from the start and end of the study.

From every sample reserve samples were taken and stored at the Laboratory Reproduction Toxicology frozen (at -20 °C). Reserve samples were described by the suffix "R" in the report.

Following finalization of the report, all analytical samples, including reserve samples, will be discarded.

All test samples, plus a duplicate set of reserve samples (described by the suffix "R"), were withdrawn by staff of the Reproduction Toxicology Lab.

Details of the sampling schedule were recorded with the raw data. More details concerning the specific samples and analyses dates can be found in PART III (SUPPLEMENT).

3.6.2. Stability analysis of the positive control substance preparation (Cyclophosphamide Monohydrate)

The analyses were carried out at the Analytical Chemistry Laboratory of Experimental Toxicology and Ecology, BASF SE, Ludwigshafen, Germany.

Analytical verifications of the stability of the positive substance in drinking water for a period of 7 days at room temperature and for a period of 32 days stored in a freezer were carried out in a comparable batch before the study was initiated.

3.6.3. Analytical methods

The respective analytical phase reports, describing details on the methods used for the analytical investigations of the test substance diet preparations can be found in PART III (SUPPLEMENT).

3.6.4. Food analyses

The food used in the study was assayed for chemical and for microbiological contaminants by the producer.

3.6.5. Drinking water analyses

The drinking water is regularly assayed for chemical contaminants as well as for the presence of (pathogenic) microorganisms by the municipal authorities of Frankenthal and the Environmental Analytics Water/Steam Monitoring of BASF SE.

3.6.6. Bedding and enrichment analyses

The bedding and the enrichment is regularly assayed for contaminants (chlorinated hydrocarbons and heavy metals) by the producer.

3.7. EXPERIMENTAL PROCEDURE

3.7.1. F0 generation animals and their progeny

The 109 male and 110 female rats were 5 and 4 weeks old, respectively when they arrived from the breeder. During an acclimatization period of about 5 days, animals with lowest and highest body weights were eliminated from the study and used for other purposes. The 96 male and 96 female animals required for the study were about 6 (males) and 5 (females) weeks old at the beginning of treatment and their weight variation did not exceed 20 percent of the mean weight of each sex.

The assignment of the animals to the different test groups was carried out using a randomization program, according to their weight two days before the beginning of the administration period (day -2).

After the acclimatization period, the test substance was administered to the animals orally by gavage, once daily at approximately the same time in the morning. Females in labor were not treated. The treatment lasted up to one day prior to sacrifice. The animals of the control group were treated with the vehicle (0.5% CMC suspension in drinking water), in the same way. The volume administered each day was 10 mL/kg body weight. The calculation of the administration volume was based on the most recent individual body weight.

After a minimum of 10 weeks after the beginning of treatment, males and females from the same dose group were mated, overnight at a ratio of 1 : 1 (for details see: Pairing of F0 and F1 generation parental animals).

The females were allowed to deliver and rear their pups (F1 generation pups) until PND 4 (standardization) or PND 21 or 22 (depending on the cohort). Pups of the F1 litter were selected (F1 rearing animals) and assigned to 5 different cohorts which were subjected to specific postweaning examinations. Cohort 1B (=F1 generation parental animals) were selected to produce F2 pups.

On PND 4 blood samples were collected from 10 surplus (culled) F1 pups per sex and group. On PND 22 blood samples were collected from 10 surplus F1 pups per sex and group.

Blood samples were taken from 10 animals per test group of the F0 parental animals and cohort 1A animals.

Before weaning of the F1 pups the F0 generation parental male animals were sacrificed. After weaning of F1 pups the F0 generation parental female animals were sacrificed.

3.7.2. F1 generation parental animals and their progeny (cohort 1B)

After weaning, 24 male and 24 female F1 pups in test groups 00, 01, 02 and 03 (0, 20, 60 and 180 mg/kg bw/d), became F1 generation parental animals in test groups 10, 11, 12 and 13. These animals were chosen by lot and each litter was taken into account as far as technically feasible. If fewer than 24 litters were available in a group or if one sex was missing in a litter, more animals were taken from the other litters of the respective test group to obtain the required number of animals to be paired.

All selected animals were treated with the test substance at the same dose level as their parents, from post-weaning through adulthood.

After a minimum of 10 weeks after assignment of the F1 generation parental animals, the males and females were mated, overnight at a ratio of 1 : 1 (for details see: Pairing of F0 and F1 generation parental animals). The partners were randomly assigned, mating of siblings was avoided.

The females were allowed to deliver and rear their pups (F2 generation pups) until PND 4 (standardization) or PND 21.

Before weaning of the F2 pups the F1 generation parental male animals were sacrificed. The F1 generation parental females were sacrificed, shortly after the F2 generation pups had been weaned.

3.7.3. F1 rearing animals

Before weaning of the F1 generation pups on PND 21, 74 male and 74 females per group were randomly selected (selection see below), to be placed into cohorts according to the scheme presented under 3.7.4. Obvious runts (those pups whose body weight was $\frac{3}{4}$ 25% below the mean body weight of the control group, separate for sexes) were not included.

Cohorts:

Cohort 1A: One male **and** one female/litter (20/sex/group)

Cohort 1B: One male **and** one female/litter (24/sex/group)

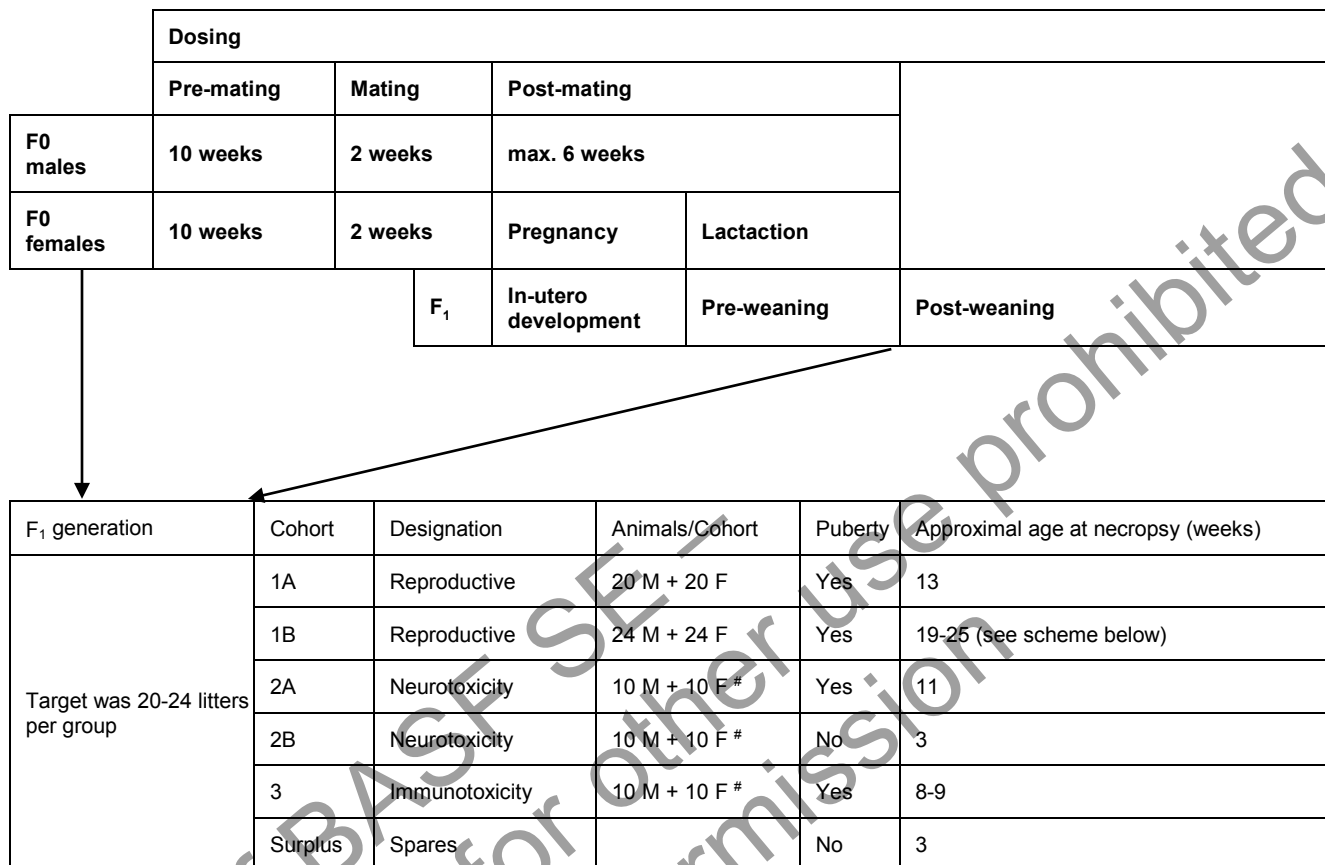
Cohort 2A: One male **or** one female/litter (10/sex/group)

Cohort 2B: One male **or** one female/litter (10/sex/group)

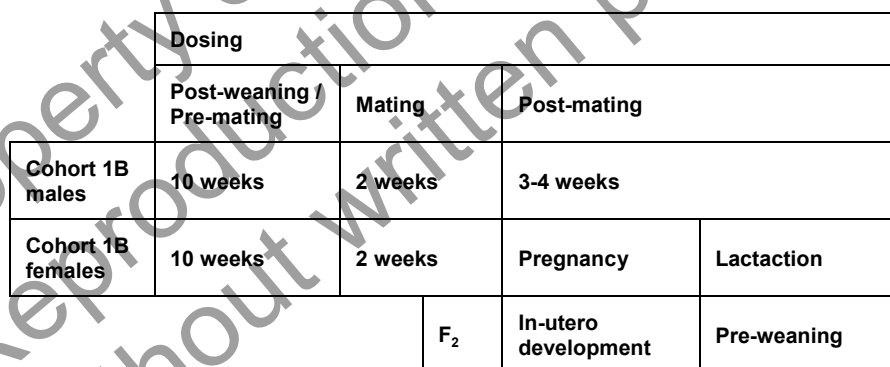
Cohort 3: One male **or** one female/litter (10/sex/group)

Selected F1 offspring (except cohort 2B) received the test substance daily by gavage until one day before sacrifice, according to the scheme presented under 3.7.4.

3.7.4. Experimental procedure scheme



one per litter and representative of 20 litters in total where possible



3.7.5. Standardization of litters (F1 and F2 generation pups)

On PND 4, the individual litters were standardized in such a way that, where possible, each litter contained 5 male and 5 female pups (always the first 5 pups/sex and litter were taken for further rearing). If individual litters did not have 5 pups/sex, the litters were processed in such a way that the most evenly distributed 10 pups per litter were present for further rearing (e.g., 6 male and 4 female pups). Standardization of litters was not performed in litters with ≤ 10 pups.

3.7.6. Pups after standardization/weaning

With the exception of those F1 generation pups, which were chosen as F1 rearing animals, and those F1 pups, which were chosen for blood sampling on PND 4 and 22, all pups were sacrificed under isoflurane anesthesia with CO₂ after standardization or weaning. The pups chosen for blood sampling were sacrificed by decapitation under isoflurane anesthesia.

All culled pups, including stillborn pups and those that died during their rearing period, were subjected to a macroscopic (external and visceral) examination.

All pups without any notable findings or abnormalities were discarded after their macroscopic evaluation. Animals with notable findings or abnormalities were further evaluated on a case-by-case basis (e.g., histopathological evaluation or special staining), depending on the findings noted.

3.7.7. Pairing of F0 and F1 generation parental animals

In general, each of the male and female animals was mated overnight at a 1 : 1 ratio for a maximum of 2 weeks. Throughout the mating period, each female animal was paired with a predetermined male animal from the same dose group.

The animals were paired by placing the female in the cage of the male mating partner from about 16.00 h until 6.30 - 9.00 h of the following morning. Deviations from the specified times were possible on weekends and public holidays and were reported in the raw data. A vaginal smear was prepared after each mating and examined for the presence of sperm. If sperm was detected, pairing of the animals was discontinued. The day on which sperm were detected was denoted "gestation day (GD) 0" and the following day "gestation day (GD) 1".

3.8. CLINICAL EXAMINATIONS AND EXAMINATION OF REPRODUCTIVE PERFORMANCE

3.8.1. Parental animals

3.8.1.1. Mortality

A check for moribund or dead animals was made twice daily on working days or once daily (Saturday, Sunday or on public holidays). If animals were in a moribund state, they were sacrificed and necropsied. The examinations of these animals were carried out according to the methods established at the pathology laboratory.

3.8.1.2. Clinical observations

A cageside examination was conducted at least daily for any signs of morbidity, pertinent behavioral changes and signs of overt toxicity before the administration as well as within 2 hours and within 5 hours after the administration. Abnormalities and changes were documented daily for each animal. Individual data of daily observations can be found in the raw data.

The parturition and lactation behavior of the dams was generally evaluated in the mornings in combination with the daily clinical inspection of the dams. Only particular findings (e.g. disability to deliver) were documented on an individual dam basis.

On weekdays (except Saturday, Sunday and public holidays) the parturition behavior of the dams was inspected in the afternoons in addition to the evaluations in the mornings.

The day of parturition was considered the 24-hour period from about 15.00 h of one day until about 15.00 h of the following day.

3.8.1.3. Water consumption

Generally, water consumption was determined once a week for male and female F0 and F1 parental animals and F1 rearing animals (for a period of 3 - 4 days), with the following exceptions:

- Water consumption was not determined after the 10th pre-mating week (male F0 and F1 animals) and during the mating period (male and female F0 and F1 parental animals).
- During pregnancy, water consumption of the F0 and F1 females with evidence of sperm was determined for GD 0-1, 3-4, 7-8, 10-11, 14-15, 17-18 and 19-20.
- During lactation, water consumption of the F0 and F1 females, which gave birth to a litter was determined for PND 1-2, 4-5, 7-8, 10-11, 14-15, 17-18 and 20-21.

Water consumption was not determined in the F0 and F1 females without positive evidence of sperm during mating and gestation periods, in the females without litter during lactation period, in the females after weaning and the positive control animals.

3.8.1.4. Food consumption

Generally, food consumption was determined once a week for male and female F0 and F1 parental animals and F1 rearing animals, with the following exceptions:

- Food consumption was not determined after the 10th premating week (male F0 and F1 animals) and during the mating period (male and female F0 and F1 parental animals).
- During pregnancy, food consumption of the F0 and F1 females with evidence of sperm was determined weekly for GD 0-7, 7-14 and 14-20.
- During lactation, food consumption of the F0 and F1 females, which gave birth to a litter was determined for PND 1-4, 4-7, 7-10, 10-14, 14-17, 17-19 and 19-21.

Food consumption was not determined in the F0 and F1 females without positive evidence of sperm during mating and gestation periods, in the females without litter during lactation period and in the females after weaning.

3.8.1.5. Body weight data

In general, the body weight of the male and female F0 and F1 parental animals and F1 rearing animals was determined once a week at the same time of the day (in the morning). The body weight of the F1 rearing animals and F1 parental animals was determined on the first day of test substance administration and then once a week at the same time of the day (in the morning), with the following exceptions:

- During pregnancy, body weight of the F0 and F1 females with evidence of sperm was determined weekly for GD 0, 7, 14 and 20.
- During lactation, body weight of the F0 and F1 females, which gave birth to a litter was determined for PND 1, 4, 7, 10, 14, 17, 19 and 21.

The body weight change of the animals was calculated from these results.

Females without positive evidence of sperm, without litter or waiting for necropsy, were weighed weekly. These body weight data were solely used for the calculations of the dose volume; therefore these values are not reported in the Summary but in the Individual Tables (PART II)

3.8.1.7. Detailed clinical observations (DCO)

Detailed clinical observations were performed in all F0 parental animals (once before the beginning of the administration period on day 0) and F1 animals in cohorts 1A, 1B, 2A and 3 at weekly intervals during the administration period. The examinations started in the morning. The findings were ranked according to the degree of severity, if applicable.

For observation, the animals were removed from their cages by the investigator and placed in a standard arena (50 × 37.5 × 25 cm). The following parameters listed were assessed:

1. Abnormal behavior in handling
2. Fur
3. Skin
4. Posture
5. Salivation
6. Respiration
7. Activity/arousal level
8. Tremors
9. Convulsions
10. Abnormal movements
11. Gait abnormalities
12. Lacrimation
13. Palpebral closure
14. Exophthalmos (Protruding eyeball)
15. Assessment of the feces excreted during the examination (appearance/consistency)
16. Assessment of the urine excreted during the examination
17. Pupil size

3.8.1.8. Estrous cycle determinations

Estrous cycle length was evaluated by daily analysis of vaginal smear for all F0 and F1 female (=cohort 1B) parental rats for a minimum of 3 weeks (F0 and F1 females) prior to mating. Determination was continued throughout the pairing period until the female exhibited evidence of copulation.

In all cohort 1A females, vaginal smears were collected after vaginal opening until the first cornified smear (estrous) was recorded. The estrous cycle also was evaluated in cohort 1A females for 2 weeks around PND 75.

At necropsy, an additional vaginal smear was examined to determine the stage of estrous cycle for each F0 and F1 female and cohort 1A female with scheduled sacrifice.

3.8.1.9. Auditory startle response habituation in cohort 2A animals

On PND 24, the auditory startle response test was carried out in all animals of cohort 2A using the SR-LAB; STARTLE RESPONSE SYSTEM (San Diego Instruments, San Diego, CA, U.S.A.) in a randomized sequence. The examinations started at midday. Age-appropriate sized enclosures were used. The animals were given a 5 minutes acclimation period in the response chamber with a 70 dBA background noise. Then the startle response was recorded in 50 trials at a startle stimulus sound level of 120 dBA with a 5 - 10 second variable interval between the trials. Response was recorded for 50 milliseconds. Measurement was carried out with the light and ventilator switched on in the measurement chambers; no food or water was provided during the test. Data (maximum amplitude, latency to the peak of the response) were analyzed in 5 blocks of 10 trials each.

3.8.1.10. Functional observational battery (FOB) in cohort 2A animals

The FOB was carried out once, on PND 75, in all animals of cohort 2A. The examinations were generally started in the morning at about 10:00 h. The FOB was carried out in a randomized sequence. Before start of the FOB the animals were transferred separately into polycarbonate cage. Drinking water was provided ad libitum whereas no food was offered during the measurements. The FOB was started with passive observations without disturbing the rats, followed by removal from the home cage, open field observations in a standard arena and sensory motor tests as well as reflex tests. The findings were ranked according to their degree or severity, if applicable.

Home cage observation

The animals were observed for a short period (about 10-30 seconds) in their cages with the lids closed in the rack, while disturbing influences (touching of the cage and loud noises) were avoided. While other abnormalities were recorded, particular attention was paid to the following parameters:

1. Posture
2. Tremors
3. Convulsions
4. Abnormal movements
5. Gait
6. Other findings

Open field observation

For observation, the animals were removed from their cages by the investigator and placed in a standard arena (50 × 50 × 25 cm). Besides noting other abnormalities, the following parameters were assessed:

1. Behavior on removal from the cage
2. Fur
3. Skin
4. Salivation
5. Nasal discharge
6. Lacrimation
7. Eyes/ pupil size
8. Posture
9. Palpebral closure
10. Respiration
11. Tremors
12. Convulsions
13. Abnormal movements/ stereotypes
14. Gait
15. Activity/ arousal level
16. Feces (consistency/color) excreted during the examination (2 minutes)
17. Urine (amount/color) excreted during the examination (2 minutes)
18. Rearing within 2 minutes
19. Other findings

Sensory-motoric test/Reflexes

The animals were removed from the open field and were subjected to the sensory motor and reflex tests listed below:

1. Reaction to an object being moved towards the face (Approach response)
2. Touch sensitivity (Touch response)
3. Vision (Visual placing response)
4. Pupillary reflex
5. Pinna reflex
6. Audition (Startle response)
7. Coordination of movements (Righting response)
8. Behavior during handling
9. Vocalization
10. Pain perception (Tail pinch)
11. Other findings
12. Grip strength of forelimbs
13. Grip strength of hindlimbs
14. Landing foot-splay test

3.8.1.11. Motor activity measurement (MA)

The measurement of motor activity (MA) was carried out on PND 75, in all animals of cohort 2A. The MA was measured from 14:00 h onwards on the same day as the FOB was performed. The examinations were performed using the TSE Labmaster System supplied by TSE Systems GmbH, Bad Homburg, Germany. For this purpose, the animals were placed in clean polycarbonate cages with a small amount of bedding for the duration of the measurement. Eighteen beams were allocated per cage. The number of beam interrupts were counted over 12 intervals for 5 minutes per interval. The sequence at which the animals were placed in the cages was selected at random. Since the starting time of each animal varied by the time needed to place the animals in the cages, the measurement periods were staggered accordingly, beginning at about 14:00 h for the first animal. The individual measurement period began when the 1st beam was interrupted and finished exactly 1 hour later. No food or water was offered to the animals during these measurements. After the transfer of the last animal in each case, the measurement room was darkened. Exception: For the measurement parameter "rearing" "Z Frame as light beam" was accidentally not selected. Therefore, the program only measured horizontal movement in upright position of the animal, and not the number of rearings.

3.8.1.12. Learning and memory test (Morris water maze) in cohort 2A animals

Spatial learning and re-learning as well as memory were tested in the Morris water maze in cohort 2A animals starting on PND 60 (+/- 2 days). The test system consisted of a round, water-filled pool, which was divided into 4 quadrants, one of which accommodated a submerged (hidden) platform. Data on movements of the animals in the pool were recorded by means of a camera and a tracking software (VideoMot2 Version Black/White, TSE Systems, Bad Homburg, Germany).

The ability of spatial learning was tested in 4 trials on each of four consecutive days, altogether 16 trials. For each of the individual trials the animals were gently placed onto the water surface at one of 4 different starting positions (S1-S4), during the placement the animals were looking towards the wall of the Morris maze pool. The task was to find the hidden platform in quadrant Q2. The tracking was launched the moment the animal was released to start swimming. The technician, who placed the animal, remained stationary at his/her position throughout the entire trial. The tracking was automatically stopped when the animal entered the platform and stayed there for 15 seconds. The maximum duration of a single trial was 2 minutes. Animals which did not find the hidden platform within this timeframe were gently guided to the platform. In the course of one study day each of the 4 possible starting positions was trained. The sequence of the starting positions was defined at random, using WinRando software.

About 48 hours after the last training trial the memory was tested in one single trial under the same condition as the spatial learning. The hidden platform was removed. The animals were placed into the pool at a position which had not been trained before, opposite to the original position of the now removed platform. This ensured that the animal was to remember the position of the platform instead of repeating a memorized swimming path. The tracking was stopped after 30 seconds and the animal taken out of the water.

After another 48 hours spatial re-learning was tested. The procedure was exactly the same as for spatial learning, with two exceptions: 1) the hidden platform was relocated to quadrant Q4, opposite to quadrant Q2; 2) because of the relocation of the platform new starting positions (S5-S8) were used. Memory was again tested 48 hours after the last training trial, in the same manner as for spatial learning.

Apart from the tracking data, records of the Morris water maze test include the temperature of the water in the pool and the names of the involved technicians.

The following parameters were evaluated:

Learning and re-learning

- Latency time: time from start until arrival at the goal (msec)
- Cumulative distance: distance (cm) of each tracking point to the goal throughout one trial

Memory

- Cumulative distance: total of the distance (cm) of each tracking point to the place of the goal throughout one trial
- % Time in target quadrant: percent time the animal spent in target quadrant (msec)

3.8.1.13. Male reproduction data

The pairing partners, the number of mating days until vaginal sperm was detected in the female animals, and the gestational status of the females were recorded for F0 and F1 breeding pairs.

For males, mating and fertility indices were calculated for F1 and F2 litters according to the following formulas:

$$\text{Male mating index (\%)} = \frac{\text{number of males with confirmed mating}^*}{\text{number of males placed with females}} \times 100$$

* defined by a female with vaginal sperm or with implants in utero

$$\text{Male fertility index (\%)} = \frac{\text{number of males proving their fertility}^*}{\text{number of males placed with females}} \times 100$$

* defined by a female with implants in utero

3.8.1.14. Female reproduction and delivery data

The pairing partners, the number of mating days until vaginal sperm were detected, and gestational status were recorded for F0 and F1 females.

For females, mating, fertility and gestation indices were calculated for F1 and F2 litters according to the following formulas:

$$\text{Female mating index (\%)} = \frac{\text{number of females mated}^*}{\text{number of females placed with males}} \times 100$$

* defined as the number of females with vaginal sperm or with implants in utero

$$\text{Female fertility index (\%)} = \frac{\text{number of females pregnant}^*}{\text{number of females mated}^{**}} \times 100$$

* defined as the number of females with implants in utero

** defined as the number of females with vaginal sperm or with implants in utero

$$\text{Gestation index (\%)} = \frac{\text{number of females with live pups on the day of birth}}{\text{number of females pregnant}^*} \times 100$$

* defined as the number of females with implants in utero

The total number of pups delivered and the number of liveborn and stillborn pups were noted, and the live birth index was calculated for F1 and F2 litters according to the following formula:

$$\text{Live birth index (\%)} = \frac{\text{number of liveborn pups at birth}}{\text{total number of pups born}} \times 100$$

The implantations were counted³ and the postimplantation loss (in %) was calculated according to the following formula:

$$\text{Postimplantation loss (\%)} = \frac{\text{number of implantations} - \text{number of pups delivered}}{\text{number of implantations}} \times 100$$

³ To determine the number of implantation sites, the apparently non-pregnant uteri were stained for about 5 minutes in 1% ammonium sulfide solution according to the method of SALEWSKI (Salewski, E.; 1964). Then the uteri were rinsed carefully with 0.9% NaCl solution. Thereafter the implantation sites were recorded for calculation of the postimplantation loss.

3.8.2. Litters/pups

3.8.2.1. Litter data

3.8.2.1.1. Pup number and status at delivery

All pups delivered from the F0 parents (F1 litter) and the F1 parents (F2 litter) were examined as soon as possible on the day of birth to determine the total number of pups, the sex and the number of liveborn and stillborn pups in each litter. At the same time, the pups were also being examined for macroscopically evident changes. Pups, which died before this initial examination, were defined as stillborn pups.

3.8.2.1.2. Pup viability/mortality

In general, a check was made for any dead or moribund pups twice daily on workdays (once in the morning and once in the afternoon) or as a rule, only in the morning on Saturdays, Sundays or public holidays. Dead pups were evaluated by the methods, which are described in detail in section "Pup necropsy observations".

The number and percentage of dead pups on the day of birth (PND 0) and of pups dying between PND 1-4, 5-7, 8-14 and 15-21 (lactation period) were determined; however, pups, which died accidentally or had to be sacrificed due to maternal death, were not included in these calculations. The number of live pups/litter was calculated on the day after birth, and on lactation days 4, 7, 14, and 21. Furthermore, viability and lactation indices were calculated according to the following formulas:

$$\text{Viability index (\%)} = \frac{\text{number of live pups on day 4* after birth}}{\text{number of live pups on the day of birth}} \times 100$$

* before standardization of litters (i.e. before culling)

$$\text{Lactation index (\%)} = \frac{\text{number of live pups on day 21 after birth}}{\text{number of live pups on day 4* after birth}} \times 100$$

* after standardization of litters (i.e. after culling)

3.8.2.1.3. Sex ratio

On the day of birth (PND 0) the sex of the pups was determined by observing the distance between the anus and the base of the genital tubercle; normally, the anogenital distance is considerably greater in male than in female pups. Later, during the course of lactation, this initial sex determination was followed up by surveying the external appearance of the anogenital region and the mammary line. The sex of the pups was finally confirmed at necropsy.

The sex ratio was calculated at PND 0 and PND 21 according to the following formula:

$$\text{Sex ratio} = \frac{\text{number of live male or female pups on PND 0 and 21}}{\text{number of live male and female pups on PND 0 and 21}} \times 100$$

3.8.2.2. Pup clinical observations

The live pups were examined daily for clinical symptoms (including gross-morphological findings) during the clinical inspection of the dams. If pups showed particular findings, these were documented with the dam concerned.

3.8.2.3. Nipple/areola anlagen

All surviving F1 and F2 male pups were examined for the presence of nipple/areola anlagen on PND 13 and were re-examined on PND 20 (F1 male pups) and on PND 21 (F2 male pups).

3.8.2.4. Pup body weight data

The pups were weighed on the day after birth (PND 1) and on PND 4 (before standardization), 7, 14 and 21.

Pups' body weight change was calculated from these results.

The individual weights were always determined at about the same time of the day (in the morning) and on PND 4 immediately before standardization of the litters.

In the summary tables pup body weights and pup body weight gains are listed for males, females and males + females.

3.8.2.5. Anogenital distance

Anogenital distance (AGD) is defined as the distance from the center of the anal opening to the base of the genital tubercle. AGD was determined in all live male and female pups on PND 1. These measurements were performed in randomized order, using a measuring ocular. They were conducted by technicians unaware of treatment group in order to minimize bias.

3.8.2.6. Anogenital index

The anogenital index was calculated according to the following formula:

$$\text{anogenital index} = \frac{\text{anogenital distance [mm]}}{\text{cubic root of pup weight [g]}}$$

3.8.2.7. Pup organ weights

After the scheduled sacrifice, the brain, spleen and thymus of 1 pup/sex per F2 litter were weighed.

Normally, the first male and the first female pups/litter were taken for these determinations. The corresponding in-life pup weights determined on PND 21 were used to calculate the relative organ weights.

3.8.2.8. Pup necropsy observations

On PND 4, as a result of standardization, selected F1 pups were sacrificed by decapitation under isoflurane anesthesia and blood was sampled for determination of serum thyroid hormone concentrations (see chapter CLINICAL PATHOLOGY).

After a similar standardization on PND 4, the surplus F2 pups were sacrificed under isoflurane anesthesia with CO₂. After sacrifice, these pups were examined externally, eviscerated and their organs were assessed macroscopically.

On PND 22, the surplus F1 generation pups that were not used for the formation of the cohorts or any investigations were sacrificed under isoflurane anesthesia with CO₂ and were examined in the pathology lab (see chapter PATHOLOGY). The selected pups for hormone analyses were sacrificed by decapitation under isoflurane anesthesia in the pathology lab and blood was sampled for thyroid hormone analyses (see chapter CLINICAL PATHOLOGY).

On PND 21, all F2 generation pups were sacrificed under isoflurane anesthesia with CO₂. After sacrifice, these pups were examined externally, eviscerated and their organs were assessed macroscopically.

The brain, spleen and thymus were weighed in one surplus F2 weanling per sex per litter (as a rule the first available male and female pup per litter). Pups' relative organ weights were calculated from these weights and the weight of the living animal at sacrifice.

Pups showing clinical symptoms or gross-morphological findings were examined using appropriate methods. Organs/tissues with gross-morphological findings were preserved in a suitable manner for potential histopathological examination.

Pups that died or were sacrificed in a moribund state were eviscerated and examined for possible defects and/or the cause of death using appropriate methods. These animals were preserved for this purpose, if necessary.

All F1 and F2 pups which were not used for other purposes without any notable findings were discarded after their macroscopic evaluation.

3.8.2.9. Sexual maturation

3.8.2.9.1. Vaginal opening

All female F1 pups selected to become the F1 parental generation females (24/group) and F1 rearing animals were evaluated daily for vaginal patency beginning on PND 27. On the day of vaginal opening the body weights of the respective animals were determined.

3.8.2.9.2. Preputial separation

All male F1 pups selected to become the F1 parental generation males (24/group) and F1 rearing animals were evaluated daily for preputial separation beginning on PND 38. On the day of preputial separation the body weights of the respective animals were determined.

3.8.3. Statistics of the clinical examinations

Statistical analyses were performed according to following tables (GROSSE System):

Parameter	Statistical test	Markers in the tables	References
Water consumption, food consumption ⁴ (parental animals), body weight and body weight change (parental animals and pups; for the pup weights, the litter means were used), estrous cycle duration, number of mating days, duration of gestation, number of implantation sites, postimplantation loss and % postimplantation loss, number of pups delivered per litter, duration of sexual maturation (days to vaginal opening, days to preputial separation), anogenital distance, anogenital index	Simultaneous comparison of all dose groups with the control group using the DUNNETT-test (two-sided) for the hypothesis of equal means	* for $p \leq 0.05$ ** for $p \leq 0.01$	Dunnett, C.W. (1955): A multiple comparison procedure for comparing several treatments with a control. JASA, Vol. 50, 1096-1121 Dunnett, C.W. (1964): New tables for multiple comparisons with a control. Biometrics, Vol. 20, 482-491
Male and female mating indices, male and female fertility indices, gestation index, females with liveborn pups, females with stillborn pups, females with all stillborn pups, live birth index, pups stillborn, pups died, pups cannibalized, pups sacrificed moribund, viability index, lactation index, number of litters with affected pups at necropsy, sexual maturation data (vaginal opening, preputial separation)	Pairwise comparison of each dose group with the control group using FISHER'S EXACT test for the hypothesis of equal proportions	* for $p \leq 0.05$ ** for $p \leq 0.01$	Siegel, S. (1956): Non-parametric statistics for behavioral sciences. McGraw-Hill New York

⁴Note: For the parameter food consumption the "mean of means" was calculated and can be found in the relevant summary tables. The "mean of means" values allow a rough estimation of the total food consumption during the different time intervals (premating, gestation and/or lactation); they are not exactly precise values, because the size of the intervals taken for calculation may differ (especially during gestation and lactation periods). For the "mean of means" values no statistical analysis was performed.

Parameter	Statistical test	Markers in the tables	References
Presence of areolae/nipples, proportions of affected pups per litter with necropsy observations	Pairwise comparison of each dose group with the control group using the WILCOXON-test (one-sided) for the hypothesis of equal medians	* for $p \leq 0.05$ ** for $p \leq 0.01$	Nijenhuis, A.; Wilf, H.S. (1978): Combinatorial Algorithms. Academic Press New York, 32-33 Hettmansperger, T.P. (1984): Statistical Inference based on Ranks. John Wiley & Sons New York, 132-142
Pup organ weights (absolute and relative)	Non-parametric one-way analysis using KRUSKAL-WALLIS-test (two-sided). If the resulting p-value was equal or less than 0.05, a pairwise comparison of each dose group with the control group was performed using the WILCOXON-test (two-sided) for the equal medians	* for $p \leq 0.05$ ** for $p \leq 0.01$	Miller, R.G. (1981): Simultaneous Statistical Inference. Springer Verlag New York Inc., 165-167 International Mathematical and Statistical Libraries, Inc., 2500 Park West Tower One, Houston, Texas 77042-3020, USA Nijenhuis, A.; Wilf, H. S. (1978): Combinatorial Algorithms, Academic Press New York, 32-33 Hettmansperger, T. P. (1984): Statistical Inference based on Ranks, John Wiley & Sons New York, 132-142
Rearing, grip strength of forelimbs and hindlimbs, landing foot-splay test, motor activity, startle response	Non-parametric one-way analysis using KRUSKAL-WALLIS test (two-sided). If the resulting p-value was equal or less than 0.05, a pairwise comparison of each dose group with the control group was performed using WILCOXON-test (two-sided) for the equal medians	* for $p \leq 0.05$ ** for $p \leq 0.01$	Siegel, S. (1956): Non-parametric statistics for the behavioural sciences. McGraw-Hill New York

Statistical analyses were performed according to following tables (ToxLIMS System):

Parameter	Statistical test	Markers in the tables	References
Water consumption, food consumption (parental and rearing animals), body weight and body weight change (parental and rearing animals)	Simultaneous comparison of all dose groups with the control group using the DUNNETT test (two-sided) for the hypothesis of equal means	* for $p \leq 0.05$ ** for $p \leq 0.01$	Dunnett, C.W. (1955): A multiple comparison procedure for comparing several treatments with a control. JASA, Vol. 50, 1096-1121 Dunnett, C.W. (1964). New tables for multiple comparisons with a

			control. Biometrics, Vol. 20, 482-491
Rearing, grip strength of forelimbs and hindlimbs, landing foot-splay test	Non-parametric one-way analysis using the KRUSKAL-WALLIS test (two-sided). If the resulting p-value was equal or less than 0.05, a pair-wise comparison of the dose groups with the control group was performed using the WILCOXON-test (two-sided) for the hypothesis of equal medians.	* for $p \leq 0.05$ ** for $p \leq 0.01$	SIEGEL, S. (1956): Non-parametric statistics for the behavioral sciences. McGraw-Hill New York

Statistical analyses were performed according to following tables (TSE System):

Parameter	Statistical test	Markers in the tables	References
Morris water maze	Pairwise comparison of each dose group with the control group using the WILCOXON-test (one-sided) for the hypothesis of equal medians	* for $p \leq 0.05$ ** for $p \leq 0.01$	Nijenhuis, A.; Wilf, H.S. (1978): Combinatorial Algorithms. Academic Press New York, 32-33 Hettmansperger, T.P. (1984): Statistical Inference based on Ranks. John Wiley & Sons New York, 132-142

3.9. CLINICAL PATHOLOGY

3.9.1. Clinical Pathology in F0 parental and cohort 1A animals

Samples were withdrawn from 10 F0 parental and cohort 1A males and females per group at termination.

Blood samples were taken from animals by puncturing the retrobulbar venous plexus following isoflurane anesthesia. Blood sampling and blood examinations were carried out in a randomized sequence. The list of randomization instructions was compiled with a computer.

In the afternoon preceding the day of urinalysis, the animals were individually transferred into metabolism cages (no food or drinking water provided); on the following morning, the individual urine specimens were examined in a randomized sequence (the list of randomization instructions was compiled with a computer).

The assays of blood and serum parameters were performed under internal laboratory quality control conditions with reference controls to assure reliable test results.

The results of clinical pathology examinations were expressed in International System (SI) units.

The following parameters were examined:

3.9.2. Hematology

The following parameters were determined in blood with EDTA-K₃ as anticoagulant using a particle counter (Advia 120 model; Bayer, Fernwald, Germany):

Parameters and methods:

Parameter	Unit	Method	References
Leukocyte count (WBC)	giga/L	cytochemistry coupled with flow cytometry	Operator's Guide for Advia 120 System
Erythrocyte count (RBC)	tera/L	flow cytometric laserlight scattering	
Hemoglobin (HGB)	mmol/L	cyanmethemoglobin method; according to ICSH	
Hematocrit (HCT)	L/L	calculation: MCV x erythrocytes	
Mean corpuscular volume (MCV)	fL	RBC/PLT method; mean of RBC volume distribution curve (histogram)	
Mean corpuscular hemoglobin (MCH)	fmol	calculation: hemoglobin erythrocytes	
Mean corpuscular hemoglobin concentration (MCHC)	mmol/L	calculation: hemoglobin hematocrit	
Platelet count (PLT)	giga/L	flow cytometric laserlight scattering	
Differential blood count	% and giga/L	cytochemistry coupled with flow cytometry	
Reticulocytes (RETA)	giga/L	cytochemistry coupled with flow cytometry	

Furthermore, blood smears were prepared and stained according to WRIGHT without being evaluated, because of non-ambiguous results of the differential blood cell counts measured by the automated instrument. (reference: Hematology: Principles and Procedures, 6th Edition, Brown AB, Lea & Febiger, Philadelphia, 1993, page 101).

Clotting tests were carried out using a ball coagulometer (AMAX destiny plus model; Trinity biotech, Lemgo, Germany).

Parameter and method:

Parameter	Unit	Method	References
Prothrombin time (Hepato Quick's test) (HQT)	seconds	citratd blood with calcium thromboplastin	Fischer, M. and Falkensammer, Ch., Klin. Wschr. <u>86</u> , 577-583 (1974)

3.9.3. Clinical chemistry

An automatic analyzer (Cobas c501; Roche, Mannheim, Germany) was used to examine the clinicochemical parameters

Parameters and methods:

Enzyme (systematic name and system number)	Unit	Method, wave-length and measuring temperature (Detection limit)	References
Alanine aminotransferase (ALT) (L-alanine: 2-oxoglutarate aminotransferase; EC 2.6.1.2.)	μkat/L	kinetic UV test, 340 nm; 37°C, (0.08 μkat/L)	Recommendations of the German Society for Clinical Chemistry: "Standardization of methods for determining enzyme activities in biological liquids". J. Clin. Chem. Clin. Biochem. <u>8</u> , 658-660 (1970); J. Clin. Chem. Clin. Biochem. <u>9</u> , 464-465 (1971); J. Clin. Chem. Clin. Biochem. <u>10</u> , 182-192 (1972)
Aspartate aminotransferase (AST) (L-aspartate: 2-oxoglutarate aminotransferase; EC 2.6.1.1.)	μkat/L	kinetic UV test, 340 nm; 37°C, (0.08 μkat/L)	Roche working instructions
Alkaline phosphatase (ALP) (orthophosphoric acid monoester phosphohydrolase; EC 3.1.3.1.)	μkat/L	kinetic color test, 415 nm; 37°C, (0.084 μkat/L)	Szasz, G. et al., J. Clin. Chem. Clin. Biochem. <u>12</u> , 228 (1974) Roche working instructions
γ-Glutamyltransferase (GGT) (γ-glutamyl) peptide: aminoacid-γ-glutamyl-transferase; EC 2.3.2.2.)	nkat/L	kinetic color test, 415 nm; 37°C, (25 nkat/L)	

Blood Chemistry Parameter	Unit	Method (Detection limit)	References
Sodium (NA)	mmol/L	ion selective electrodes (ISE), (Na: 80, K: 1.5, Cl: 60 nmol/L)	Roche - working instructions
Potassium (K)	mmol/L		
Chloride (CL)	mmol/L		
Inorganic phosphate (INP)	mmol/L	molybdate reaction (0.1 mmol/L)	Henry, R.J. in: "Clinical Chemistry", Harper and Row Publishers, New York (1974); Roche working instructions
Calcium (CA)	mmol/L	o-cresolphthalein complex without deproteinization (0.2 mmol/L)	Ray Sarkar, B.C. and Chauhan, U.P.S., Anal. Biochem. <u>20</u> , 155 (1967); Roche working instructions
Urea (UREA)	mmol/L	enzymatic determination with the urease/ glutamate dehydrogenase method (0.5 mmol/L)	Neumann, U. and Ziegenhorn, J.: XVI, Nordiska kongressen for klinisk kemi och klinisk fysiologi 1977, Oulu, Finland; Roche working instructions
Creatinine (CREA)	µmol/L	enzymatic determination with the creatininase/ creatinase /sarcosinoxidase method (5 µmol/L)	Guder et al., J.Clin.Chem.Clin.Biochem. <u>24</u> , 889-902 (1986); Roche working instructions
Glucose (GLUC)	mmol/L	hexokinase/glucose-6-phosphate dehydrogenase method (0.11 mmol/L)	Schmidt, F.H., Klin. Wschr. <u>39</u> , 1244-1247 (1961); Roche working instructions
Total bilirubin (TBIL)	µmol/L	DPD method (0.56 µmol/L)	Wahlefeld, A.W. et al., Scand. J. Clin. Lab. Invest. <u>29</u> , Suppl. 126 (1972) Abstract 11.12; Roche working instructions
Total protein (TPROT)	g/L	biuret method (2 g/L)	Luxton, R.W.; Patel, P. Keir, G. Thompson, E.J., Clin Chem 1989, <u>35</u> (8), 1731-1734
Albumin (ALB)	g/L	bromocresol green method (3.2 g/L)	Doumas et al., Clin. Chim. Acta <u>31</u> , 87 (1971); Randox working instructions
Globulins (GLOB)	g/L	difference between total protein and albumin	
Triglycerides (TRIG)	mmol/L	enzymatic color test with lipase esterase/ glycerokinase/ glycerol-3-phosphate oxidase/4-amino-phenazone (0.1 mmol/L)	mod. method by Wahlefeld, A.W., in "Methoden der enzymatischen Analyse" [Methods of enzymatic analysis] (Bergmeyer, H.U., ed.) Vol. II, 3rd ed., Verlag Chemie Weinheim, GERMANY, pp. 1878-1882 (1974); Roche working instructions
Cholesterol (CHOL)	mmol/L	enzymatic determination with cholesterol esterase/ cholesterol oxidase/4-amino-phenazone (CHOD-PAP method) (0.1 mmol/L)	Siedel, J. et al., J. Clin. Chem. Clin. Biochem. <u>19</u> , 838 (1981); Roche working instructions

3.9.4. Hormones

The concentrations of TSH were determined by radioimmunoassay (RIA), using commercially available RIA test kits and a Gamma-Counter (LB 2111, Berthold, Germany). T4 Elisas was measured with a Sunrise MTP-reader, Tecan AG, Maennedorf, Switzerland, and evaluated with the Magellan-Software of the instrument producer.

Parameters and methods:

Hormone parameter	Unit	Method	References
Total thyroxine (T4)	nmol/L	ELISA (LOQ 15 nmol/L; in fetus and PND 4 pup samples 7.5 nmo/L)	DRG instruments (Marburg, Germany)
Thyroid stimulating hormone (TSH)	µg/L	direct, competitive radioimmuno- assay (LOQ 1 µg/L)	Institute of Isotopes Co., Ltd. (Budapest, Hungary)

3.9.5. Urinalysis

The dry chemical reactions on test strips (Combur-Test 10 M; Sysmex, Norderstedt, Germany) used to determine urine constituents semiquantitatively were evaluated with a reflection photometer (Meditron M; Sysmex, Norderstedt, Germany).

Parameters and methods:

Parameter	Method	References
pH	methyl red and bromothymol blue	Test strip book by Roche, Mannheim, GERMANY (1977)
Protein (PRO)	tetrabromophenol-phthaleinethylester (TBPE)	
Glucose (GLU)	GOD-POD reaction	
Ketones (KET)	sodium nitroprusside	
Urobilinogen (UBG)	p-methoxyaniline-diazonium-salt	
Bilirubin (BIL)	2,5-dichloroaniline diazonium salt	
Blood	2,5-dimethylhexane-2,5-dihydroperoxide, tetramethylbenzidine	Hamilton or Atago operating instructions
Specific gravity (SP.GR.) [g/L]	refractometer	
Sediment	microscopy	Hallmann, L., [Clinical Chemistry and Microscopy] 10, ed., 233-246, Georg Thieme, Stuttgart, Germany (1966)
Color, turbidity (COL, TURB)	by visual evaluation	
Volume (VOL) [mL]	graduated tubes	

3.9.6. Sperm parameters

After the organ weight determination, the following parameters were determined in the right testis or right epididymis of all male F0 parental animals and all cohort 1A males sacrificed on schedule:

Sperm motility examinations were carried out in a randomized sequence.

Parameters and methods:

Parameter	Unit	Method	References
Sperm motility	%	microscopic evaluation	Slott, Suarez and Perreault, "Rat sperm motility analysis: Methodological considerations" in: "Reproductive Toxicology", Vol 5, pp. 449-458 (1991)
Sperm morphology	%	vital staining with eosin; microscopic evaluation	M.H. Feuston, K.R. Bodnar, S.L. Kerstetter, C.P. Grink, M.J. Belcak and E.J. Singer, "Reproductive Toxicity of 2-Methoxyethanol Applied Dermally to Occluded and Nonoccluded Sites in Male Rats" in: Toxicology and applied Pharmacology 100, 145-161 (1989) (Laboratory modification)
Sperm head count (cauda epididymis)	Mio/g cauda epididymis	microscopic evaluation with MAKLER chamber after homogenization	
Sperm head count (testis)	Mio/g testis	microscopic evaluation with MAKLER chamber after homogenization	

3.9.7. Hormones in PND 4 and 22 F1-offspring

3.9.7.1. Blood sampling

Blood samples were withdrawn from 10 surplus (culled) PND 4 offspring (as far as possible of different litters) per sex and group. PND 4 samples were pooled per sex and litter if the available amount is not sufficient for a hormone analysis

Blood samples were withdrawn from 10 surplus PND 22 offspring (as far as possible of different litters) per sex and group.

The blood samples was collected after decapitation (following isoflurane anesthesia) from the Vena cava cranialis.

3.9.8. Hormones

The concentrations of TSH were determined by radioimmunoassay (RIA), using commercially available RIA test kits and a Gamma-Counter (LB 2111, Berthold, Germany). T4 Elisas was measured with a Sunrise MTP-reader, Tecan AG, Maennedorf, Switzerland, and evaluated with the Magellan-Software of the instrument producer.

Parameters and methods:

Hormone parameter	Unit	Method	References
Total thyroxine (T4)	nmol/L	ELISA (LOQ 15 nmol/L; in fetus and PND 4 pup samples 7.5 nmo/L)	DRG instruments (Marburg, Germany)
Thyroid stimulating hormone (TSH)	µg/L	direct, competitive radioimmuno- assay (LOQ 1 µg/L)	Institute of Isotopes Co., Ltd. (Budapest, Hungary)

3.9.9. Developmental immunotoxicity examinations in cohort 3 animals and positive control animals

3.9.9.1. Cyclophosphamide dependent immune system response

Ten male and ten female offspring derived from test group 00 (as far as possible from different litters) were selected at weaning to become a positive control group in this study. These animals were treated with Cyclophosphamide monohydrate to prove the functional responsiveness of major components of the immune system of the rats against an immunosuppressant. The animals were treated by daily oral gavage from PND 35 onwards, for **about four weeks**.

The following dose level of Cyclophosphamide monohydrate was selected to be sufficient to cause immunosuppressive activity as positive control substance:

4.5 mg/kg body weight/day: as dose level with expected immunosuppressive effects

The oral route was selected since this was proven to be suitable for the detection of a toxicological hazard.

POSITIVE CONTROL SUBSTANCE PREPARATIONS AND ADMINISTRATION (IN REPRODUCTION LABORATORY)

Route of administration: Oral administration by gavage using 3 or 5 mL syringes.

Frequency of administration: Once daily

Volume to be administered: 10 mL/kg body weight; the body weight determined most recently were used to calculate the administration volume.

Preparation: For details on the technical procedure see 3.5.

Preparation frequency: At least once before the administration period.

Storage conditions of the positive control substance preparations: The positive control substance preparations were split in daily aliquots and stored closed in a freezer at -18°C.

Duration of administration: **About 4 weeks**

Immunization on PND 56+/-3 (in Reproduction Laboratory):

Route of administration: Intraperitoneal, using 1 mL tuberculin-syringes

Preparation: Details of preparation of the sheep red blood cells were described in the raw data (4×10^8 SRBC/mL)

Frequency of administration: twice (within one action)

Administration volume: 1 mL per animal, split into two portions of 0.5 mL

Six days after immunization blood samples were taken by puncturing the retrobulbar venous plexus following isoflurane anesthesia. Blood sampling and blood examinations were carried out in a randomized sequence. The list of randomization instructions was compiled with a computer.

3.9.9.2. T-cell dependent antibody response

All males and females of cohort 3 and the positive control animals were used to assess the functional responsiveness of major components of the immune system to a T-cell dependent antigen, sheep red blood cells (SRBC). For this purpose, the Anti SRBC-IgM ELISA of Life Diagnostics Inc, West Chester, USA (cat. no. 4200-2), was performed. Each sample was diluted 1:500. SRBC-IgM concentrations outside the standard curve range were measured in a second test run with an appropriate dilution. Generally, two in-house controls were measured with each test run. The ELISA was measured with a Sunrise MTP-reader, Tecan AG, Maennedorf, Switzerland, and evaluated with the Magellan-Software of the instrument producer.

3.9.9.3. Splenic lymphocyte subpopulation analysis

The immunophenotyping was performed with a FACS Calibur flow cytometer (Becton Dickinson, Heidelberg, Germany).

10 males and 10 females of cohort 1A were used to perform a splenic lymphocyte subpopulation analysis using one half of the spleen.

Parameter	Unit	Method	References
B lymphocytes (B_SPL)	% and Mio/g	Flow cytometry	E. Cortes-Barberena et al (2008), Clinical and Experimental Immunology, 152, 585-592
T lymphocytes (T_SPL)			
CD4+ lymphocytes (CD4_SPL)			
CD8+ lymphocytes (CD8_SPL)			
Natural killer cells (NK_SPL)			

Because of a technical defect of the FACS Calibur flow cytometer in the clinical pathology lab of the test site on 15 Feb 2018, analysis of the splenic lymphocyte subpopulations for the scheduled samples could not be performed on this instrument in the test facility. To obtain comparable results with samples of the same cohort (F1A) analysed the day before, this analysis had to be performed on the same instrument type, with high urgency due to limited stability of the samples. Therefore, the samples were immediately transported by staff of the test facility laboratory clinical pathology at ambient temperature to the instrument and reagent supplier, Becton Dickinson, Tullastr. 8–12, Heidelberg, Germany (without GLP status), where the measurements of the samples were conducted using the same FACS Calibur instrument type (without GLP status). Results were transferred on an USB flash drive (list mode FCS 2.0 format) to the laboratory of clinical pathology of the test facility due to a lacking printer connected to the instrument in Heidelberg and printed out on the test facility printer.

Due to the lacking GLP status of the Becton-Dickinson facility, these measurements had to be performed without GLP status.

3.9.10. Statistics of clinical pathology

Means, medians and standard deviations of each test group were calculated for several parameters (see tables).

The following table contains the statistical analyses used in this report. Details were explained in the summary tables in PART IB:

Parameter	Statistical test	Markers in the tables	References
Blood parameters and splenic lymphocytes subpopulations	For parameters with bidirectional changes: Non-parametric one-way analysis using KRUSKAL-WALLIS test. If the resulting p-value was equal or less than 0.05, a pairwise comparison of each dose group with the control group was performed using WILCOXON-test (two-sided) for the hypothesis of equal medians For parameters with unidirectional changes: Pairwise comparison of each dose group with the control group using the WILCOXON-test (one-sided) for the hypothesis of equal medians	* for $p \leq 0.05$ ** for $p \leq 0.01$	SIEGEL, S. (1956): Non-parametric statistics for the behavioural sciences. McGraw-Hill New York
Urinalysis parameters (apart from pH, urine volume, specific gravity, color and turbidity)	Pairwise comparison of each dose group with the control group using the WILCOXON-test (one-sided) for the hypothesis of equal medians. In case of exactly the same numbers of the dose group and the control, no statistical test is performed.	* for $p \leq 0.05$ ** for $p \leq 0.01$	SIEGEL, S. (1956): Non-parametric statistics for the behavioural sciences. McGraw-Hill New York
Urine pH, volume and specific gravity	Non-parametric one-way analysis using KRUSKAL-WALLIS test. If the resulting p-value was equal or less than 0.05, a pairwise comparison of each dose group with the control group was performed using WILCOXON-test (two-sided) for the hypothesis of equal medians.	* for $p \leq 0.05$ ** for $p \leq 0.01$	SIEGEL, S. (1956): Non-parametric statistics for the behavioural sciences. McGraw-Hill New York
Urine color and turbidity	Urine color and turbidity are not evaluated statistically.		
Spermanalysis parameters	Pairwise comparison of each dose group with the control group using the WILCOXON-test (one-sided) with Bonferroni-Holm adjustment for the hypothesis of equal medians. For the percentage of abnormal sperms (ABNORMAL6_C) values < 6 % were set to 6 % (cut off 6 %)	* for $p \leq 0.05$ ** for $p \leq 0.01$	Holm (1979): A Simple Sequentially Rejective Multiple Test Procedure. Scand. J. Statist. 6, 65-70

3.10. PATHOLOGY

3.10.1. Pathological examinations of F0 generation, parental animals and cohort 1A

3.10.1.1. Necropsy

All **F0 parental animals and all cohort 1A animals** were sacrificed by decapitation under isoflurane anesthesia. The exsanguinated animals were necropsied and assessed by gross pathology, special attention being given to the reproductive organs.

The animal No 127 (female F0 parental animal, test group 01) was sacrificed in a moribund state and animal No. 362 (female cohort 1A animal, test group 13) died intercurrently. They were necropsied and assessed by gross pathology as soon as possible after their death.

3.10.1.2. Organ weights

The following weights were determined in all animals sacrificed on schedule:

1. Anesthetized animals (terminal body weight)
2. Adrenal glands (fixed)
3. Brain
4. Cauda epididymis
5. Epididymides
6. Heart
7. Kidneys
8. Liver
9. Lymph nodes, axillary (10 animals per sex per group, cohort 1A animals only)
10. Lymph nodes, mesenteric (10 animals per sex per group, cohort 1A animals only)
11. Ovaries
12. Pituitary gland (fixed)
13. Prostate (ventral and dorsolateral part together, fixed)
14. Testes
15. Seminal vesicles including coagulating glands (fixed)
16. Spleen
17. Thymus (fixed)
18. Thyroid glands (with parathyroid glands) (fixed)
19. Uterus with cervix

All paired organs were weighed together (left and right).

3.10.1.3. Organ/tissue fixation

The following organs or tissues were fixed in 4% neutral buffered formaldehyde solution or in modified Davidson's solution:

1. All gross lesions
2. Adrenal glands
3. Bone marrow (femur)
4. Brain
5. Cecum
6. Cervix
7. Coagulating glands
8. Colon
9. Duodenum
10. Epididymis, left (fixed in modified Davidson's solution)
11. Esophagus
12. Eyes with optic nerve (fixed in modified Davidson's solution)
13. Heart
14. Ileum
15. Jejunum (with Peyer's patches)
16. Kidneys
17. Liver
18. Lungs
19. Lymph nodes, axillary
20. Lymph nodes, mesenteric
21. Mammary gland (male and female), right
- 21a. Mammary gland fat pad, left (selected animals of F0 and Cohort 1A, fixed in Carnoy's solution)
22. Ovaries (fixed in modified Davidson's solution)
23. Oviducts
24. Pancreas
25. Pituitary gland
26. Prostate
27. Rectum
28. Sciatic nerve
29. Seminal vesicles
30. Skeletal muscle
31. Spinal cord (cervical, thoracic and lumbar cord)
32. Spleen
33. Stomach (forestomach and glandular stomach)
34. Testis, left (fixed in modified Davidson's solution)
35. Thymus
36. Thyroid glands (with parathyroid glands)
37. Trachea
38. Urinary bladder
39. Uterus
40. Vagina
41. Vas deferens

The ovaries and eyes with optic nerve of animals that died or were sacrificed intercurrently were fixed in 4% neutral buffered formaldehyde solution.

The left testis and left epididymis of all male F0 parental and Cohort 1A animals sacrificed at scheduled dates were fixed in modified Davidson's solution, whereas the right testis and epididymis were used for sperm parameters analysis.

In case of macroscopic findings in the right testis or right epididymis, this testis as well as the corresponding epididymis were fixed for histopathological examination and the left testis and epididymis were used for sperm analysis.

For technical reasons, after about 24 hours fixation the ovaries of all F0 and cohort 1A females of all test groups were transferred to 70% ethanol.

The uteri of all cohabited female **F0 parental animals** were examined for the presence and number of implantation sites. The uteri of apparently nonpregnant animals or empty uterus horns were placed in 1% ammonium sulfide solutions for about 5 minutes in order to be able to identify early resorptions or implantations (SALEWSKI's method ⁽¹⁾). Then the uteri were rinsed carefully in physiologic salt solution (0.9 % NaCl). When the examinations were completed, the uteri were transferred to the Pathology Laboratory for further processing.

Spleens of 10 animals per sex per group of **cohort 1A** were split in two comparable parts (transversally). One part of the spleen was fixed in 4% neutral buffered formaldehyde and afterwards embedded in paraplast. The other part of the spleen was frozen at -80° C, being used to perform a splenic lymphocyte subpopulation analysis (CD4+ and CD8+ T lymphocytes, B lymphocytes, and natural killer cells).

The left fourth and fifth mammary complex incl. the respective inguinal lymph nodes (mammary gland fat pad without skin) were sampled in total in 10 male and 10 female **F0 and cohort 1A** animals per group and were fixed in Carnoy's solution for at least 48 hours. The tissue was fixed in a flatted manner in cranio-caudal direction.

3.10.1.4. Histopathology

Fixation was followed by histotechnical processing, examination by light microscopy and assessment of findings according to the table below:

F0 generation parental animals

Organs	Test groups			
	00	01	02	03
1. All gross lesions	A2	A2	A2	A2
2. Adrenal glands	A1	A3	A3	A1
3. Bone marrow (femur)	A1			A1
4. Brain	A1			A1

Organs	Test groups			
	00	01	02	03
5. Cecum	A1/A4	A4	A4	A1/A4
6. Cervix	A1	A3	A3	A1
7. Coagulating glands	A1	A3	A3	A1
8. Colon	A1			A1
9. Duodenum	A1			A1
10. Epididymis, left	A1*	A3	A3	A1*
11. Esophagus	A1			A1
12. Eyes with optic nerve	A1*			A1*
13. Heart	A1			A1
14. Ileum	A1			A1
15. Jejunum	A1			A1
16. Kidneys	A1/A5	A5	A5	A1/A5
17. Liver	A1			A1
18. Lungs	A1			A1
19. Lymph nodes, axillary	A1			A1
20. Lymph nodes, mesenteric	A1			A1
21. Mammary gland fat pad (selected F0 males and females), left	A1**	B1**	B1**	A1**
22. Mammary gland (male and female), right	A1			A1
23. Ovaries	A1	A3	A3	A1
24. Oviducts	A1	A3	A3	A1
25. Pancreas	A1			A1
26. Parathyroid glands	A1			A1
27. Pituitary gland	A1	A3	A3	A1
28. Prostate	A1	A3	A3	A1
29. Peyer's patches	A1			A1
30. Rectum	A1			A1
31. Sciatic nerve	A1			A1
32. Seminal vesicles	A1	A3	A3	A1
33. Skeletal muscle	A1			A1
34. Spinal cord (cervical, thoracic, lumbar)	A1			A1
35. Spleen	A1			A1
36. Stomach (forestomach and glandular stomach)	A1/A5	A5	A5	A1/A5
37. Testis, left	A1*	A3	A3	A1*
38. Thymus	A1			A1
39. Thyroid glands	A1			A1
40. Trachea	A1			A1
41. Urinary bladder	A1			A1
42. Uterus	A1	A3	A3	A1

Organs	Test groups			
	00	01	02	03
43. Vagina	A1	A3	A3	A1
44. Vas (Ductus) deferens	A1	A3	A3	A1

A = Hematoxylin and Eosin (H&E) stain

B = Paraplast embedding

1 = F0: 20 animals per sex (first 20 surviving pairs and with offspring)

2 = all animals affected/test group

3 = mating pairs suspected of reduced fertility (all F0 animals/test group)

4 = all 24 female animals/test group

5 = all 24 male animals/test group

* = paraplast embedding for all 24 animals per group (F0 generation)

**= selected animals

F1 generation animals of cohort 1A

Organs	Test groups			
	10	11	12	13
1. All gross lesions	A2	A2	A2	A2
2. Adrenal glands	A1	A3	A3	A1
3. Bone marrow (femur)	A1			A1
4. Brain	A1			A1
5. Cecum	A1			A1
6. Cervix	A1	A1	A1	A1
7. Coagulating glands	A1	A3	A3	A1
8. Colon	A1			A1
9. Duodenum	A1			A1
10. Epididymis, left	A1	A3	A3	A1
11. Esophagus	A1			A1
12. Eyes with optic nerve	A1			A1
13. Heart	A1			A1
14. Ileum	A1			A1
15. Jejunum	A1			A1
16. Kidneys	A1	A6	A6	A1
17. Liver	A1			A1
18. Lungs	A1			A1
19. Lymph nodes, axillary	A1			A1
20. Lymph nodes, mesenteric	A1			A1
21. Mammary gland fat pad (selected F1A males and females), left	A1**	B1**/A6**	B1**/A6**	A1**
22. Mammary gland, right (male and female)	A1	A6	A6	A1
23. Ovaries	A1/C1#	A3/C1#	A3/C1#	A1/C1#
24. Oviducts	A1	A3	A3	A1
25. Pancreas	A1			A1

Organs	Test groups			
	10	11	12	13
26. Parathyroid glands	A1			A1
27. Pituitary gland	A1	A3	A3	A1
28. Prostate	A1	A3	A3	A1
29. Peyer's patches	A1			A1
30. Rectum	A1			A1
31. Sciatic nerve	A1			A1
32. Seminal vesicles	A1	A3	A3	A1
33. Skeletal muscle	A1			A1
34. Spinal cord (cervical, thoracic, lumbar)	A1			A1
35. Spleen	A1			A1
36. Stomach (forestomach and glandular stomach)	A1	A6	A6	A1
37. Testis, left	A1	A3	A3	A1
38. Thymus	A1			A1
39. Thyroid glands	A1			A1
40. Trachea	A1			A1
41. Urinary bladder	A1			A1
42. Uterus	A1	A1	A1	A1
43. Vagina	A1	A1	A1	A1
44. Vas (Ductus) deferens	A1	A3	A3	A1

A = Hematoxylin and Eosin (H&E) stain

B = Paraplast embedding

C = MVH immunohistochemical staining (evaluation only test group 10 and 13)

1 = all F1A animals/test group

2 = all animals affected/test group

3 = mating pairs suspected of reduced fertility (all F1A animals/test group)

6 = all male animals/test group

**= selected animals

= F1 generation animals of cohort 1A

The organs were trimmed according to the "Revised guides for organ sampling and trimming in rats and mice" (Ruehl-Fehlert et al., 2003; Kittel et al., 2004; Morawietz et al., 2004).

A correlation between gross lesions and histopathological findings was attempted.

Special attention was given to stages of spermatogenesis in the male gonads.

Special attention was also given to the synchrony of the morphology in ovaries, uterus, cervix, and vagina to the estrous cycle status.

Animals that died were processed histotechnically and assessed like control animals.

Reproductive organs of **all F0** animals suspected of reduced fertility were subjected to histopathological investigation.

A differential ovarian follicle count (**DOFC**) was conducted in test groups 10 and 13 (Cohort 1A females) according to Plowchalk et.al. (1993).

Differential Ovarian Follicle Count (DOFC) in F1 generation:

Both ovaries from each female (test groups 10 and 13) were embedded in paraffin blocks. The ovaries of up to 4 animals from the same test group were embedded together in one block. Each block was sectioned serially until the total ovary was laminated. Sections were prepared with 2 µm thickness and every 100 µm each 2 serial sections (1a, 1b / 2a, 2b / 3a, 3b ...) were taken and mounted on glass slides:

- the first slides of the serial sections (1a/2a/3a ...) were used for immuno-histochemistry (using MVH antibody [mouse vasa homolog], a protein expressed in all oocyte stages).
- the second slides of the serial sections (1b/2b/3b ...) were taken as reserve slides.

After the eighth serial sections (8a, 8b), one further section for a negative control for immunohistochemistry, one further section for hematoxylin and eosin staining and 10 further sections without any staining were taken for possible further investigations.

Then further serial sections (9a, 9b/10a, 10b/ ...) were taken until no more ovarian tissue was within the blocks.

All immunohistochemically-stained slides were scanned with a Hamamatsu NanoZoomer 2.0 slidescanner and counting of primordial and growing follicles was performed on the computer screen with the NDP.view software (magnification: 100x). Both ovaries of each female were evaluated. Primordial follicles and growing follicles were counted according to the definitions given by Plowchalk et al. (1993).

To prevent multiple counting for growing follicles, only follicles with an oocyte with a visible nucleus were counted.

The number of each type of follicle was recorded individually for both ovaries of every animal, giving in summary the incidence of each type of follicle. Finally, the results of all types of follicles were summarized for all animals per group in test groups 10 and 13. As primordial follicles continuously develop into growing follicles, the assessment of the follicles was extended to the combined incidence of primordial plus growing follicles.

In general, the 8th sections of both ovaries stained with hematoxylin and eosin from all females of test groups 10 and 13 were evaluated for histological findings.

Whenever in the ovary the diagnosis: "no abnormalities detected" was used that implies that all different stages of functional bodies (especially corpora lutea) were present and normal.

3.10.2. Pathological examinations of cohort 1B animals (= F1 parental animals)

3.10.2.1. Necropsy

After weaning of F2 offspring, all **cohort 1B animals** were sacrificed by decapitation under isoflurane anesthesia. The exsanguinated animals were necropsied and assessed by gross pathology, special attention being given to the reproductive organs.

The animal No. 550 died intercurrently. It was necropsied and assessed by gross pathology as soon as possible after its death.

3.10.2.2. Organ weights

The following weights were determined in all animals sacrificed on schedule:

1. Anesthetized animals (terminal body weight)
2. Adrenal glands (fixed)
3. Cauda epididymis
4. Epididymides
5. Kidneys
6. Liver
7. Ovaries
8. Pituitary gland (fixed)
9. Prostate (ventral and dorsolateral part together, fixed)
10. Testes
11. Seminal vesicles including coagulating glands (fixed)
12. Uterus (with cervix)

All paired organs were weighed together (left and right).

3.10.2.3. Organ/Tissue fixation

The following organs or tissues were fixed in 4% formaldehyde solution or in modified Davidson's solution:

1. All gross lesions
2. Adrenal glands
3. Cecum
4. Cervix
5. Coagulating glands
6. Epididymides (fixed in modified Davidson's solution)
7. Kidneys
8. Liver
9. Mammary gland (male and female), right
10. Mammary gland fat pad, left (selected animals of cohort 1B)
11. Ovaries (fixed in modified Davidson's solution)

12. Pituitary gland
13. Prostate
14. Seminal vesicles
15. Testes (fixed in modified Davidson 's solution)
16. Uterus
17. Vagina

The ovaries of the animal that died were fixed in 4% buffered formaldehyde solution.

The left fourth and fifth mammary complex incl. the respective inguinal lymph nodes (mammary gland fat pad without skin) were sampled in total in 10 male and 10 female cohort 1B animals per group and were fixed in Carnoy's solution for at least 48 hours. The tissue was fixed in a flattened manner in cranio-caudal direction.

The uteri of all cohabited female **cohort 1B animals (= F1 parental animals)** were examined for the presence and number of implantation sites. The uteri of apparently nonpregnant animals or empty uterus horns were placed in 1% ammonium sulfide solutions for about 5 minutes in order to be able to identify early resorptions or implantations (SALEWSKI's method ⁽¹⁾). Then the uteri were rinsed carefully in physiologic salt solution (0.9 % NaCl). After these examinations, the uteri were transferred to the Pathology Laboratory for further processing.

3.10.2.4. Histopathology

Histotechnical processing, examination by light microscopy and assessment of findings was conducted according to the table below:

Organs	Test groups			
	10	11	12	13
1. Adrenal glands	A3	A3	A3	A3
2. Cervix	A4	A4	A4	A4
3. Coagulating glands	A3	A3	A3	A3
4. Epididymides	A3	A3	A3	A3
5. Mammary gland fat pad (selected F1B males and females), left	A3*/A5*	A3*/A5*	A3*/A5*	A3*/A5*
6. Mammary gland, right	A3/A5	A3/A5	A3/A5	A3/A5
7. Ovaries	A3	A3	A3	A3
8. Oviducts	A3	A3	A3	A3
9. Prostate	A3	A3	A3	A3
10. Pituitary gland	A3	A3	A3	A3
11. Seminal vesicle	A3	A3	A3	A3
12. Testes	A3	A3	A3	A3
13. Uterus	A4	A4	A4	A4
14. Vagina	A4	A4	A4	A4

A = Hematoxylin-eosin

3 = cohort 1B mating pairs suspected of reduced fertility

4 = all 24 female animals/test group

5 = all 24 male animals/test group

* = Selected animals

3.10.3. Pathological examinations of cohort 3 (Immunotoxicity cohort) and animals of the positive control

3.10.3.1. Necropsy

All **cohort 3** animals and the animals of the positive control were sacrificed by decapitation under isoflurane anesthesia. The exsanguinated animals were necropsied and assessed by gross pathology.

The animal No. 1111 died intercurrently. It was necropsied and assessed by gross pathology as soon as possible after its death.

3.10.3.2. Organ weights

The following weights were determined in all animals sacrificed on schedule:

1. Anesthetized animals (terminal body weight)
2. Spleen
3. Thymus

3.10.3.3. Organ/Tissue fixation

The following organs or tissues were fixed in 4% buffered formaldehyde solution:

1. All gross lesions
2. Spleen
3. Thymus

3.10.3.4. Histopathology

Histotechnical processing and examination was not performed.

3.10.4. Pathological examinations of surplus F1 generation pups on PND 22 (F1 weanlings not selected for cohorts)

3.10.4.1. Necropsy

All **surplus F1 generation pups** that were not used for the following organ weight determinations were sacrificed under isoflurane anesthesia with CO₂. The selected pups for organ weight determination were sacrificed by decapitation under isoflurane anesthesia. All animals were necropsied and assessed by gross pathology with special emphasis on the reproductive organs.

3.10.4.2. Organ weights

The following weights were determined in up to 10 animals per sex per group sacrificed on schedule:

1. Anesthetized animals (terminal body weight)
2. Brain
3. Spleen
4. Thymus

3.10.4.3. Organ/Tissue fixation

The following organs or tissues of up to 10 animals per sex per group were fixed in 4% buffered formaldehyde solution:

1. All gross lesions
2. Brain
3. Cecum
4. Kidneys
5. Liver
6. Mammary gland (male and female), right
7. Mammary gland fat pad, left
8. Spleen
9. Thymus
10. Thyroid glands

The left fourth and fifth mammary complex incl. the respective inguinal lymph nodes (mammary gland fat pad without skin) were sampled in total in 10 male and 10 female **surplus F1 generation pups** per group and were fixed in Carnoy's solution for at least 48 hours. The tissue was fixed in a flattened manner in cranio-caudal direction.

3.10.4.4. Histopathology

Fixation was followed by histotechnical processing, examination by light microscopy and assessment of findings according to the following table:

Organs	Test groups			
	10	11	12	13
1. Mammary gland (males and females), right	A1			A1
2. Mammary gland fat pad (males and females), left	A1	B1	B1	A1

A = hematoxylin and eosin (H&E) stain

B = paraplast embedding

1 = all animals/group

Peer review

A peer review was performed by Dr. Karin Küttler (BASF SE, Ludwigshafen) including kidneys and glandular stomach in males of all test groups of both the F0 generation parental animals and F1 rearing animals, cohort 1A; mammary gland in all male F0 parental animals and F1 rearing animals, cohort 1A and 1B; uterus, cervix and vagina and cecum in all female F1 rearing animals, cohort 1A and uterus, cervix and vagina in cohort 1B.

Results presented in the pathology report reflect the consensus opinion of the study pathologist and the peer review pathologist.

3.10.5. Statistics of Pathology

Parameter	Statistical test	Markers in the tables	References
Weight parameters	Non-parametric one-way analysis using KRUSKAL-WALLIS test (two-sided). If the resulting p-value was equal or less than 0.05, a pairwise comparison of each dose group with the control group was performed using WILCOXON-test (two-sided) for the equal medians	* for $p \leq 0.05$ ** for $p \leq 0.01$	HETTMANNSPERGER, T.P. (1984): Statistical Inference based on Ranks, John Wiley & Sons New York, 132-140 International Mathematical and Statistical Libraries, Inc., 2500 Park West Tower One, Houston, Texas 77042-3020, USA, nakl-1 - nakl-3 MILLER, R.G. (1981): Simultaneous Statistical Inference, Springer-Verlag New York Inc., 165-167
	Pairwise comparison of test group 14 with the control group 10 was performed using the WILCOXON test (two-sided)	* for $p \leq 0.05$ ** for $p \leq 0.01$	NIJENHUIS, A. and S.W. WILF (1978): Combinatorial Algorithms, Academic Press, New York, 32-33 SIEGEL, S. (1956): Non-parametric statistics for behavioural sciences. McGraw-Hill New York
DOFC (differential ovarian follicular count)	Pair-wise comparison of the dose group with the control group using the WILCOXON-test (one-sided) for the hypothesis of equal medians	* for $p \leq 0.05$ ** for $p \leq 0.01$	

3.11. NEUROPATHOLOGY

3.11.1. Pathological examinations of cohort 2A animals (Developmental Neurotoxicity Cohort, adults)

3.11.1.1. Necropsy

On postnatal day 77, all cohort 2A animals were weighed, subjected to deep anesthesia (pentobarbital) and sacrificed by perfusion fixation.

SOERENSEN phosphate buffer was used as the rinsing solution, and a fixation solution according to KARNOVSKY was used as a fixative.

The perfusion fixed animals were necropsied with regard to the question of neuropathology, and the visible organs were assessed by gross pathology as accurately as is possible after a perfusion fixation. The cranial vault and the spinal cord were opened and the skin was removed from both hind extremities. In this state, the perfused animals were stored in a fixation solution according to KARNOVSKY for at least 48 hours.

3.11.1.2. Organ weights

The following weights were determined (the brain was weighed after its removal but before further preparation):

1. Terminal body weight
2. Brain (including olfactory bulb)

3.11.1.3. Length and width of brain

The length and maximum width of the brain were measured in all animals (length: on a line extending from the rostral end of the frontal lobe to the caudal medulla oblongata of the cerebellum; width: pituitary region).

3.11.1.4. Organ/Tissue fixation

The following organs/tissue specimens were carefully removed and processed histotechnically in accordance with the data given in the respective sections of this report:

1. All gross lesions
2. Brain with olfactory bulb
3. Eyes with retina and optic nerve
4. M. gastrocnemius
5. Nose (nasal cavity) with olfactory epithelium
6. Pituitary gland
7. Sciatic nerve, proximal section
8. Spinal cord, cervical part (C1 – C6)
9. Spinal cord, thoracic part (Th5 – Th8)
10. Spinal cord, lumbar part (L1 – L4)
11. Spinal ganglia (C1 – C6 [3x])
12. Spinal ganglia (L1 – L4 [3x])
13. Tibial nerve (on the knee), proximal section
14. Tibial nerve (nerve branch in the lower leg muscles), distal section
15. Trigeminal ganglia
16. Root fibers, dorsal (C1 – C6 and L1 – L4)
17. Root fibers, ventral (C1 – C6 and L1 – L4)

The remaining animal body after trimming was stored in neutrally buffered, 4% formaldehyde solution.

3.11.1.5. Neurohistopathology

The histotechnical processing, examination by light microscopy and assessment of findings was performed according to the tables below:

Paraplast embedding and storage

Organ specimens from:	Test groups			
	10	11	12	13
All gross lesions	A2	A2	A2	A2
Brain (cross sections):				
- Olfactory bulb	A1	B1	B1	A1
- Prosencephalon with frontal lobe	A1	B1	B1	A1
- Diencephalon with parietal lobe	A1	B1	B1	A1
- Mesencephalon with occipital lobe and temporal lobe	A1	B1	B1	A1
- Pons	A1	B1	B1	A1
- Cerebellum (2 planes of section) ⁵	A1	B1	B1	A1
- Medulla oblongata	A1	B1	B1	A1
Spinal cord (longitudinal and cross sections):				
- Cervical cord I (C1-C3)	A1	B1	B1	A1
- Cervical cord II (C3-C6)	A1	B1	B1	A1
- Thoracic cord (T5-T8)	A1	B1	B1	A1
- Lumbar cord (L1-L4)	A1	B1	B1	A1
Brain-associated organs/tissues:				
- Eyes with retina and optic nerve	A1	F1	F1	A1
- Pituitary gland	A1	F1	F1	A1
- Olfactory epithelium (nose level III)	A1	F1	F1	A1
Peripheral nervous system:				
- Trigeminal ganglia with part of nerve	A1	F1	F1	A1
- M. gastrocnemius (longitudinal and cross sections)	A1	F1	F1	A1

A = Hematoxylin-Eosin (HE) stain

B = Paraplast embedding

F = Preservation in neutrally buffered, 4% formaldehyde solution

1 = All perfused animals per sex and group

2 = All affected, perfused animals per sex and group

bold = Cross section

⁵ The cerebellum was separated from the remaining brain in the cerebellar peduncle and divided into two halves. A cross section in the region of the midcerebellum will be made in one half, and a longitudinal section will be made through the vermis in the other half.

Plastic embedding and storage

Organ specimens from:	Test groups			
	10	11	12	13
Peripheral nervous system:				
– Dorsal root ganglia (3 out of C3-C6),	T1	P1	P1	T1
– Dorsal root fibers (C1-C6)	T1	P1	P1	T1
– Ventral root fibers (C1-C6)	T1	P1	P1	T1
– Dorsal root ganglia (3 out of L1-L4),	T1	P1	P1	T1
– Dorsal root fibers (L1-L4)	T1	P1	P1	T1
– Ventral root fibers (L1-L4)	T1	P1	P1	T1
– Proximal sciatic nerve (<i>longitudinal and cross sections</i>)	T1	P1	P1	T1
– Proximal tibial nerve (on the knee) (<i>longitudinal and cross sections</i>)	T1	P1	P1	T1
– Distal tibial nerve (nerve branch in the lower leg muscles) (<i>longitudinal and cross sections</i>)	T1	P1	P1	T1

- T = Secondary fixation in 5% glutaraldehyde solution, plastic embedding (epoxy resin), semithin sectioning and staining with Azure-II-methylene blue-basic fuchsin (AMbF)
- P = Secondary fixation in 5% glutaraldehyde solution with storage in buffer solution
- 1 = All perfused animals per sex and group

3.11.1.6. Morphometry

Thickness measurements of major brain layers (neocortex: frontal and parietal cortices, caudate nucleus/putamen, hippocampus, corpus callosum, cerebellum) were performed. Measurements were carried out bilaterally in the left and right halves of the brain with the exception of the corpus callosum and the cerebellum.

Selection of the planes:

- Measurements for the thickness of the neocortex, corpus callosum and caudate nucleus/putamen were carried out in a cross section which approximates the plane of section on page 88 in Sherwood and Timiras (1970).
- Measurements for the thickness of the hippocampus were carried out in a cross section which approximates the plane of section on page 110 in Sherwood and Timiras (1970).
- Measurements for the thickness of select folia of the cerebellum were carried out in a midsagittal section through the vermis of the cerebellum which approximates the plane of section on page 134 in Sherwood and Timiras (1970).

Conduct of the measurements:

- Neocortex (frontal and parietal cortices):
The width of the total cortical mantle (layers I-VI – from the surface of the pia mater to the white substance) was measured vertically to a tangent over a region of the frontal and parietal cortices determined beforehand (No 1: frontal cortex left; No 2: frontal cortex right; No 5: parietal cortex left; No 6: parietal cortex right)
- Caudate nucleus/putamen:
The largest lateral extension was measured (No 3: Nucleus caudatus width left; No 4: Nucleus caudatus width right)
- Corpus callosum:
The width was measured at the middle line of the cross section (No 7: Corpus callosum width)
- Hippocampus:
The largest dorsoventral extension was measured (No 8: Hippocampus left; No 9: Hippocampus right)
- Cerebellum:
The width of a selected folium (lobus vermis cerebelli No 8) was measured at the base of the folium from the secondary fissure to the prepyramidal fissure (No 10: base of lobus vermis cerebelli No 8)

3.11.1.7. Statistics

Means and standard deviations were calculated. In addition, the following statistical analyses were carried out:

Parameter	Statistical test	Markers in the tables	References
Weight parameters (brain)	Non-parametric one-way analysis using KRUSKAL-WALLIS test (two-sided). If the resulting p-value was equal or less than 0.05, a pairwise comparison of each dose group with the control group was performed using WILCOXON-test (two-sided) for the equal medians. (control group 10 with test groups 11, 12 and 13)	* for $p \leq 0.05$ ** for $p \leq 0.01$	HETTMANNSPERGER, T.P. (1984): Statistical Inference based on Ranks, John Wiley & Sons New York, 132-140. International Mathematical and Statistical Libraries, Inc., 2500 Park West Tower One, Houston, Texas 77042-3020, USA, nakl-1 - nakl-3 MILLER, R.G. (1981): Simultaneous Statistical Inference, Springer-Verlag New York Inc., 165-167 NIJENHUIS, A. and S.W. WILF (1978): Combinatorial Algorithms, Academic Press, New York, 32-33
Brain width and length	Pair-wise comparison of control group 10 with test groups 11, 12 and 13 using the WILCOXON-test (two-sided) with Bonferroni-Holm-Adjustment for the hypothesis of equal medians	* for $p \leq 0.05$ ** for $p \leq 0.01$	Siegel S. (1956): Non-parametric statistics for behavioral sciences. McGraw-Hill, New York Holm (1979): A simple sequentially rejective multiple test procedure. Scand J Statist, 6, 65-70
Brain morphometry: linear measurements of selected brain regions	Pair-wise comparison of control group 10 with test group 13 using the WILCOXON-test (two-sided) for the hypothesis of equal medians.	* for $p \leq 0.05$ ** for $p \leq 0.01$	Siegel, S. (1956): Non parametric statistics for behavioural sciences. McGraw Hill New York

3.11.2. Pathological examinations of cohort 2B animals (Developmental Neurotoxicity Cohort, weanlings)

3.11.2.1. Necropsy

On postnatal day 22, **cohort 2B animals** were weighed, subjected to deep anesthesia (pentobarbital) and sacrificed by perfusion fixation.

SOERENSEN phosphate buffer was used as the rinsing solution, and neutrally buffered, 4% formaldehyde solution was used as a fixative.

The perfusion fixed animals were necropsied with regard to the question of neuropathology, and the visible organs were assessed by gross pathology as accurately as is possible after a perfusion fixation. The cranial vault and the spinal cord were opened and the skin was removed from both hind extremities. In this state, the perfused animals were stored in neutrally buffered, 4% formaldehyde solution for at least 48 hours.

3.11.2.2. Organ weights

The following weights were determined (the brain was weighed after its removal but before further preparation):

1. Terminal body weight
2. Brain (including olfactory bulb)

3.11.2.3. Length and width of brain

The length and maximum width of the brain was measured in all animals (length: on a line extending from the rostral end of the frontal lobe to the caudal medulla oblongata of the cerebellum; width: pituitary region).

3.11.2.4. Organ/Tissue fixation

The following organs/tissue specimens were carefully removed and processed histotechnically in accordance with the data given in the respective sections of this report:

1. All gross lesions
2. Brain with olfactory bulb
3. Eyes with retina and optic nerve
4. Nose (nasal cavity)
5. Pituitary gland
6. Trigeminal ganglia

The animals and the tissue or organ material remaining after trimming was stored in neutrally buffered, 4% formaldehyde solution.

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3.11.2.5. Neurohistopathology

Paraplast embedding and preservation

The histotechnical processing, examination by light microscopy and assessment of findings was performed according to the table below:

Organ specimens from:	Test groups			
	10	11	12	13
All gross lesions	A2	A2	A2	A2
Brain (cross sections):				
- Olfactory bulb	A1	B1	B1	A1
- Prosencephalon with frontal lobe	A1	B1	B1	A1
- Diencephalon with parietal lobe	A1	B1	B1	A1
- Mesencephalon with occipital lobe and temporal lobe	A1	B1	B1	A1
- Pons	A1	B1	B1	A1
- Cerebellum (2 planes of section) ⁶	A1	B1	B1	A1
- Medulla oblongata	A1	B1	B1	A1
Brain-associated organs/tissues:				
- Pituitary gland	A1	F1	F1	A1
Peripheral nervous system:				
- Trigeminal ganglia with part of nerve	A1	F1	F1	A1

- A = Hematoxylin-Eosin (HE) stain
 B = Paraplast embedding
 F = Preservation in neutrally buffered, 4% formaldehyde solution
 1 = All animals per sex and group
 2 = All affected animals per sex and group

⁶ The cerebellum will be separated from the remaining brain in the cerebellar peduncle and divided into two halves. A cross section in the region of the midcerebellum will be made in one half, and a longitudinal section will be made through the vermis in the other half.

3.11.2.6. Statistics

Means and standard deviations were calculated. In addition, the following statistical analyses were carried out:

Parameter	Statistical test	Markers in the tables	References
Weight parameters (brain)	Non-parametric one-way analysis using KRUSKAL-WALLIS test (two-sided). If the resulting p-value was equal or less than 0.05, a pairwise comparison of each dose group with the control group was performed using WILCOXON-test (two-sided) for the equal medians. (control group 10 test groups 11, 12 and 13)	* for $p \leq 0.05$ ** for $p \leq 0.01$	HETTMANNSPERGER, T.P. (1984): Statistical Inference based on Ranks, John Wiley & Sons New York, 132-140. International Mathematical and Statistical Libraries, Inc., 2500 Park West Tower One, Houston, Texas 77042-3020, USA, nakl-1 - nakl-3 MILLER, R.G. (1981): Simultaneous Statistical Inference, Springer-Verlag New York Inc., 165-167 NIJENHUIS, A. and S.W. WILF (1978): Combinatorial Algorithms, Academic Press, New York, 32-33
Brain width and length	Pair-wise comparison of control group 10 with test groups 11, 12 and 13 using the WILCOXON-test (two-sided) with Bonferroni-Holm-Adjustment for the hypothesis of equal medians	* for $p \leq 0.05$ ** for $p \leq 0.01$	Siegel S. (1956): Non-parametric statistics for behavioral sciences. McGraw-Hill, New York Holm (1979): A simple sequentially rejective multiple test procedure. Scand J Statist, 6, 65-70

4. RESULTS

4.1. ANALYSES

4.1.1. Stability analyses

The stability of the test substance in 1% CMC suspension in drinking water was demonstrated over a period of 4 days at ambient temperature and over a period of 7 days in a refrigerator (see PART III, SUPPLEMENT).

4.1.2. Homogeneity analyses

The homogeneity of the mixtures was verified, (see PART III, SUPPLEMENT).

4.1.3. Concentration control analyses

All measured values for **DHDPS** were in the expected range of the target concentrations (90 - 110%), demonstrating the correctness of the preparations (see PART III, SUPPLEMENT).

4.1.4. Diet analyses

With regard to the analytical findings of chemical and microbiological contaminants and the duration of application, the diet was found to be suitable. Fed. Reg. Vol. 44, No. 91 of 09 May 1979, p. 27354 (EPA), served as a guideline for maximum tolerable chemical contaminants. The concentration of microorganisms did not exceed $1 \cdot 10^5$ /g feed.

The individual results are found in the archives of Experimental Toxicology and Ecology, BASF SE, Ludwigshafen, Germany.

4.1.5. Drinking water analyses

On the basis of the analytical findings, the drinking water was found to be suitable. German Drinking Water Regulation (Trinkwasserverordnung, Bundesgesetzblatt, 05 Dec 1990) served as a guideline for maximum tolerable contaminants.

The individual results are found in the archives of Experimental Toxicology and Ecology, BASF SE, Ludwigshafen, Germany.

4.1.6. Bedding and enrichment analyses

On the basis of the analytical findings, bedding and cage enrichment were found to be suitable. Levels given in Lab Animal (Nov-Dec 1979, pp. 24-34) served as a guideline for maximum tolerable contaminants.

The individual results are found in the archives of Experimental Toxicology and Ecology, BASF SE, Ludwigshafen, Germany.

4.2. CLINICAL EXAMINATIONS AND EXAMINATION OF REPRODUCTIVE PERFORMANCE

Summary tables of the results are given in the Appendix of PART I, PART A; individual values and findings are given in PART A of PART II.

Summary tables generated with the ToxLIMS:

Descriptive statistical measures are calculated without rounding by the computer system using the original individual values. Any calculation of measures using the rounded values given in the tables may result in discrepancies in comparison with the measures calculated by the system.

The tables "Summary - Clinical Observations" sum up all clinical findings observed and noted for individual animals during the different phases of the administration period, i.e. premating, mating, postmating, gestation and lactation. Consequently, findings can be listed in these tables although the status "normal, NAD" was assigned for all animals at the beginning of the administration period. For each finding, the days of occurrence can be found in the individual tables (PART A of PART II).

4.2.1. F0 generation parental animals (05R034M0/F0/L1)

4.2.1.1. Mortality

(Tabs. IA-001 - IA-015)

There were no test substance-related mortalities in any of the groups.

One female animal (No. 127) of test group 01 showed abdominal respiration on study day 49, piloerection during study days 51 - 56 and was sacrificed moribund on study day 63 after exhibiting piloerection, encrusted nose (red), unsteady gait (grade: slight), closed eyelid, hypothermia, poor general condition (grade: moderate), labored respiration (grade: moderate) and pale skin (entire body). Histopathological findings consistent with a gavage error were detected.

4.2.1.2. Clinical observations

(Tabs. IA-001 - IA-015)

4.2.1.2.1. Clinical observations for males and females

(except gestation and lactation period)

(Tabs. IA-001 - IA-012)

Transient salivation was noted for several high-dose (180 mg/kg bw/d) male and female animals during major parts of the treatment period.

This dose-dependent temporary salivation was considered to be test substance-induced. From the temporary, short appearance of the finding immediately after dosing it is likely, that this

finding was induced by a bad taste of the test substance and/or local affection of the upper respiratory and/or digestive tract. It is, however, not considered to be a sign of systemic toxicity. No clinical signs or changes of general behavior, which may be attributed to the test substance, were detected in any of the male and female F0 parental animals in the low- and mid-dose groups.

One male animal (No. 83) of test group 03 showed a discolored eye (right, white) from study day 67 until the end of the study. One control animal (No. 115) showed a skin lesion (groin region) from study week 11 until GD 18. Both are incidental findings.

4.2.1.2.2. Clinical observations for females during gestation of F1 litters (Tab. IA-013 - IA-014)

Transient salivation was noted for several high-dose (180 mg/kg bw/d) female animals as described in section 4.2.1.2.1. There were no other test substance-related clinical findings in any females of all dose groups during the gestation period for F1 litter.

One sperm positive control female (No. 105 - 0 mg/kg bw/d), two sperm positive females of the low-dose group (Nos. 141 and 145 - 20 mg/kg bw/d) and one sperm positive female of the high-dose group (No. 183 - 180 mg/kg bw/d) did not deliver F1 pups (for female fertility see 4.4.1.2 and 4.4.1.3 Gross- and Histopathology F0 animals). These observations were not considered to be associated with the test compound.

4.2.1.2.3. Clinical observations for females and offspring during lactation of F1 litters (Tab. IA-015)

Transient salivation was noted for several high-dose (180 mg/kg bw/d) female animals as described in section 4.2.1.2.1. There were no other test substance-related clinical findings in all F0 females of all dose groups during the lactation period.

4.2.1.3. Water consumption (Tabs. IA-016 - IA-021)

Water consumption of the high-dose F0 males (180 mg/kg bw/d) was statistically significantly above the concurrent control values during major parts of the pre-mating period (up to 22%).

Water consumption of the low- and mid-dose F0 males (20 and 60 mg/kg bw/d) was comparable to the concurrent control values throughout the entire study.

Water consumption of the high-dose F0 females was statistically significantly above the concurrent control values during major parts of the pre-mating and gestation period (up to 25% and 28%, respectively). Water consumption of the low- and mid-dose F0 females was statistically significantly above the concurrent control values during GD 17 - 18 and GD 17 - 20 (about 14% and 22%, respectively). The extent and temporary appearance of the finding suggest an incidental origin in the latter groups.

Water consumption was comparable to the concurrent control values in the high-dose females during the lactation period and in the low- and mid-dose females during the pre-mating and lactation period.

4.2.1.4. Food consumption

(Tabs. IA-022 - IA-029)

Food consumption of all male F0 animals of all test substance-treated groups was comparable to the concurrent control values throughout the entire study.

Food consumption of the high-dose F0 females was statistically significantly above the concurrent control values during major parts of the pre-mating period and during GD 14 - 20 (up to 36% and 8%, respectively). Food consumption of the mid-dose F0 females was statistically significantly above the concurrent control values during pre-mating days 0 - 7, 28 - 35 and during GD 14 - 20 (up to 9%, 14% and 6%, respectively).

Food consumption was comparable to the concurrent control values in the mid- and high-dose females during the lactation period and in the low-dose females during the entire study period.

4.2.1.5. Body weight data

(Tabs. IA-030 - IA-043; Figs. 4.2.1.5.1. - 4.2.1.5.4.)

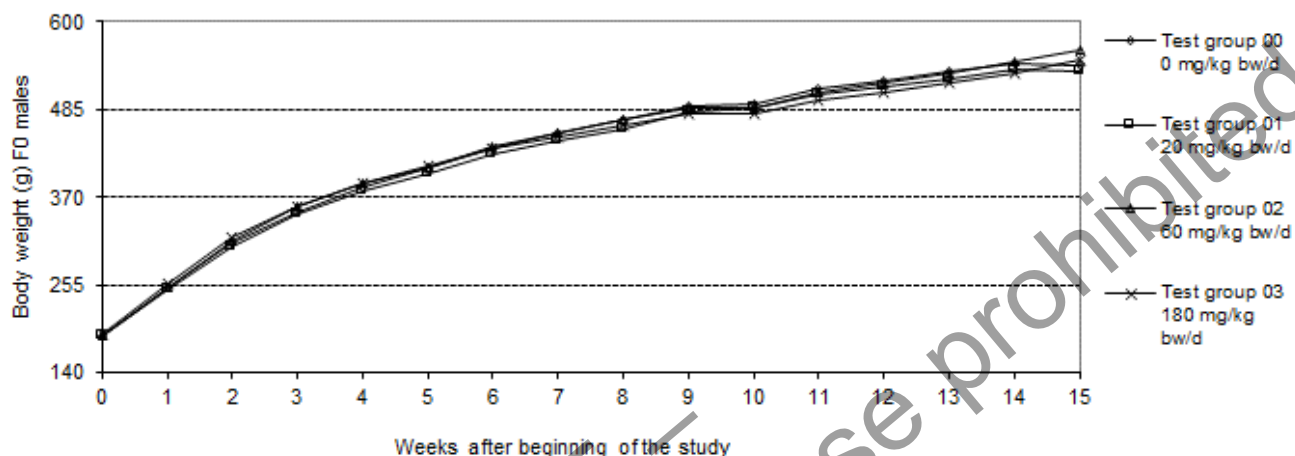
The body weights of all test substance treated male and female F0 rats (20, 60 and 180 mg/kg bw/d) were comparable to the concurrent control values throughout the entire study.

Body weights were statistically significantly increased in the mid-dose females during pre-mating days 7 - 14. Body weight change of the high-dose males was statistically significantly below the concurrent control values during pre-mating days 56 - 63 (about 26%). Both findings were considered as spontaneous in nature.

The body weight change of the low- and mid-dose male rats and of all test substance treated F0 female rats was comparable to the concurrent control values throughout the entire study period.

The statistically significantly increased body weight change in the mid-dose male animals during the weeks 3 - 4 after the pre-mating period (study weeks 14 - 15) and in the mid-dose females during pre-mating days 0 - 7 were considered as spontaneous in nature.

Fig. 4.2.1.5.1.: Mean body weight of F0 males during the study



Body weight data as shown in Figure 4.2.1.5.1. are based on premating days 0 - 63 (study weeks 0 - 9) and weeks after premating 0 - 5 (study weeks 10 - 15).

Fig. 4.2.1.5.2.: Mean body weight of F0 females during premating

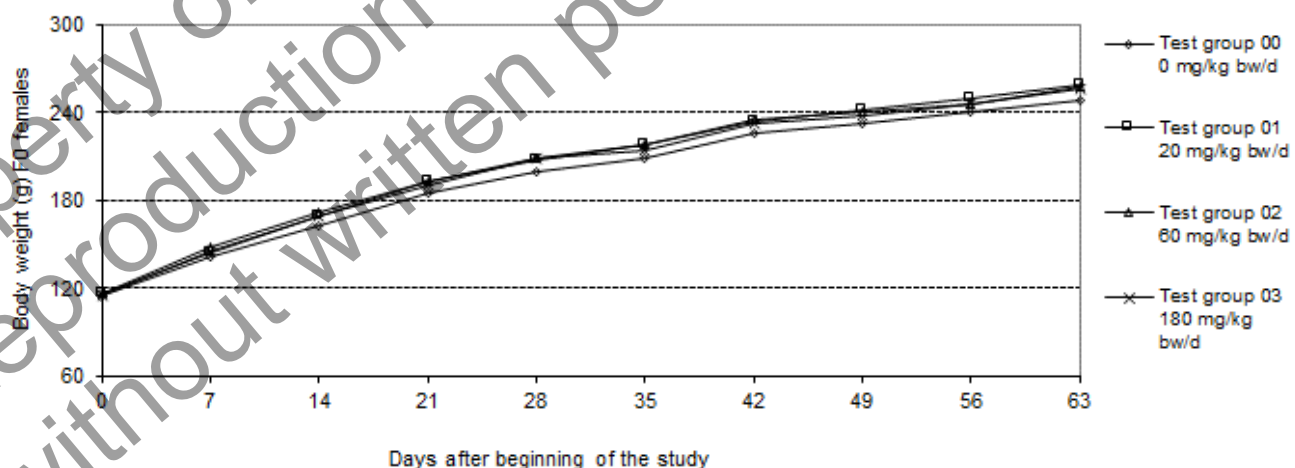


Fig. 4.2.1.5.3.: Mean body weight of F0 females during gestation of F1 litters

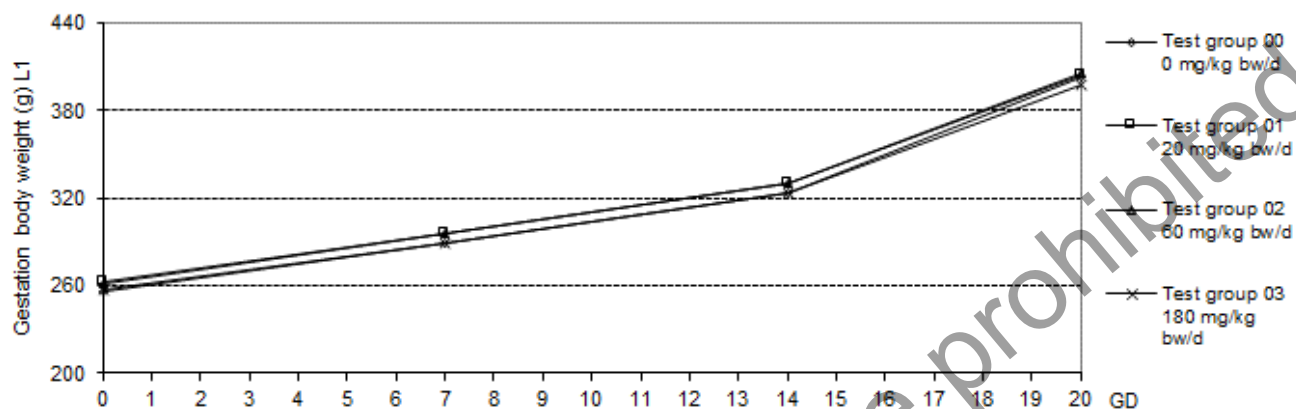
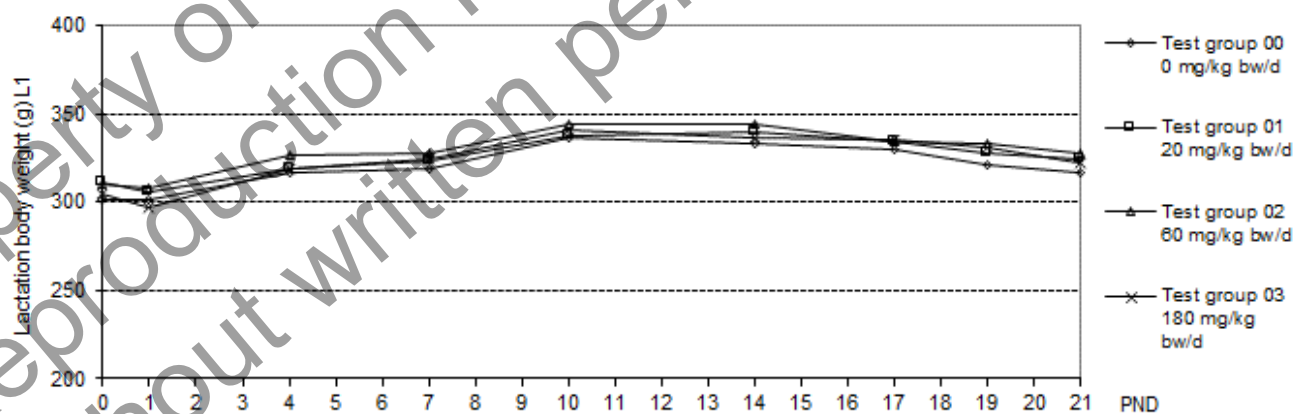


Fig. 4.2.1.5.4.: Mean body weight of F0 females during lactation of F1 litters



4.2.1.6. Detailed clinical observations (DCO)

(Tabs. IA-044 - IA-045)

No clinical signs or changes of general behavior, which may be attributed to the test substance, were detected in any of the male and female animals in any of the groups.

One female animal (No. 127) of test group 01 was sacrificed moribund on study day 63 (DCO week 9 for details see 4.2.1.1.). One high-dose male animal (No. 83) showed discolored eye(s) during DCO weeks 10 - 14 and one control female (No. 115) had a skin lesion (groin region) during DCO weeks 10 - 12. These observations were not considered to be associated with the test compound.

4.2.1.7. Estrous cycle data

(Tab. IA-046)

Estrous cycle data, generated during the last 3 weeks prior to mating to produce the F1 litter, revealed overall regular cycles in all females. However, the mean estrous cycle duration in the high-dose females was slightly but statistically significantly above the concurrent control: 3.9 days in control and test groups 01 - 02 and 4.1* (* = $p \leq 0.05$) days in the high-dose group.

The tables with the individual estrous cycle status on the day of sacrifice can be found in PART III (SUPPLEMENT).

4.2.1.8. Male reproduction data

(Tab. IA-047)

For all F0 parental males, which were placed with females to generate F1 pups, copulation was confirmed. Thus, the male mating index was 100% in all test groups (00 - 03).

Fertility was proven for most of the F0 parental males within the scheduled mating interval for F1 litter.

One control male (No. 5 - 0 mg/kg bw/d), two males of the low-dose group (Nos. 41 and 45 - 20 mg/kg bw/d) and one male of the high-dose group (No. 83 - 180 mg/kg bw/d) did not generate F1 pups.

Thus, the male fertility index ranged between 91% and 100% without showing a dose-response. This reflects a normal range of biological variation in rat (multi)generation studies.

The apparently infertile male rats did not show histopathological findings that could explain infertility (for details see 4.4.1.3. Histopathology F0 animals).

4.2.1.9. Female reproduction and delivery data

(Tabs. IA-048 - IA-049)

The female mating index calculated after the mating period for F1 litter was 100% in all test groups.

The mean duration until copulation was detected (GD 0) varied between 2.0 and 2.3 days.

All female rats delivered pups or had implants in utero with the following exception:

- Test group 00
female No. 105 (mated with male No. 5) did not become pregnant
- Test group 01
female No. 141 (mated with male No. 41) did not become pregnant
female No. 145 (mated with male No. 45) did not become pregnant
- Test group 03
female No. 183 (mated with male No. 83) did not become pregnant

The apparently infertile female rats did not show histopathological findings that could explain infertility (for details see 4.4.1.3. Histopathology F0 animals).

The fertility index ranged between 91% and 100%, reflecting a normal range of biological variation in rat (multi)generation studies.

The mean duration of gestation values was 22.0 days in all test groups without any relation to dosing.

The gestation index was 100% in all test groups.

Implantation was not affected by the treatment since the mean number of implantation sites was comparable between all test substance-treated groups and the control, taking normal biological variation into account (15.3 / 14.8 / 14.9 and 14.3 implants/dam in test groups 00 - 03, respectively).

The mean number of resorptions and postimplantation loss were statistically significantly above the concurrent control values in the mid- and high-dose groups (0.5 / 0.8 / 1.3* / 1.5** [$*= p \leq 0.05$ / $**= p \leq 0.01$] and 3.1% / 5.9% / 9.4%* and 10.5%** in test groups 00 - 03, respectively)

Subsequently the mean number of F1 pups delivered per dam (average litter size) was lower in the mid- and high-dose groups (14.9 / 14.0 / 13.5 and 12.7 pups/dam, respectively in test groups 00 - 03), although the difference to the control did not reach statistical significance.

4.2.2. F1 generation pups/litters (05R034L1)

4.2.2.1. Litter data

(Tabs. IA-050 - IA-052; Fig. 4.2.2.1.2.1.)

4.2.2.1.1. Pup number and status at delivery

Subsequent to a higher resorption rate the mean number of F1 pups delivered per dam (average litter size) was lower in the mid- and high-dose groups (14.9 / 14.0 / 13.5 and 12.7 pups/dam, respectively in test groups 00 - 03), although the difference to the control did not reach statistical significance.

The number of liveborn pups was statistically significantly below the concurrent control values in the high-dose group (340 / 289 / 322 / 285*, respectively in test groups 00 - 03). The rate of liveborn pups was indicated by live birth indices of 99% / 98% / 99% and 97% in test groups 00 - 03, showing no significant difference between control and treated groups.

The number of stillborn pups was statistically significantly above the concurrent control values in the high-dose group (2 / 5 / 3 / 8*, respectively in test groups 00 - 03). The number of 8 stillborn pups seems, however, not to be unusually high in this rat strain, as shown by 6 stillborn control pups in the F2 generation.

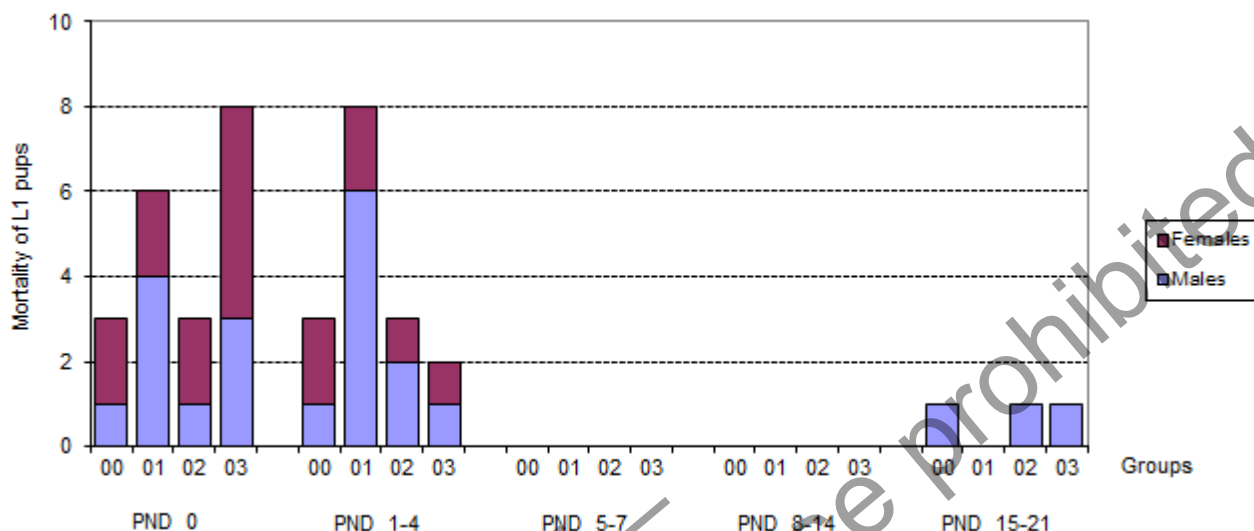
4.2.2.1.2. Pup viability/mortality

The number of cannibalized and dead F1 pups were evenly distributed about the groups.

The viability index indicating pup survival during early lactation (PND 0 - 4) varied between 99% / 97% / 99% and 99% in test groups 00 - 03, showing no treatment-related effect.

The lactation index indicating pup survival on PND 4 - 21 was 100% in all test groups.

Fig. 4.2.2.1.2.1.: Mortality of F1 pups



Mortality data as shown in Figure 4.2.2.1.2.1 are based on stillborn pups, died pups, pups sacrificed moribund and cannibalized pups, but do not include pups which were culled on PND 4.

4.2.2.1.3. Sex ratio

The sex distribution and sex ratios of live F1 pups on the day of birth and on PND 21 did not show substantial differences between the control and the test substance-treated groups; slight differences were regarded to be spontaneous in nature.

4.2.2.2. Pup clinical observations

(Tab. IA-015)

There were no test substance-related adverse clinical signs observed in any of the F1 generation pups of the different test groups.

4.2.2.3. Nipple/ areola Anlagen

(Tabs. IA-053 - IA-054)

The percentage of male pups having nipples/areolae was not influenced by the test substance when examined on PND 13.

During the re-examination on PND 20 no nipples/areolae were detected in any male pups of all test groups.

4.2.2.4. Pup body weight data

(Tabs. IA-055 - IA-058; Fig. 4.2.2.4.1.)

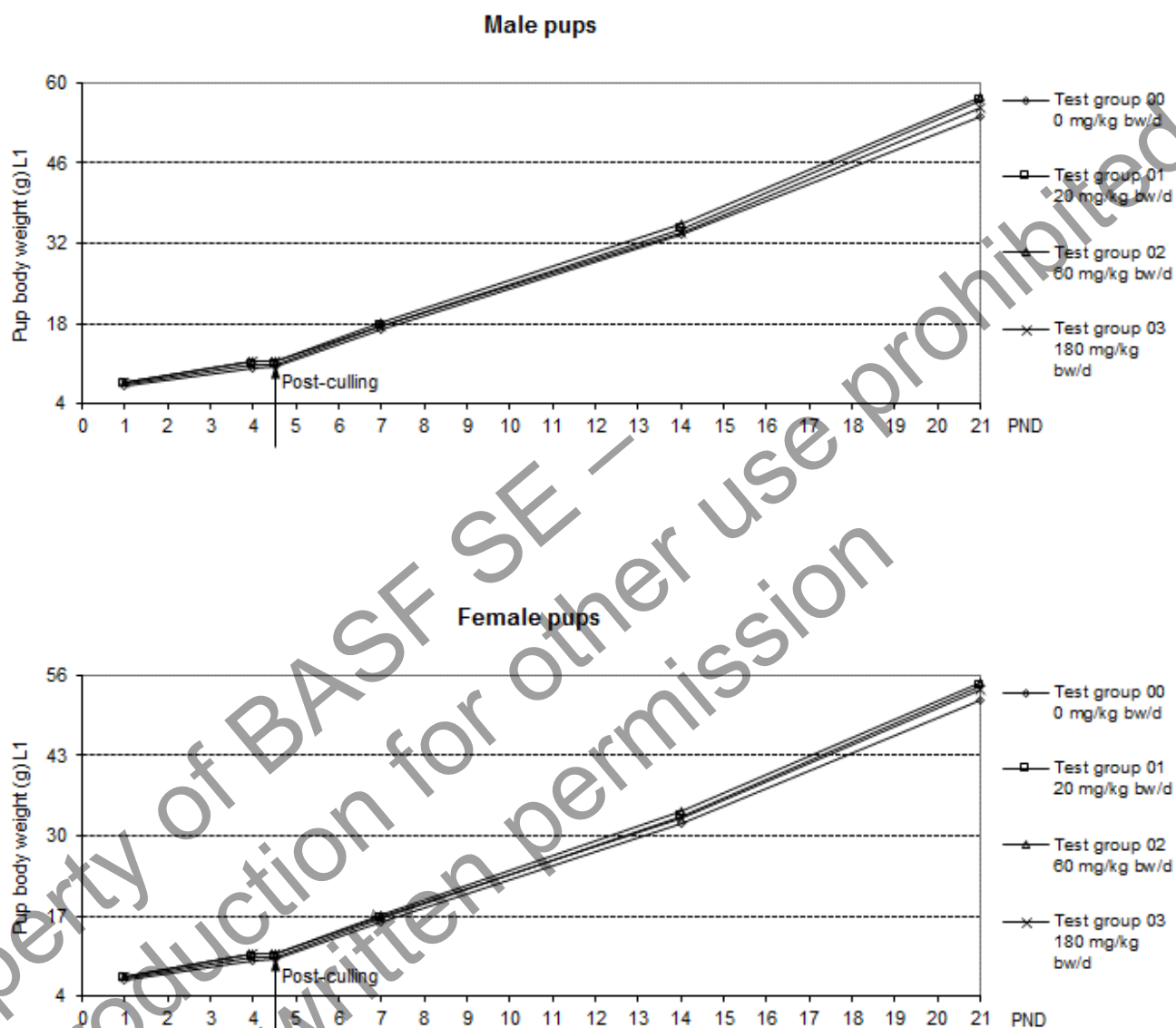
Mean body weights of the high-dose male and female pups and both sexes combined were statistically significantly above the concurrent control values during PND 1 - 4 (up to 10%, respectively) and in the mid-dose male and female pups and both sexes combined statistically significantly above the concurrent control values during PND 1 - 7 and on PND 21 (up to 12%, 11%, 10% and 6%, 5%, 6%, respectively). At the beginning of lactation these increased weights may reflect the advantageous nutritional condition of the pups in the smaller mid- and high-dose litters, while at later timepoints the statistical changes may have been sporadic. Per se they do not constitute an adverse effect.

No test compound-related influence on F1 pup body weights were noted in all pups of the low-dose group during the entire lactation period.

Mean body weight change of high-dose male pups was statistically significantly above the concurrent control values during PND 1 - 4 (about 16%), in the mid-dose male and female pups and both sexes combined during PND 1 - 4 (about 19%, 16% and 19%, respectively) and in the low-dose female pups and both sexes combined during PND 14 - 21 (about 7%, respectively). As for pup body weights these increased weight gains may reflect the advantageous nutritional condition of the pups in the smaller mid- and high-dose litters, or they may have been sporadic. Per se they do not constitute an adverse effect.

No test compound-related influence on F1 pup body weight change was noted in the high-dose female pups and both sexes combined and in the low-dose male pups during the entire lactation period.

Fig. 4.2.2.4.1.: Mean body weight of F1 pups



4.2.2.5. Anogenital distance/anogenital index (Tabs. IA-059 - IA-060)

The anogenital distance and anogenital index of all test substance treated male and female pups was comparable to the concurrent control values.

4.2.2.6. Pup necropsy observations in culled pups and decedents

(Tabs. IA-063 - IA-064)

A few F1 pups showed spontaneous findings at gross necropsy, such as post mortem autolysis, discolored eye(s), empty stomach and hemorrhagic testis.

These findings occurred without any relation to dosing. Thus, all these findings were not considered to be associated with the test substance.

4.2.2.7. Sexual maturation data

(Tabs. IA-065 - IA-068)

4.2.2.7.1. Vaginal opening

(Tab. IA-065 - IA-066)

Each female F1 pup, which was selected to become a rearing female (across all cohorts which have been taken beyond this age), was evaluated for commencement of sexual maturity. The first day when vaginal opening was observed was PND 28, the last was PND 40. The mean number of days to reach the criterion in the control and 20, 60 and 180 mg/kg bw/d test groups was 32.3, 33.2* (* = $p \leq 0.05$), 32.3 and 31.8 days, respectively. The mean body weight on the day, when vaginal opening was recorded, amounted to 105.8 g, 112.6* g, 113.4* g and 109.9 g in test groups 00-03.

The inexistent dose-response and the slowness of the changes indicate that the statistically significantly later puberty in the low-dose female animals and the statistically significantly increased body weights at puberty in the low- and mid-dose females were spontaneous in nature. Instead, these data reflect a normal range of biological variation in rat (multi)generation studies.

4.2.2.7.2. Preputial separation

(Tab. IA-067 - IA-068)

Each male F1 pup, which was selected to become a rearing male, was evaluated for commencement of sexual maturity. The first day when preputial separation was observed was PND 38, the last was PND 55. The mean number of days to reach the criterion in the control and 20, 60 and 180 mg/kg bw/d test groups was 43.1, 43.0, 42.5 and 43.3 days, respectively. The mean body weight on the day, when preputial separation was recorded, amounted to 221.1 g, 222.8 g, 223.3 g and 222.5 g in test groups 00-03. Neither a statistically significant nor a toxicologically relevant effect was noted in any of the treatment groups.

4.2.3. F1 rearing animals, Cohort 1A (05R0341A)

4.2.3.1. Mortality

(Tabs. IA-069 - IA-076)

There were no test substance-related mortalities in any of the groups.

One female animal (No. 362) of test group 13 showed abdominal position and gasping on study day 0 and was found dead thereafter on study day 0. Histopathology revealed a slight fibrinous inflammation in the lung, focal hyperplasia in the mammary gland and an atrophic uterus. No association to the test substance is assumed.

4.2.3.2. Clinical observations

(Tabs. IA-069 - IA-076)

Transient salivation was noted for several high-dose (180 mg/kg bw/d) male and female animals during several parts of the treatment period.

This dose-dependent temporary salivation was considered to be test substance-induced. From the temporary, short appearance of the finding immediately after dosing it is likely, that this finding was induced by a bad taste of the test substance and/or local affection of the upper respiratory and/or digestive tract. It is, however, not considered to be a sign of systemic toxicity.

No clinical signs or changes of general behavior, which may be attributed to the test substance, were detected in any of the male and female animals in the low- and mid-dose groups.

4.2.3.3. Water consumption

(Tabs. IA-077 - IA-080)

Water consumption of all male animals of all test substance-treated groups was comparable to the concurrent control values throughout the entire study.

Water consumption of the high-dose females was statistically significantly above the concurrent control values during major parts of the study period (up to 25%). Water consumption of the mid-dose females was statistically significantly above the concurrent control values during study days 7 - 17 (up to 20%).

Water consumption of the low-dose females was comparable to the concurrent control values during the entire study period.

4.2.3.4. Food consumption

(Tabs. IA-081 - IA-084)

Food consumption of all male animals of all test substance-treated groups was comparable to the concurrent control values throughout the entire study.

Food consumption of the high-dose females was statistically significantly above the concurrent control values during major parts of the study period (up to 21%).

Food consumption of the low- and mid-dose females was comparable to the concurrent control values during the entire study period.

4.2.3.5. Body weight data

(Tabs. IA-085 - IA-092; Figs. 4.2.3.5.1. - 4.2.3.5.2.)

The body weights of all test substance treated male rats were comparable to the concurrent control values throughout the entire study.

Body weights of the high and mid-dose females were statistically significantly above the concurrent control values on study days 14 and 28 (up to 7%, respectively).

The body weights of the low-dose female rats were comparable to the concurrent control values throughout the entire study.

The body weight change of the high-dose males was statistically significantly below the concurrent control values during study days 56 - 63 (about 52%). As this had no impact on average body weights this is considered as an incidental finding.

Body weight change of the high- and mid-dose females was statistically significantly above the concurrent control values during study days 7 - 14 and 0 - 7 (about 19% and 9%, respectively). The statistically significantly decreased body weight change in the mid-dose females during study days 56 - 63 was considered as spontaneous in nature.

The body weight change of the low- and mid-dose male rats and of the low-dose female rats was comparable to the concurrent control values throughout the entire study period.

Fig. 4.2.3.5.1.: Mean body weight of cohort 1A males during the study

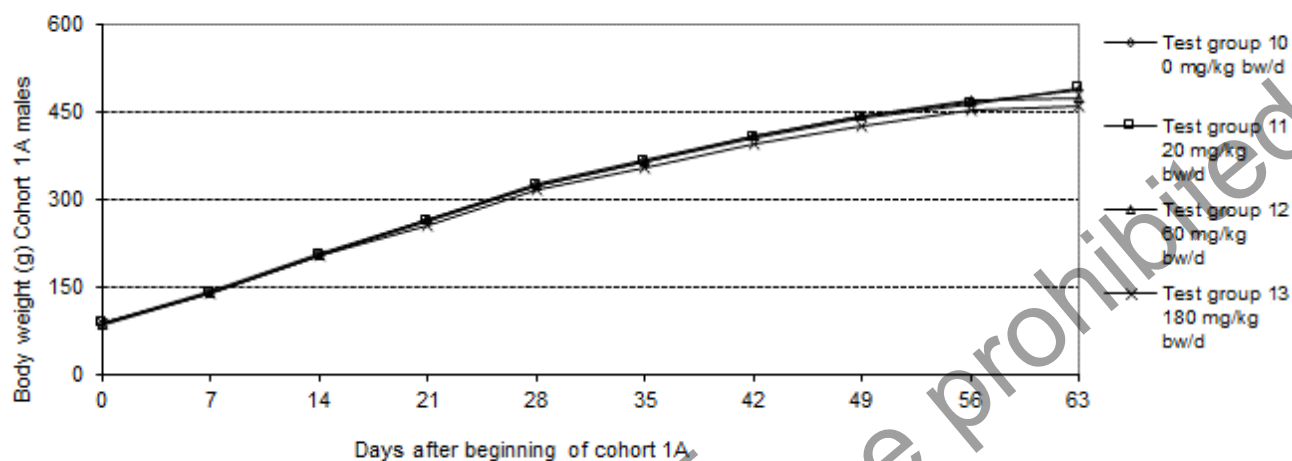
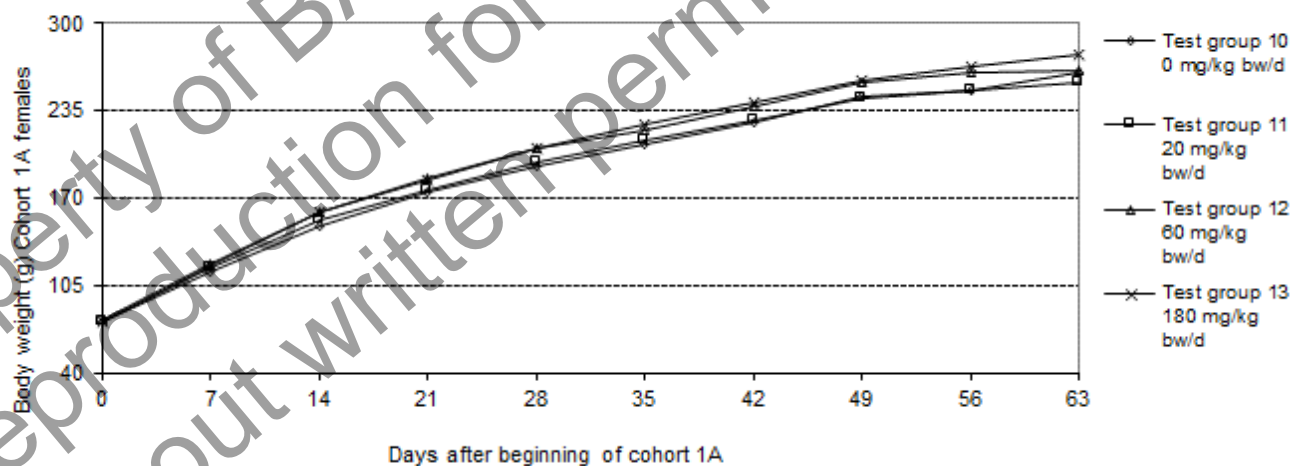


Fig. 4.2.3.5.2.: Mean body weight of cohort 1A females during the study



4.2.3.6. Detailed clinical observations (DCO)

(Tabs. IA-093 - IA-094)

No clinical signs or changes of general behavior, which may be attributed to the test substance, were detected in any of the male and female animals in any of the groups.

One female animal (No. 362) of test group 13 was found dead on study day 0 (DCO week 0 for details see 4.2.3.1.).

4.2.3.7. Estrous cycle data

(Tab. IA-095)

Estrous cycle data, generated during 2 weeks, revealed regular cycles in the females of all test groups including the control. The mean estrous cycle duration in the different test groups was exactly the same: 4.1 days in all test groups (10 - 13).

The tables with the individual estrous cycle status on the day of sacrifice can be found in PART III (SUPPLEMENT).

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4.2.4. F1 generation parental animals, Cohort 1B (05R034M1/F1/L2)**4.2.4.1. Mortality**

(Tabs. IA-096 - IA-108)

There were no test substance-related mortalities in any of the groups.

One female animal (No. 550) of test group 12 was found dead on pre-mating day 3. As the animal was partly cannibalized and no histopathological examination was conducted the cause of the death was not determined.

4.2.4.2. Clinical observations

(Tabs. IA-096 - IA-108)

4.2.4.2.1. Clinical observations for males and females

(except gestation and lactation period)

(Tabs. IA-096 - IA-106)

Transient salivation was noted for several high-dose (180 mg/kg bw/d) male and female animals during major parts of the treatment period.

This dose-dependent temporary salivation was considered to be test substance-induced. From the temporary, short appearance of the finding immediately after dosing it is likely, that this finding was induced by a bad taste of the test substance and/or local affection of the upper respiratory and/or digestive tract. It is, however, not considered to be a sign of systemic toxicity.

One female animal (No. 575) of test group 13 showed a vaginal hemorrhage during study weeks 4 - 5 after the pre-mating period. A relationship to the treatment is unlikely.

No clinical signs or changes of general behavior, which may be attributed to the test substance, were detected in any of the male and female F1 parental animals in the low- and mid-dose groups.

4.2.4.2.2. Clinical observations for females during gestation of F2 litters

(Tab. IA-107)

There were no test substance-related clinical findings in the F1B females of all dose groups during the gestation period for F2 litter.

One female animal of the high-dose group (No. 581) showed vaginal hemorrhage on GD 23. This isolated observation is considered to be an incidental event.

One sperm positive female of the mid-dose group (No. 553) and one sperm positive female of the high-dose group (No. 593) did not deliver F2 pups (for female fertility see 4.4.3. Pathology Cohort 1B). These observations were not considered to be associated with the test compound.

4.2.4.2.3. Clinical observations for females and offspring during lactation of F2 litters (Tab. IA-108)

There were no test substance-related clinical findings in the F1B females of all dose groups during the lactation period for F2 litter.

4.2.4.3. Water consumption (Tabs. IA-109 - IA-112)

Water consumption of the male F1B rats in all treated groups was comparable to the concurrent control values throughout the entire study. The statistically significantly increased water consumption in the mid-dose males during premating days 0 - 17 was considered as spontaneous in nature.

Water consumption of the high-dose F1B females was statistically significantly above the concurrent control values during major parts of the premating period (up to 26%). Water consumption of the mid-dose F1B females was statistically significantly above the concurrent control values during premating days 14 - 17 and 42 - 45 (about 14% and 15%, respectively).

Water consumption was comparable to the concurrent control values in the high and mid-dose females during the gestation and lactation period and in the low-dose females during the entire study period.

The statistically significantly decreased water consumption in the high-dose females during PND 4 - 5 was considered as spontaneous in nature.

4.2.4.4. Food consumption (Tabs. IA-115 - IA-122)

Food consumption of the male F1B rats in all treated groups was comparable to the concurrent control throughout the entire study. The statistically significantly decreased food consumption in the high-dose males during premating days 7 - 14 was considered as spontaneous in nature.

Food consumption of the high-dose F1B females was statistically significantly above the concurrent control values during premating days 28 - 49 and 0 - 70 (up to 22% and 13%, respectively). Food consumption of the mid-dose F1B females was statistically significantly above the concurrent control values during premating days 7 - 14 (about 13%).

Food consumption was comparable to the concurrent control values in the mid- and high-dose females during the gestation and lactation period and in the low-dose females during the entire study period.

The statistically significantly decreased food consumption in the high-dose females during PND 4 - 7 was considered as spontaneous in nature.

4.2.4.5. Body weight data

(Tabs. IA-123 - IA-138; Figs. 4.2.4.5.1. - 4.2.4.5.4.)

The body weights of the high- and mid-dose male F1B rats were statistically significantly below the concurrent control values on pre-mating day 14 (about 9% and 7%, respectively). This was a single event which is unlikely to be treatment-related.

The body weights of the low-dose male rats were comparable to the concurrent control values throughout the entire study period.

The body weights of the high- and mid-dose female F1B rats were statistically significantly above the concurrent control values during major parts of the pre-mating period (up to 10% and 9%, respectively) and for the mid-dose females additionally on PND 14 (about 6%).

The body weights of the high-dose females during the gestation and lactation period, of the mid-dose females during the gestation period and of the low-dose females during the entire study period were comparable to the concurrent control values.

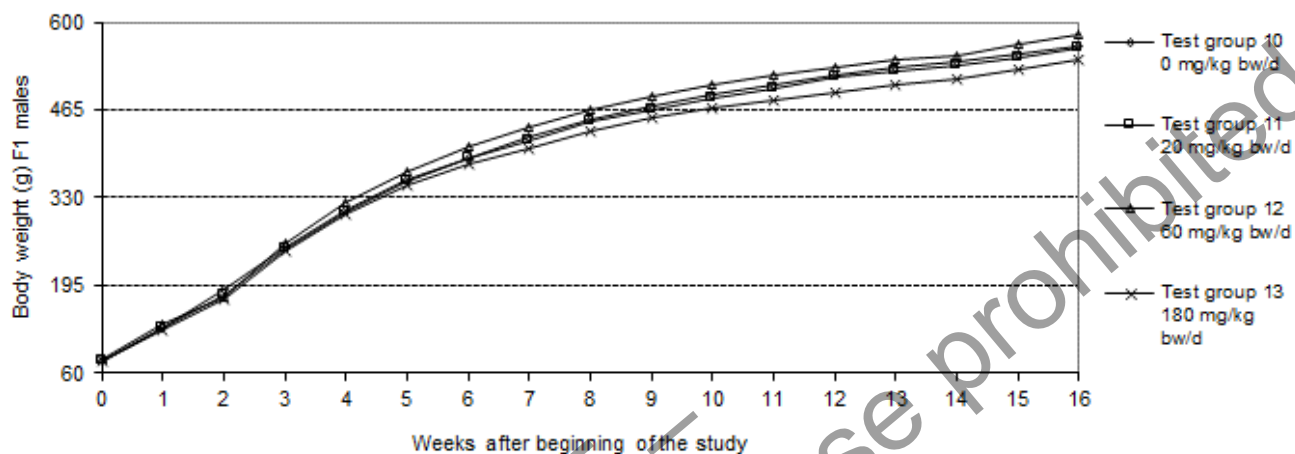
The body weight change of the high-dose males was statistically significantly below the concurrent control values during pre-mating days 7 - 14, 42 - 49 and 63 - 70 (up to 27%), for the mid-dose males statistically significantly below the concurrent control values during pre-mating days 7 - 14 (about 29%) and for the low-dose males statistically significantly below the concurrent control values during pre-mating days 7 - 14 (about 18%). Also, there was a statistically significantly increased body weight change in the high-dose male animals during pre-mating days 14 - 21 and in the mid-dose males during pre-mating days 14 - 21, 35 - 42 and study weeks 3 - 4 after pre-mating was considered as spontaneous in nature. All of these changes were inconsistent in terms of timing and direction of the apparent effect. Thus, they are not considered to be test substance-related.

The body weight change of the high-dose females was statistically significantly above the concurrent control values during pre-mating days 0 - 21 and 0 - 70 (up to 18% and 10%, respectively) and for the mid-dose females statistically significantly above the concurrent control values during pre-mating days 0 - 21 (up to 20%).

The body weight change of the high-dose females during the gestation and lactation period, of the mid-dose females during the lactation period and of the low-dose females during the entire study period was comparable to the concurrent control values.

The statistically significantly decreased body weight change in the high-dose female animals during GD 14 - 20, 0 - 20 and PND 14 - 17 as well as mid-dose females during PND 14-17 were considered as spontaneous in nature.

Fig. 4.2.4.5.1.: Mean body weight of F1 males during the study



Body weight data as shown in Figure 4.2.4.5.1. are based on pre-mating days 0 - 70 (study weeks 0 - 10) and weeks after pre-mating 0 - 5 (study weeks 11 - 16).

Fig. 4.2.4.5.2.: Mean body weight of F1 females during pre-mating

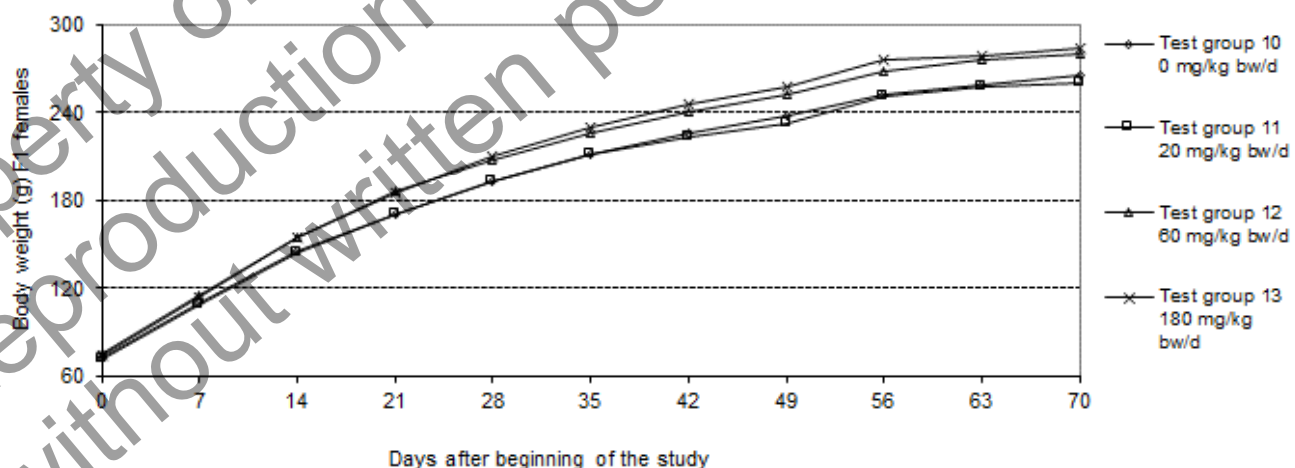


Fig. 4.2.4.5.3.: Mean body weight of F1 females during gestation of F2 litters

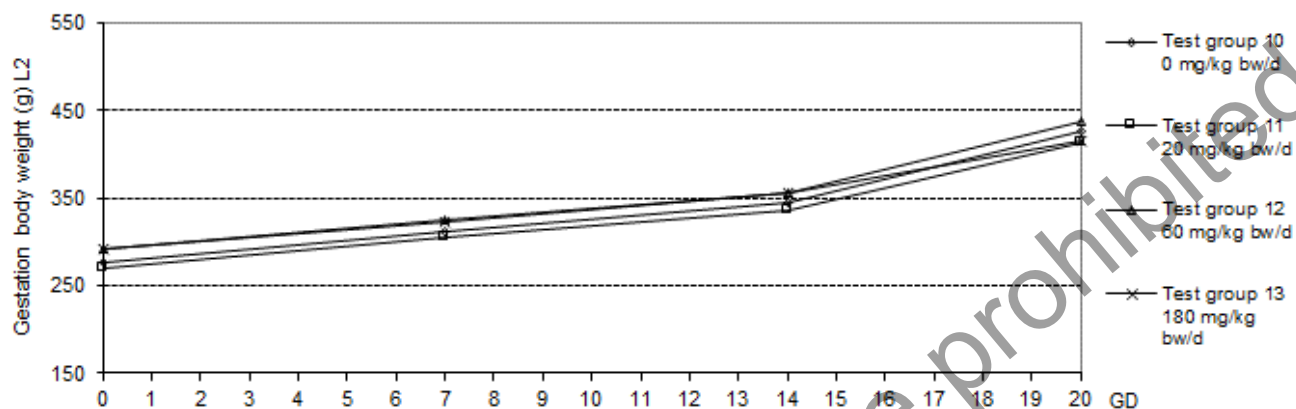
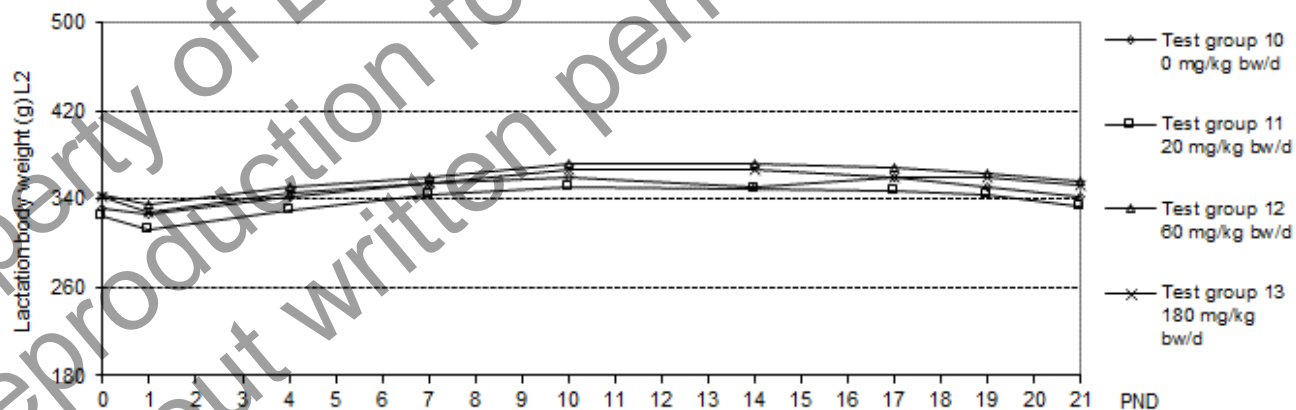


Fig. 4.2.4.5.4.: Mean body weight of F1 females during lactation of F2 litters



4.2.4.6. Detailed clinical observations (DCO)

(Tabs. IA-139 - IA-140)

No clinical signs or changes of general behavior, which may be attributed to the test substance, were detected in any of the male and female animals in any of the groups.

One female animal of the high-dose group (No. 575) showed vaginal hemorrhage on DCO week 16. This observation was not considered to be associated with the test compound.

One female animal (No. 550) of test group 12 was found dead on pre-mating day 3 (DCO week 0, for details see 4.2.4.1.).

4.2.4.7. Estrous cycle data

(Tab. IA-141)

Estrous cycle data, generated during the last 3 weeks prior to mating to produce the F2 litter, revealed regular cycles in the females of all test groups including the control. The mean estrous cycle duration in the different test groups was statistically comparable: 3.9 days in control, 4.0 in the low- and mid-dose group and 4.5 days in the high-dose group.

The tables with the individual estrous cycle status on the day of sacrifice can be found in PART III (SUPPLEMENT).

4.2.4.8. Male reproduction data

(Tab. IA-142)

For all F1 parental males, which were placed with females to generate F2 pups, copulation was confirmed. Thus, the male mating index was 100% in all test groups (10 - 13).

Fertility was proven for most of the F1 parental males within the scheduled mating interval for F2 litter.

One mid-dose male (No. 468 - 60 mg/kg bw/d) and one high-dose male (No. 476 - 180 mg/kg bw/d) did not generate F2 pups.

Thus, the male fertility index ranged between 96% and 100% without showing any relation to the dose. These data reflect a normal range of biological variation in rat (multi)generation studies.

The apparently infertile male rats did not show histopathological findings that could explain infertility (for details see 4.4.3. Pathology Cohort 1B).

4.2.4.9. Female reproduction and delivery data

(Tabs. IA-143 - IA-144)

The female mating index calculated after the mating period for F2 litter was 100% in all test groups.

The mean duration until sperm was detected (GD 0) varied between 2.4 and 3.0 days without any relation to the dose.

All female rats delivered pups or had implants in utero with the following exception:

- Test group 12
female No. 553 (mated with male No. 468) did not become pregnant
- Test group 13
female No. 593 (mated with male No. 476) did not become pregnant

The apparently infertile female rats did not show histopathological findings that could explain infertility (for details see 4.4.3. Pathology Cohort 1B).

The fertility index ranged between 96% and 100% reflecting a normal range of biological variation in rat (multi)generation studies.

The mean duration of gestation values varied between 21.9 and 22.0 days without any relation to the dose.

The gestation index was 100% / 100% / 95% / 91% in test groups 10 - 13, respectively. These data reflect a normal range of biological variation in rat (multi)generation studies.

Implantation was not affected by the treatment since the mean number of implantation sites was comparable between all test substance-treated groups and the control, taking normal biological variation into account (15.2 / 14.6 / 15.4 and 13.7 implants/dam in test groups 10 - 13, respectively).

The mean number of resorptions and the postimplantation loss were statistically significantly above the concurrent control values in the high-dose group (0.9 / 0.8 / 1.1 / 3.3** [*= $p \leq 0.05$ / **= $p \leq 0.01$] and 6.4% / 5.3% / 11.1% and 24.6%** in test groups 10 - 13, respectively). Two high-dose females (575, 581) had a complete litter loss.

The mean number of F2 pups delivered per dam (average litter size) was statistically significantly below the concurrent control values in the high-dose group (14.3 / 13.8 / 14.9 and 11.4** pups/dam, respectively in test groups 10 - 13).

4.2.5. F2 generation pups/litters (05R034L2)

4.2.5.1. Litter data

(Tabs. IA-145 - IA-147; Fig. 4.2.5.1.2.1.)

4.2.5.1.1. Pup number and status at delivery

The mean number of F2 pups delivered per dam (average litter size) was statistically significantly below the concurrent control values in the high-dose group (14.3 / 13.8 / 14.9 and 11.4** pups/dam, respectively in test groups 10 - 13).

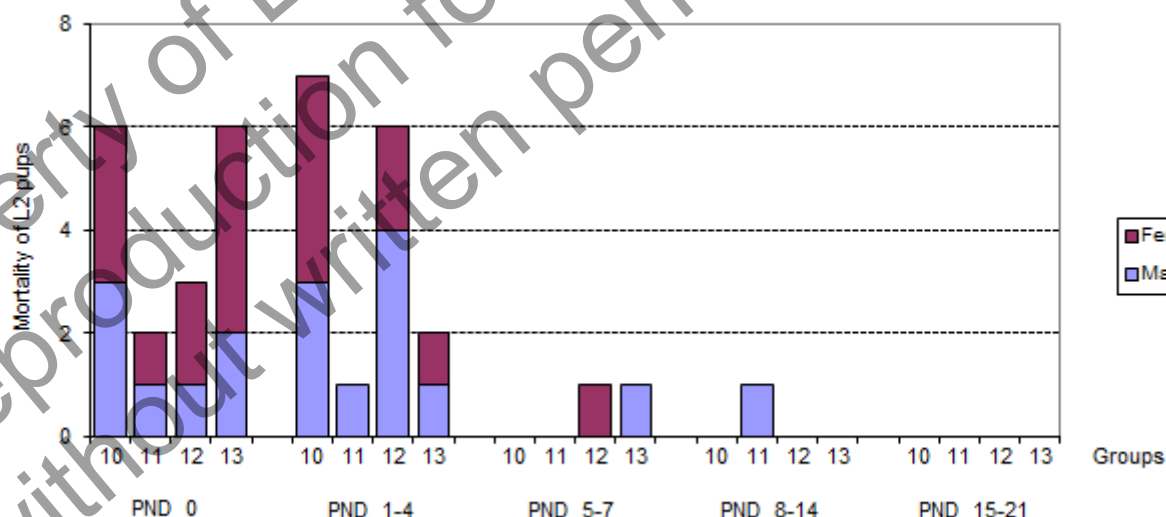
The rate of liveborn pups was not affected by the test substance, as indicated by live birth indices of 98% / 99% / 99% and 98% in test groups 10 - 13. Moreover, the number of stillborn pups was comparable between the groups (6 / 2 / 2 and 6 pups in test groups 10 - 13, respectively).

4.2.5.1.2. Pup viability/mortality

The number of cannibalized and dead F2 pups were evenly distributed about the groups.

The viability index indicating pup survival during early lactation (PND 0 - 4) varied between 98% / 100% / 98% and 99% in test groups 10 - 13. The lactation index indicating pup survival on PND 4 - 21 was 100% / 100% / 100% and 99% in test groups 10 - 13.

Fig. 4.2.5.1.2.1. Mortality of F2 pups



Mortality data as shown in Figure 4.2.5.1.2.1 are based on stillborn pups, died pups, pups sacrificed moribund and cannibalized pups, but do not include pups which were culled on PND 4.

4.2.5.1.3. Sex ratio

The sex distribution and sex ratios of live F2 pups on the day of birth and on PND 21 did not show substantial differences between the control and the test substance-treated groups; slight differences were regarded to be spontaneous in nature.

4.2.5.2. Pup clinical observations

(Tab. IA-108)

There were no test substance-related adverse clinical signs observed in any of the F2 generation pups of the different test groups.

4.2.5.3. Nipple/ areola anlagen

(Tabs. IA-148 - IA-149)

The percentage of male pups having nipples/areolae was not influenced by the test substance when examined on PND 13.

During the re-examination on PND 21 no nipples/areolae were detected in any male pup of all test groups.

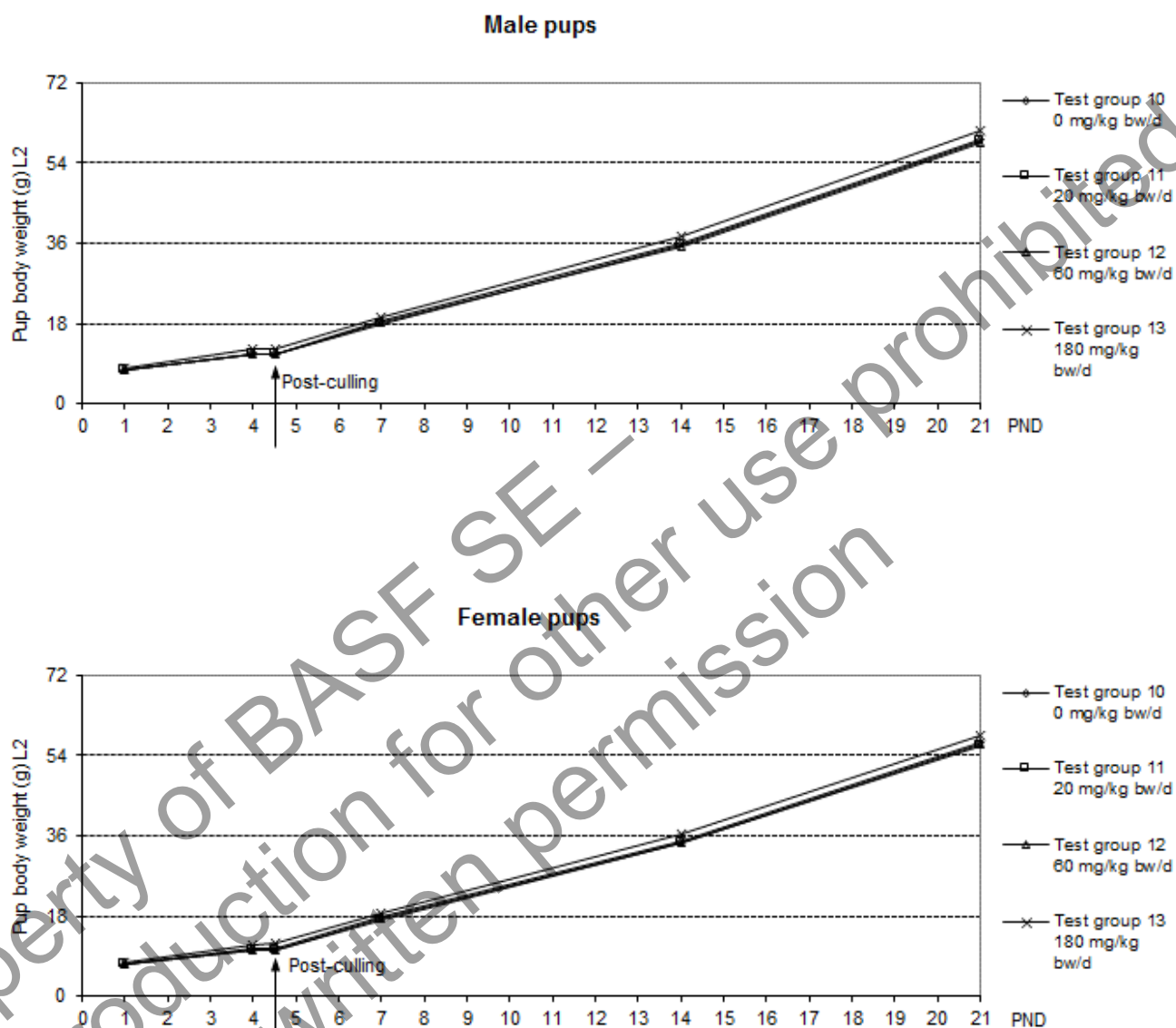
4.2.5.4. Pup body weight data

(Tabs. IA-150 - IA-153; Figs. 4.2.5.4.1.)

The body weights of all test substance treated male and all low-and mid-dose female F2 pups during lactation were comparable to the concurrent control. Mean body weights of the high-dose female pups were statistically significantly above the concurrent control values on PND 1 (about 7%). However, this isolated finding was considered to be incidental.

The body weight change of all test substance treated male and female F2 pups during lactation were comparable to the concurrent control.

Fig. 4.2.5.4.1.: Mean body weight of F2 pups



4.2.5.5. Anogenital distance/anogenital index (Tabs. IA-154 - IA-157)

The anogenital distance and anogenital index of all test substance treated male and female pups was comparable to the concurrent control values.

4.2.5.6. Pup organ weights

(Tabs. IA-158 - IA-159)

The absolute and relative pup organ weights (brain, thymus and spleen) of all test substance treated male and female F2 pups (20, 60 and 180 mg/kg bw/d) were comparable to the concurrent control values.

4.2.5.7. Pup necropsy observations

(Tabs. IA-160 - IA-161)

A few F2 pups showed spontaneous findings at gross necropsy, such as post mortem autolysis, empty stomach, dilated renal pelvis and small testis.

These findings occurred without any relation to dosing. Thus, all these findings were not considered to be associated to the test substance.

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4.2.6. F1 rearing animals, Cohort 2A (05R0342A)

4.2.6.1. Mortality

(Tabs. IA-162 - IA-169)

There were no test substance-related or spontaneous mortalities in any of the groups.

4.2.6.2. Clinical observations

(Tabs. IA-162 - IA-169)

Transient salivation was noted for a few high-dose (180 mg/kg bw/d) male and female animals during several parts of the treatment period.

This dose-dependent temporary salivation was considered to be test substance-induced. From the temporary, short appearance of the finding immediately after dosing it is likely, that this finding was induced by a bad taste of the test substance and/or local affection of the upper respiratory and/or digestive tract. It is, however, not considered to be a sign of systemic toxicity.

No clinical signs or changes of general behavior, which may be attributed to the test substance, were detected in any of the male and female animals in the low- and mid-dose groups.

4.2.6.3. Water consumption

(Tabs. IA-170 - IA-173)

Water consumption of all test substance treated male and female rats (20, 60 and 180 mg/kg bw/d) was comparable to the concurrent control values throughout the entire study.

4.2.6.4. Food consumption

(Tabs. IA-174 - IA-177)

Food consumption of all test substance treated male and female rats (20, 60 and 180 mg/kg bw/d) was statistically comparable to the concurrent control values throughout the entire study. Slightly higher average female high-dose food intake did not gather statistical significance.

4.2.6.5. Body weight data

(Tabs. IA-178 - IA-183; Figs. 4.2.6.5.1. - 4.2.6.5.2.)

The body weights and body weight change of all test substance treated male and female rats were statistically comparable to the concurrent control values throughout the entire study period. Slightly higher average female high-dose body weights did not gather statistical significance.

Fig. 4.2.6.5.1.: Mean body weight of cohort 2A males during the study

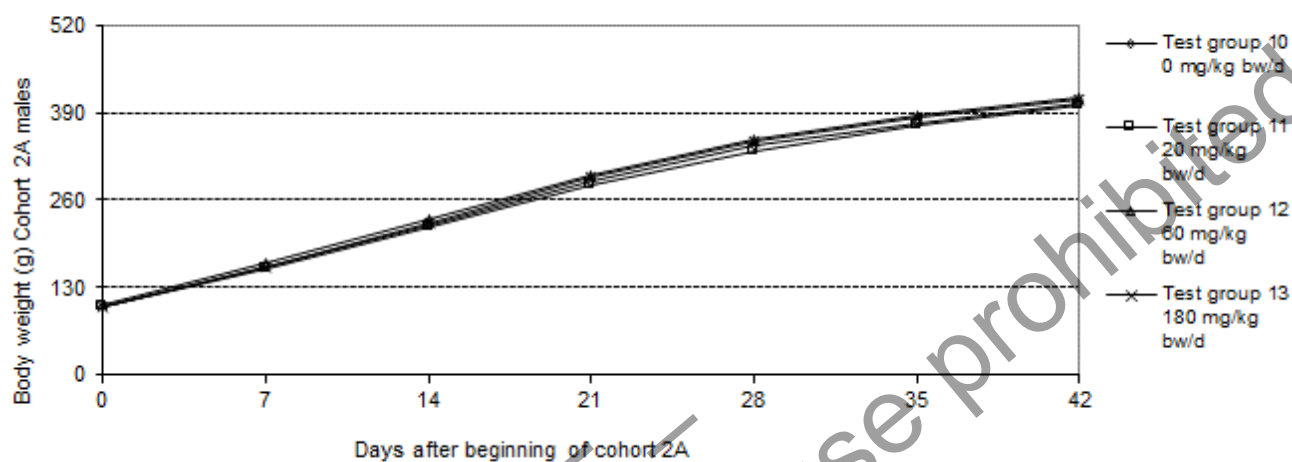
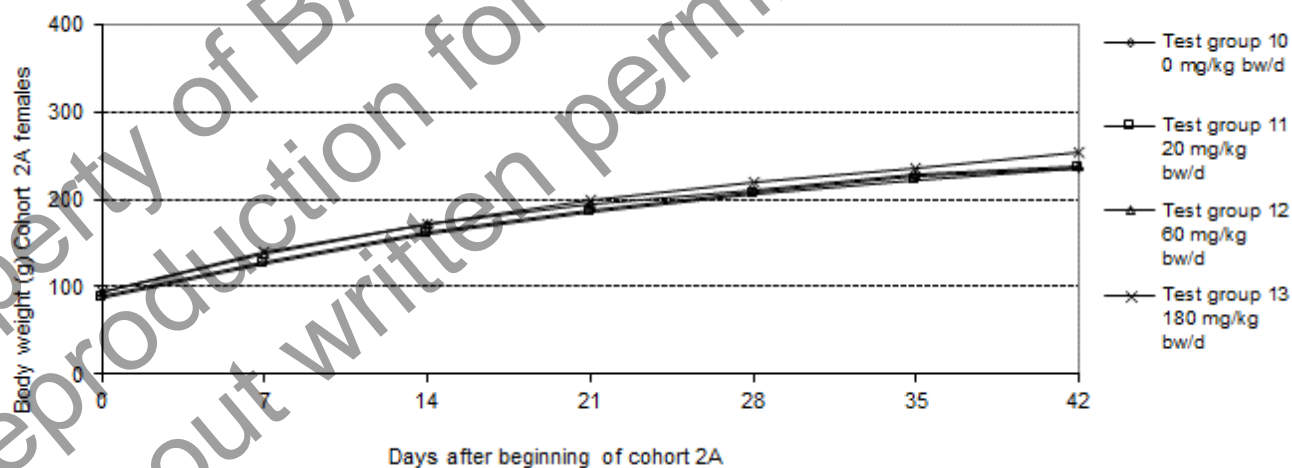


Fig. 4.2.6.5.2.: Mean body weight of cohort 2A females during the study



4.2.6.6. Detailed clinical observations (DCO)

(Tabs. IA-184 - IA-185)

No clinical signs or changes of general behavior, which may be attributed to the test substance, were detected in any of the male and female animals in any of the groups.

4.2.6.7. Auditory Startle Response

(Tabs. IA-186 - IA-189)

No influence of the test substance on auditory startle habituation (maximum amplitude and latency) was observed in any male or female animal in all treated groups.

The statistically significantly decreased maximum amplitude in the low-dose males during measurement block 2, 4 - 5 and 1 - 5 (mean) was considered as spontaneous in nature.

4.2.6.8. Functional observational battery (FOB)**Home cage observations:**

(Tab. IA-190 (males); Tab. IA-197 (females))

No test substance-related or spontaneous findings were observed in male and female animals of all test groups during the home cage observation.

Open field observations:

(Tabs. IA-191 - IA-194 (males); Tabs. IA-198 - IA-201 (females))

The open field observations did not reveal any test substance-related findings in male and female animals of all test groups.

Sensorimotor tests/reflexes:

(Tabs. IA-195 - IA-196 (males); Tabs. IA-202 - IA-203 (females))

There were no test substance-related findings in male and female animals of all test groups.

Quantitative Parameters:

(Tab. IA-204 (males); Tab. IA-205 (females))

No test substance-related impaired parameters were observed in male and female animals of all test groups.

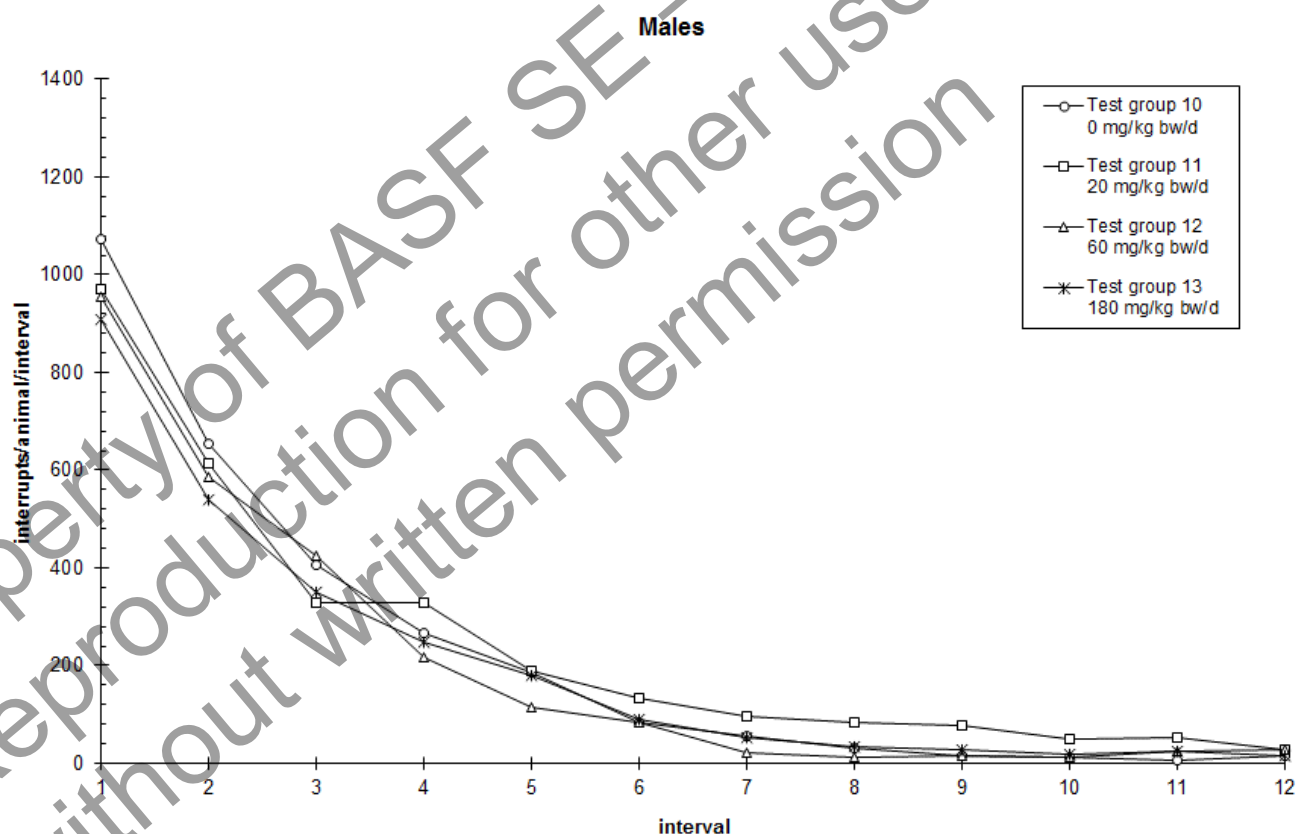
4.2.6.9. Motor activity measurement (MA)

(Tabs. IA-206 - IA-213; Figs. 4.2.6.9.1. - 4.2.6.9.2.)

Motor activity of the cohort 2A animals was not influenced by the test compound at all dose levels (20, 60 and 180 mg/kg bw/d). Overall activity levels and habituation to the test environment corresponded to the age of these animals at the specific testing date, if usual biological variation inherent in rats used for this type of experiment was considered.

There were statistically significant increases in activity during interval 11 in low-, mid- and high-dose males. This isolated finding was not related to the dose and did neither influence the total session beam interruptions significantly, nor did it impair habituation. Thus, it was not considered to be related to the test substance.

Fig. 4.2.6.9.1.: Motor activity measurement males on PND 75



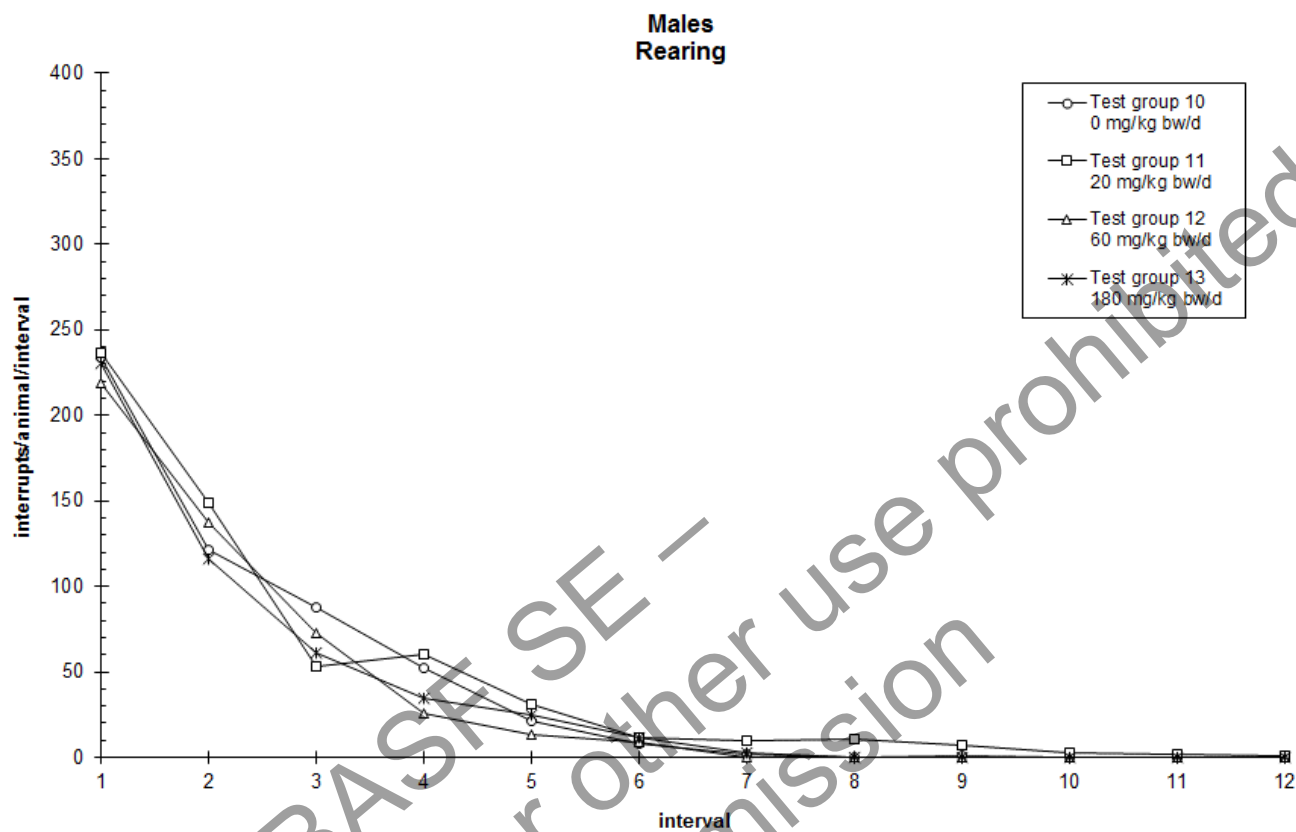
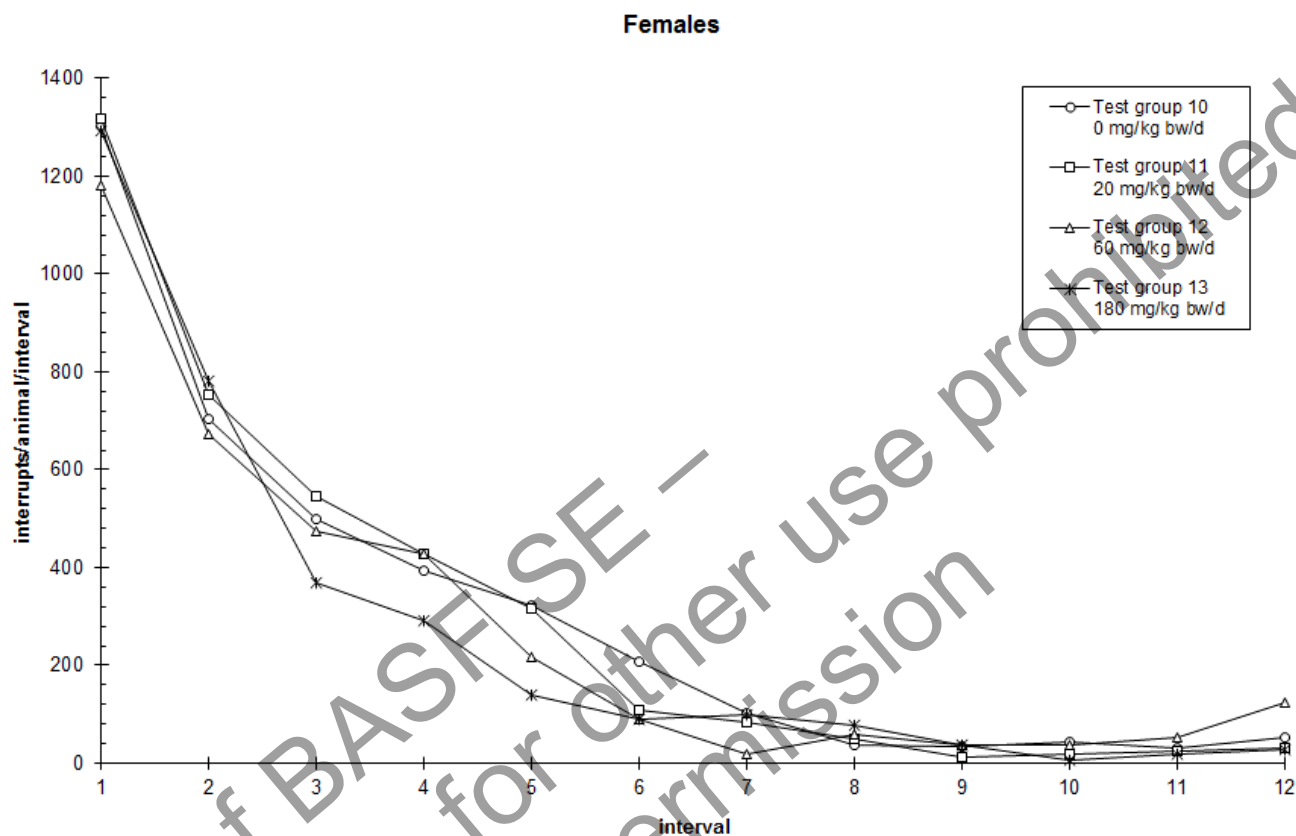
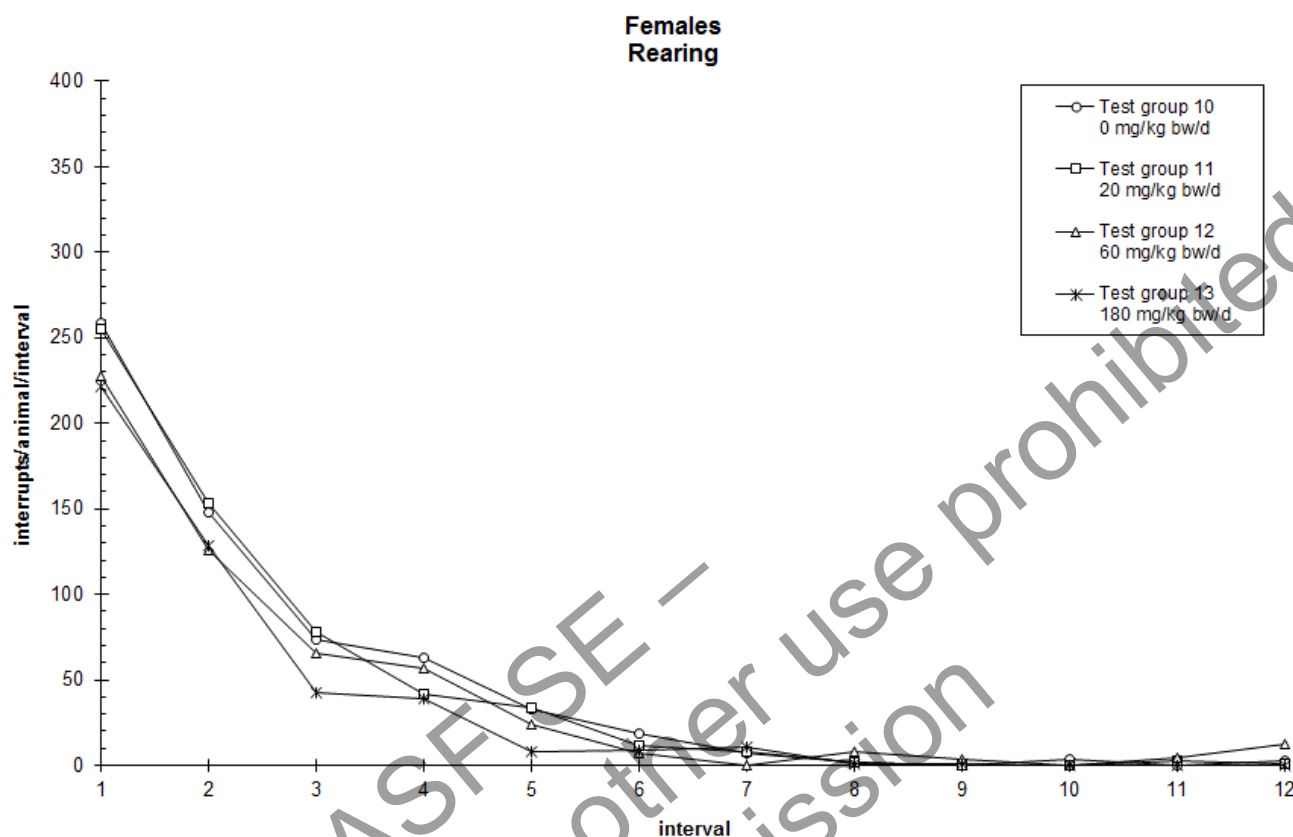


Fig. 4.2.6.9.2.: Motor activity measurement females on PND 75





4.2.6.10. Learning and memory test (Morris water maze)

(Tabs. IA-214 - IA-245; Figs. 4.2.6.10.1. - 4.2.6.10.12.)

The test substance did not influence the ability of the rats to acquire the position of a hidden platform in a circular pool. Time and distance to the goal decreased across learning trials in control and treatment groups alike. Slightly higher values in the low- and high-dose females on the initial training day were likely to be due to a slightly more pronounced exploratory behavior of these rats and thus considered to be incidental. They do not represent an effect on learning ability.

As there was no difference in the distance to and the time spent in the target quadrant between control and treatment groups, memory is also considered to be unaffected by the treatment.

Fig. 4.2.6.10.1. Learning cumulative distance (median) in cohort 2A males

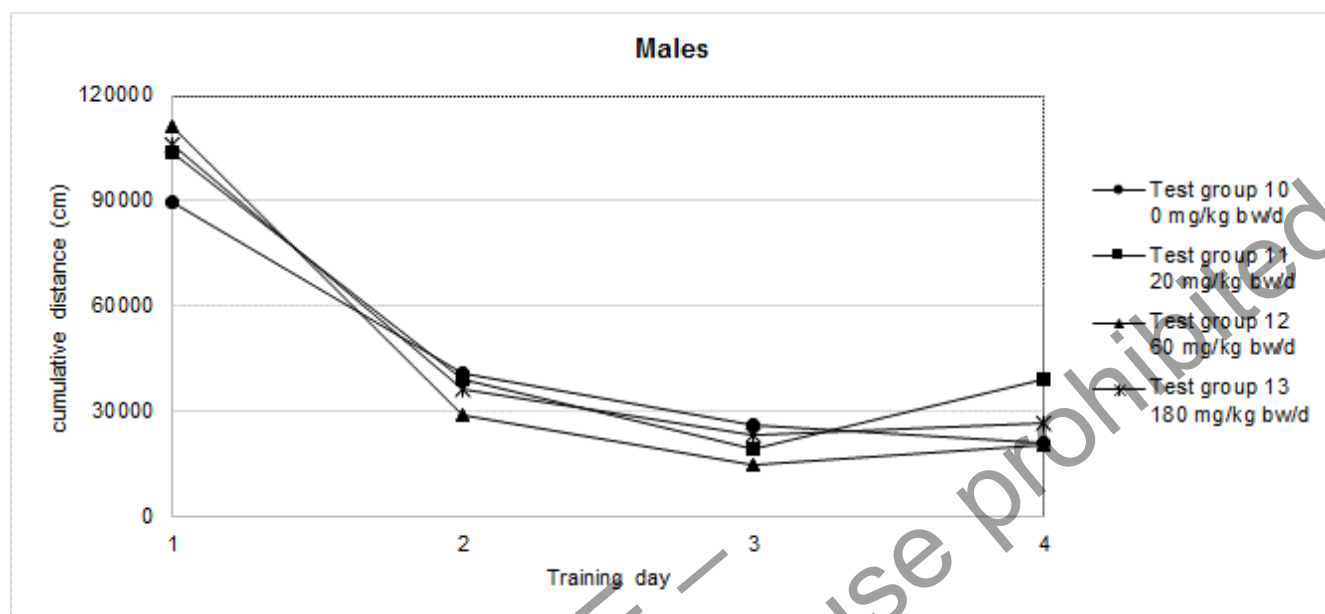


Fig. 4.2.6.10.2. Learning cumulative distance (median) in cohort 2A females

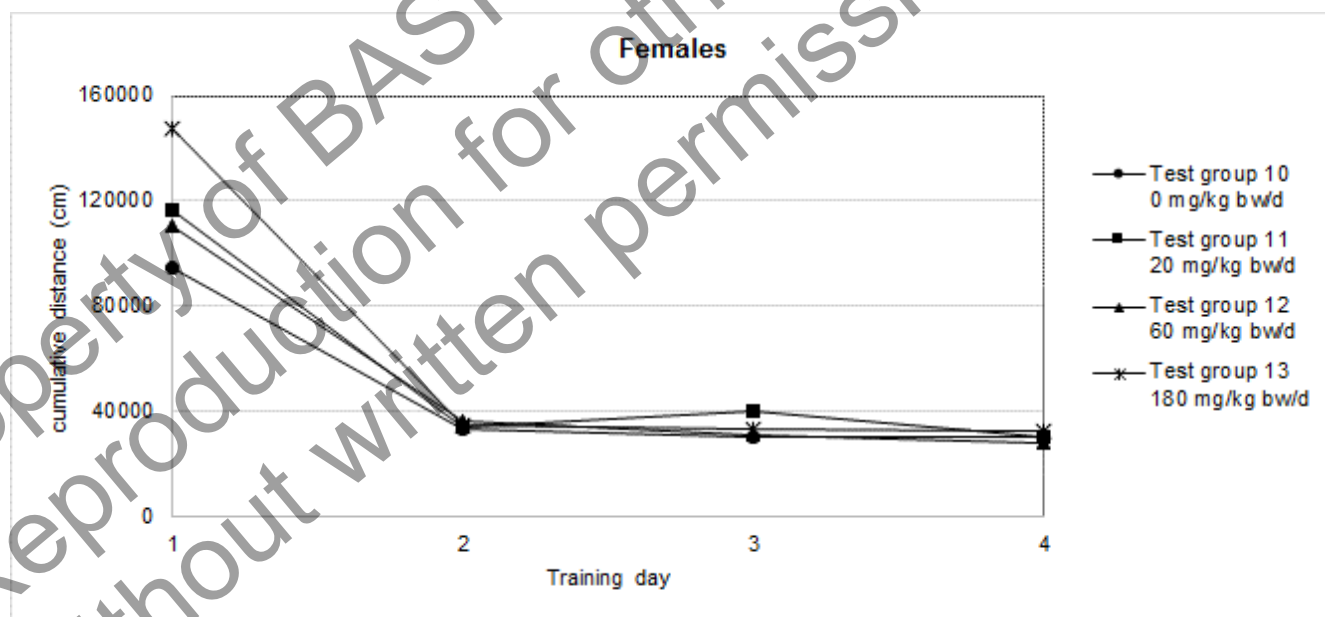


Fig. 4.2.6.10.3. Learning latency time (median) in cohort 2A males

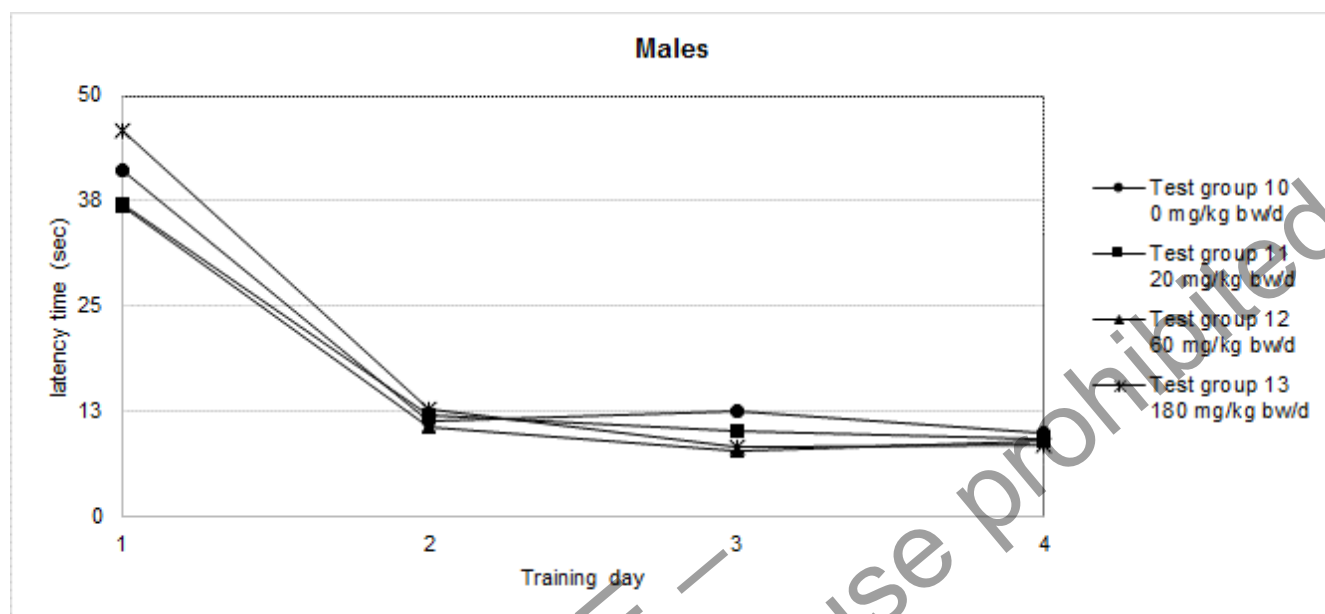


Fig. 4.2.6.10.4. Learning latency time (median) in cohort 2A females

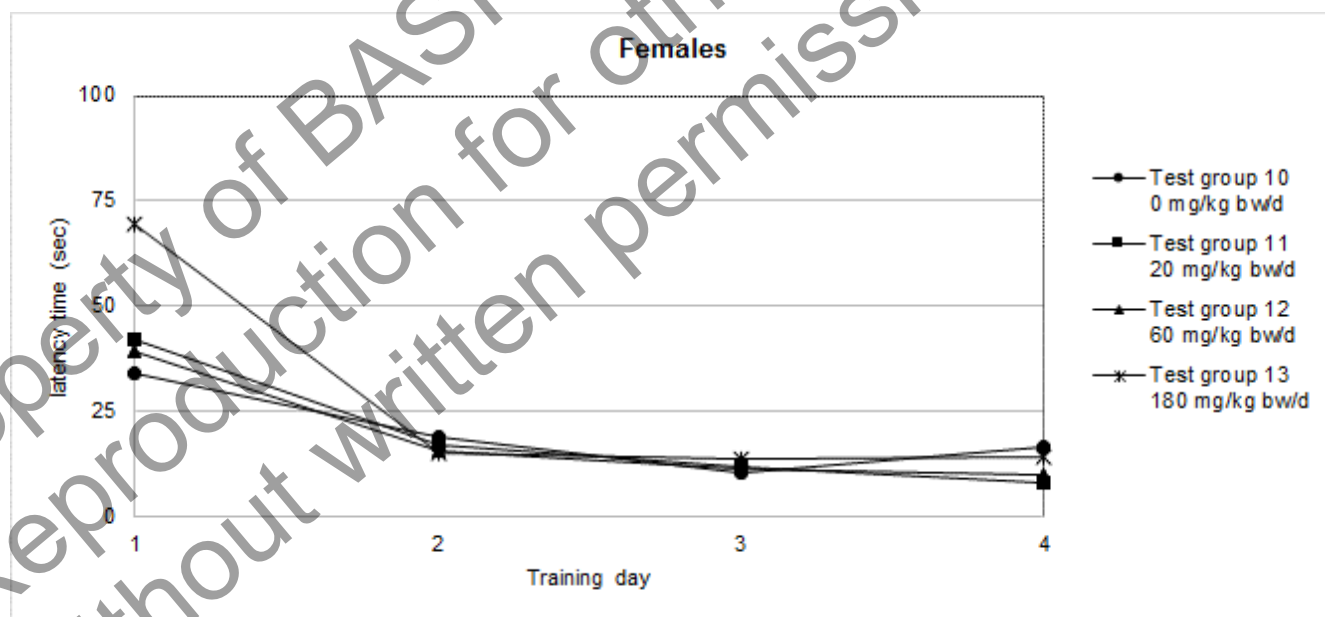


Fig. 4.2.6.10.5. Memory 1 (median) in cohort 2A males

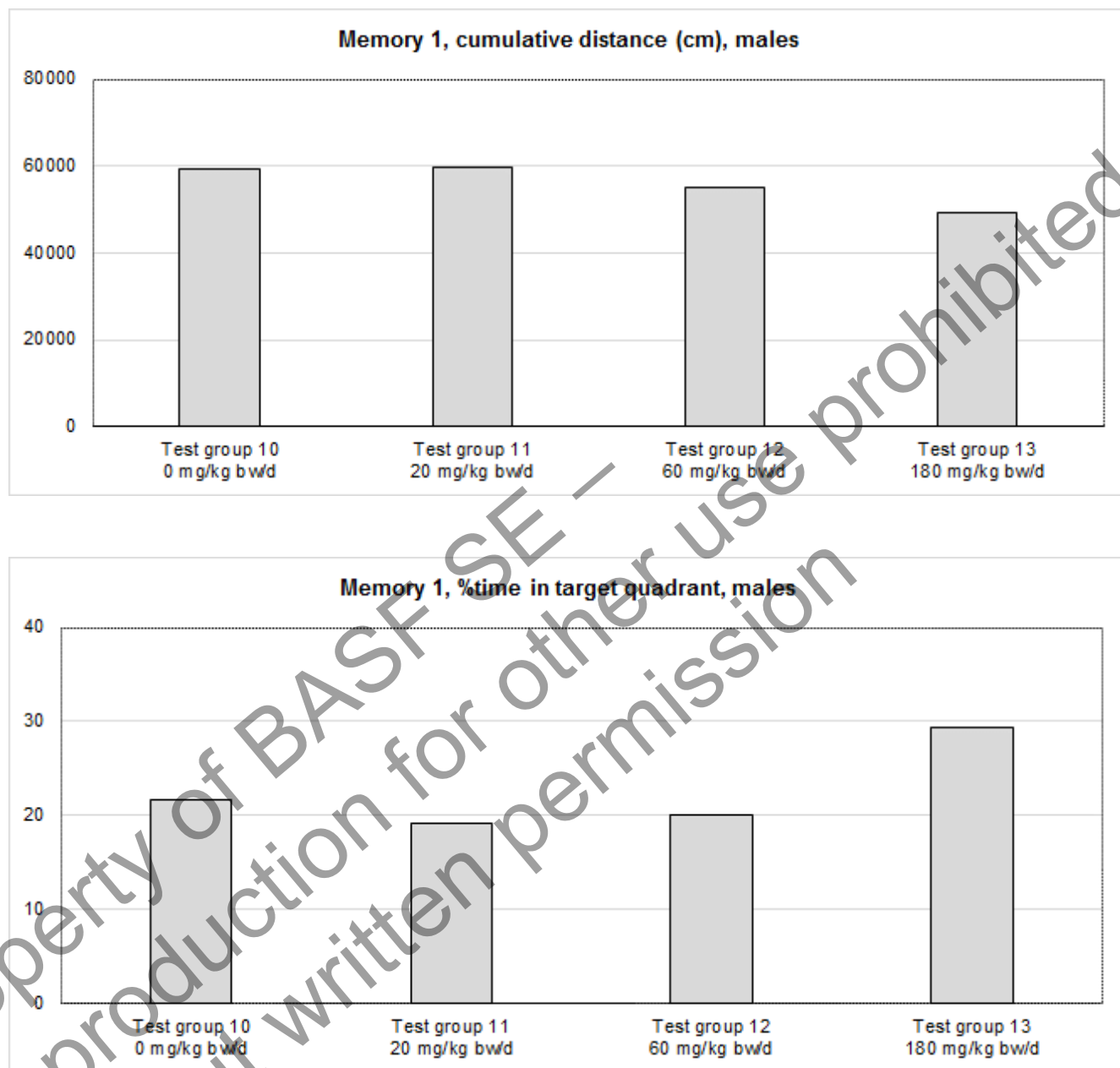


Fig. 4.2.6.10.6. Memory 1 (median) in cohort 2A females

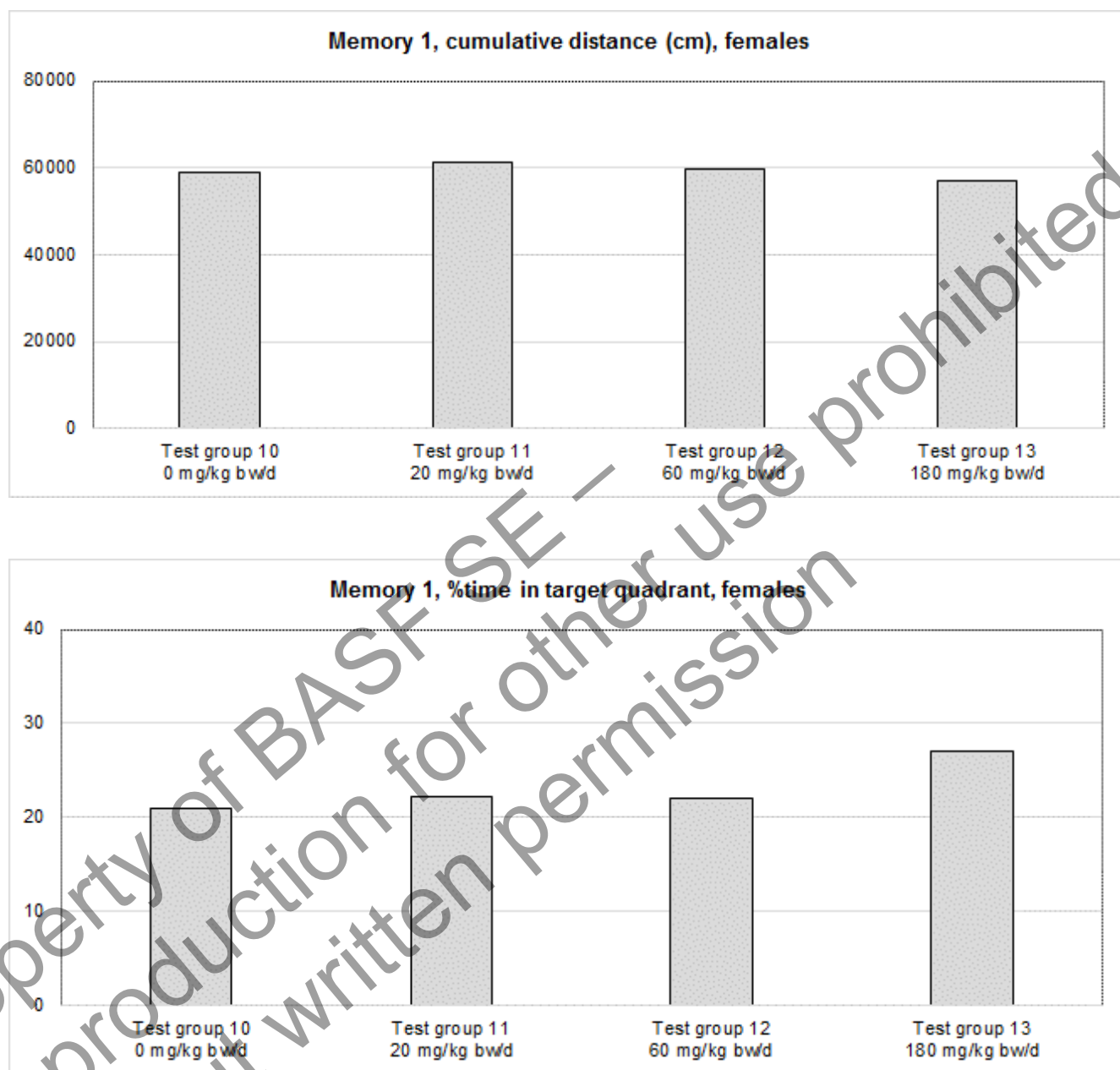


Fig. 4.2.6.10.7. Re-learning cumulative distance (median) in cohort 2A males

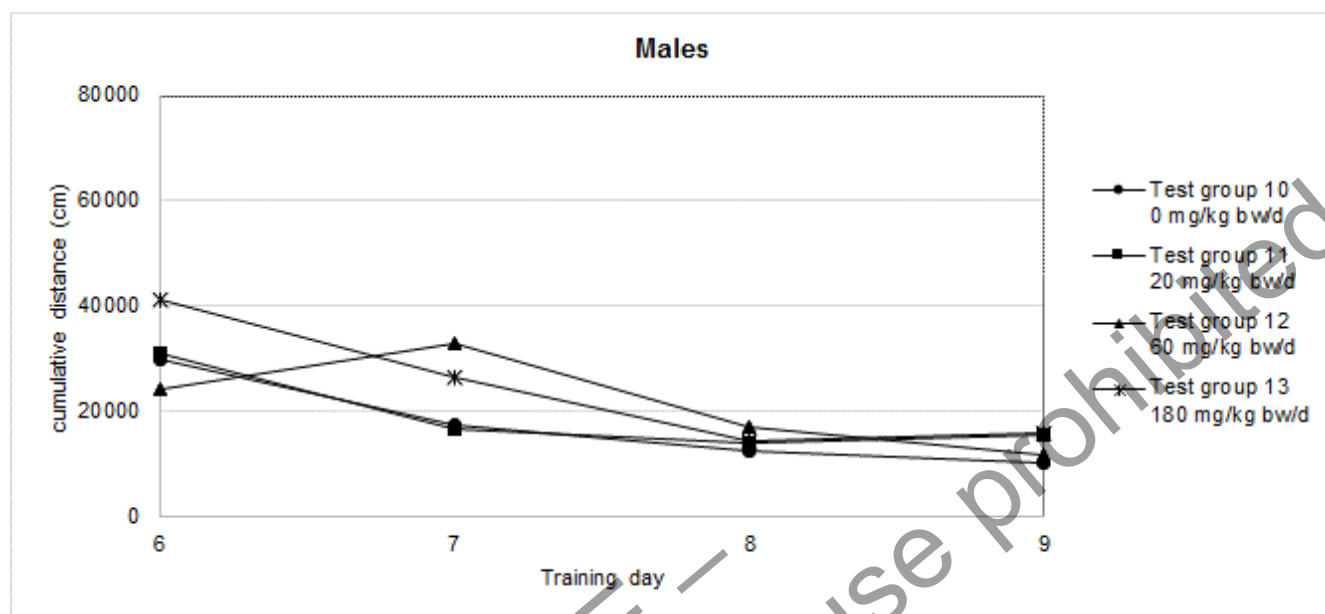


Fig. 4.2.6.10.8. Re-learning cumulative distance (median) in cohort 2A females

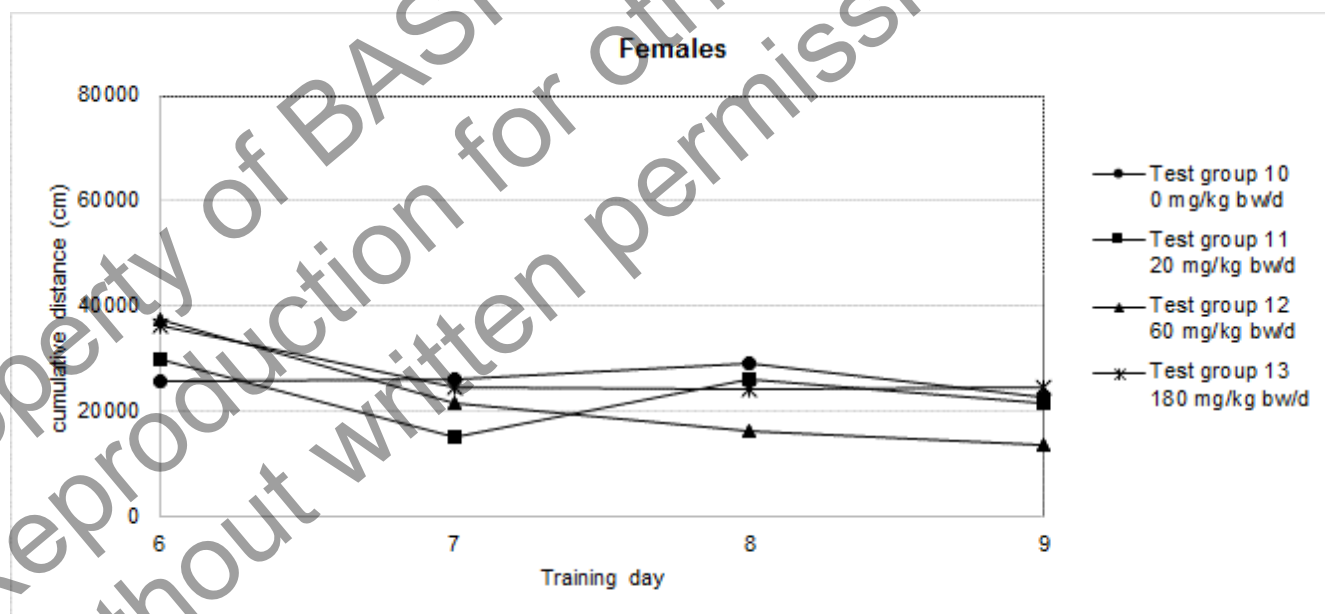


Fig. 4.2.6.10.9. Re-learning latency time (median) in cohort 2A males

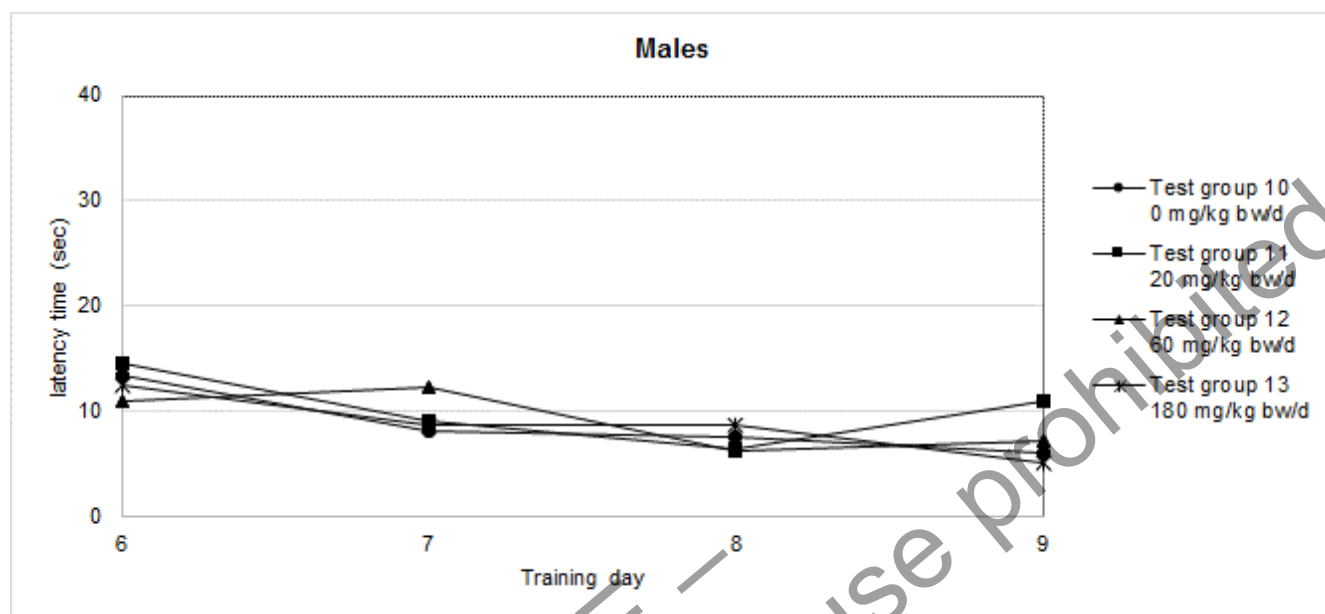


Fig. 4.2.6.10.10. Re-learning latency time (median) in cohort 2A females

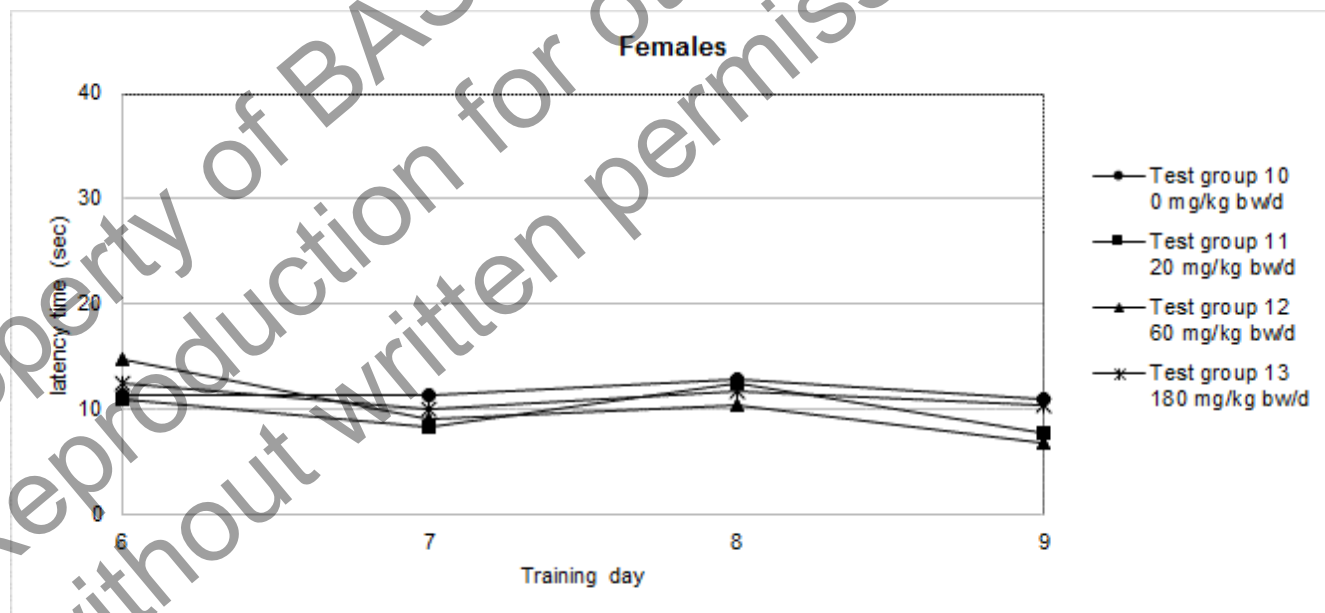
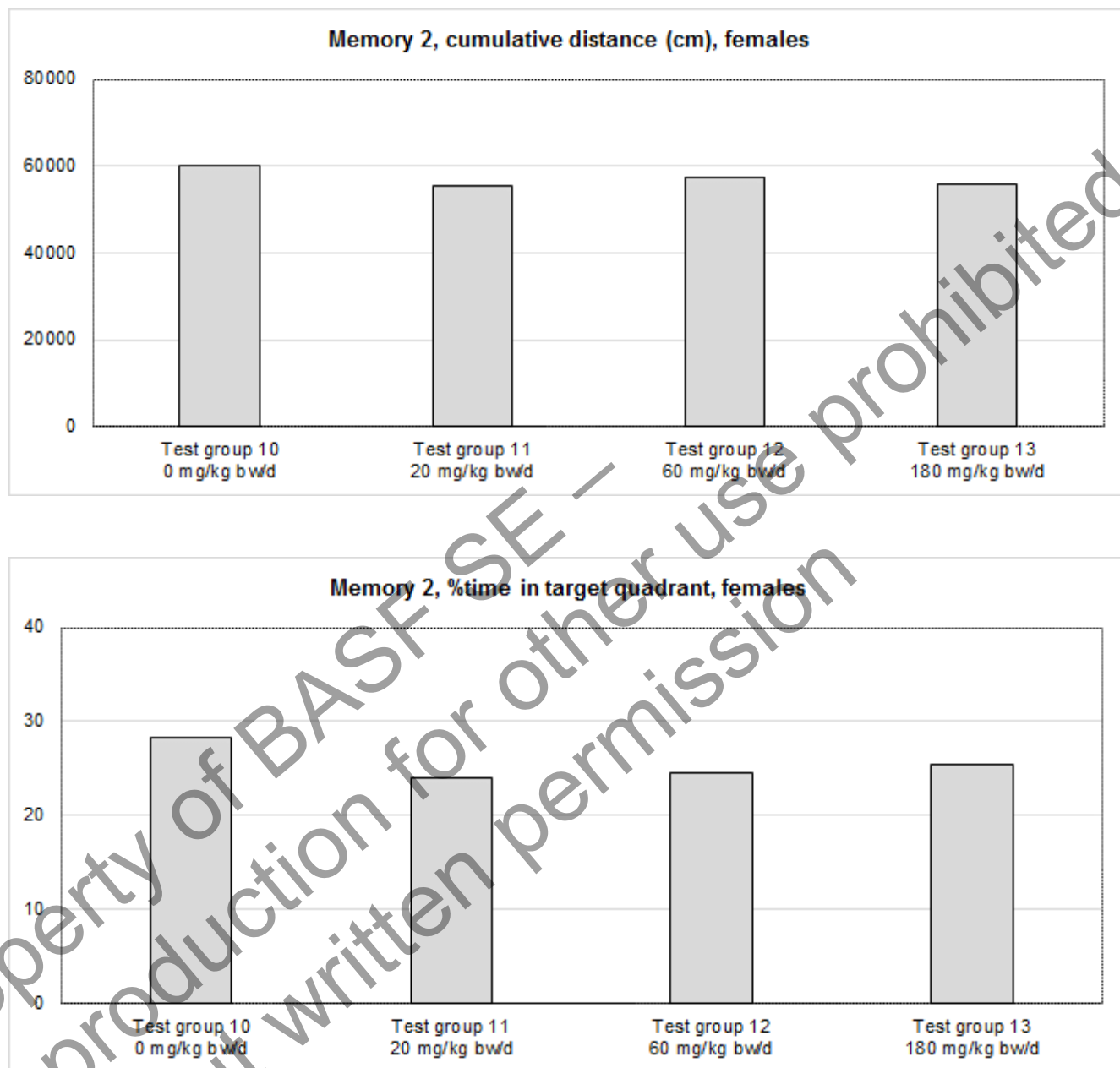


Fig. 4.2.6.10.11. Memory 2 (median) in cohort 2A males



Fig. 4.2.6.10.12. Memory 2 (median) in cohort 2A females



4.2.7. F1 rearing animals, Cohort 3 (05R0343)**4.2.7.1. Mortality**

(Tabs. IA-246 - IA-253)

There were no test substance-related mortalities in any of the groups.

One female animal (No. 1111) of test group 11 was found dead on study day 18. As the animal was not investigated histopathologically, no cause of the death could be ascertained. A relationship to the treatment is not assumed.

4.2.7.2. Clinical observations

(Tabs. IA-246 - IA-253)

No clinical signs or changes of general behavior, which may be attributed to the test substance, were detected in any of the male and female animals in any of the groups.

4.2.7.3. Water consumption

(Tabs. IA-254 - IA-255)

Water consumption of all test substance treated male and female rats (20, 60 and 180 mg/kg bw/d) was comparable to the concurrent control values throughout the entire study.

4.2.7.4. Food consumption

(Tabs. IA-256 - IA-257)

Food consumption of all test substance treated male and female rats was statistically comparable to the concurrent control values throughout the entire study. Slightly higher average female high-dose food intake did not gather statistical significance.

4.2.7.5. Body weight data

(Tabs. IA-258 - IA-261; Figs. 4.2.7.4.1. - 4.2.7.4.2.)

The mean body weights and body weight change of all test substance treated male and female rats were statistically comparable to the concurrent control values throughout the entire study. Slightly higher average female high-dose body weights did not gather statistical significance.

Fig. 4.2.7.4.1.: Mean body weight of cohort 3 males during the study

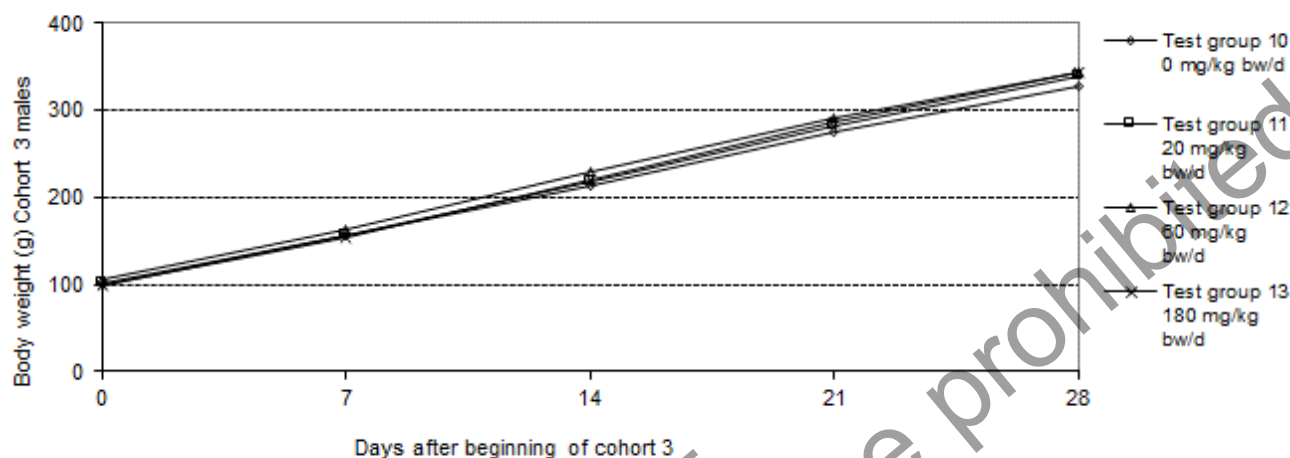
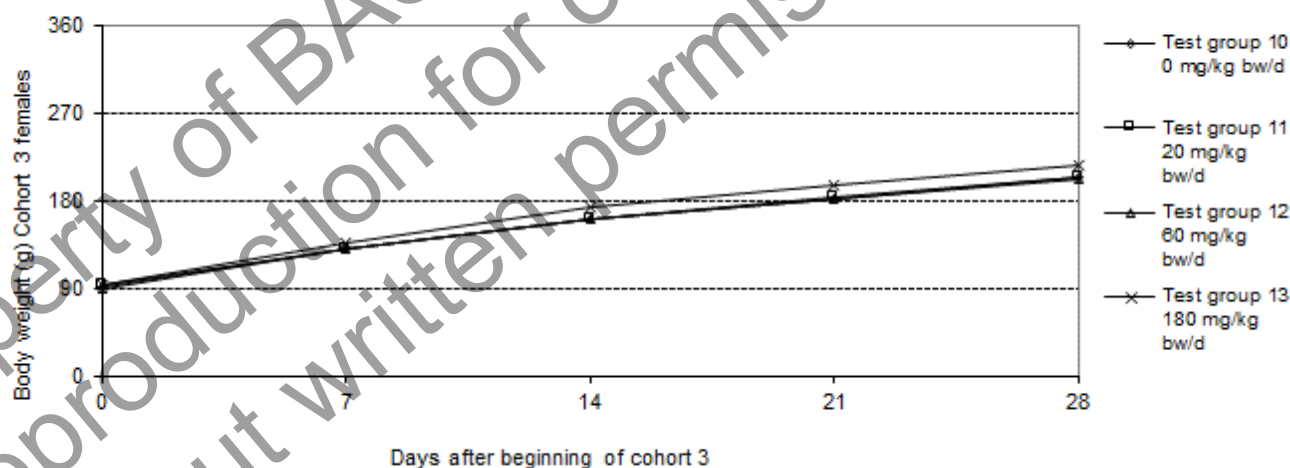


Fig. 4.2.7.4.2.: Mean body weight of cohort 3 females during the study



4.2.7.6. Detailed clinical observations (DCO)

(Tabs. IA-262 - IA-263)

No clinical signs or changes of general behavior, which may be attributed to the test substance, were detected in any of the male and female animals in any of the groups.

One female animal (No. 1111) of test group 11 was found dead on study day 18 (DCO week 2 for details see 4.2.7.1.).

4.3. CLINICAL PATHOLOGY

Summary tables of the results are given in the Appendix of PART I; individual values are given in PART B of PART II. Historical control values are presented in Part III, SUPPLEMENT.

4.3.1. F0 generation

4.3.1.1. Hematology

(Tables IB 1 – IB 2 Red blood cell and coagulation parameters)

(Tables IB 3 – IB 6 Total white and differential blood cell count)

No treatment-related changes of hematological parameters were observed.

At the end of the administration period in males of test group 03 (180 mg/kg bw/d) mean corpuscular hemoglobin (MCH) content was significantly increased. This parameter was calculated from the measured parameters hemoglobin and red blood cell (RBC) counts. Both measured parameters were not statistically significantly altered. Therefore, the MCH change was regarded as incidental and not treatment-related.

In males of test group 01 (20 mg/kg bw/d) relative basophil cell counts were significantly lower compared to controls, but the values were not dose-dependently changed. Therefore, this alteration was regarded as incidental and not treatment-related.

4.3.1.2. Clinical chemistry

(Tables IB 7 – IB 8 Enzymes)

(Tables IB 9 – IB 10 Substrates)

(Tables IB 11 – IB 12 Electrolytes + minerals)

No treatment-related changes of clinical chemistry parameters were observed.

At the end of the administration period in females of test group 02 (60 mg/kg bw/d) cholesterol values were significantly increased. However, this change was not dose-dependent. Therefore, it was regarded as incidental and not treatment-related.

4.3.1.3. Thyroid hormones

(Tables IB 13 – IB 14)

In parental male and female rats (test groups 01, 02 and 03; 20, 60 and 180 mg/kg bw/d) no treatment-related alterations of T₄ and TSH levels were observed.

4.3.1.4. Urinalysis

(Tables IB 15 – IB 18)

No treatment-related, adverse changes among urinalysis parameters were observed.

In males and females of test group 03 (180 mg/kg bw/d) urine pH values were decreased (in females not statistically significant). This pH value decrease may be treatment-related but without any other findings in the urine it is regarded as non-adverse.

4.3.1.5. Spermanalysis

(Table IB 19)

Concerning the incidence of abnormal sperm in the cauda epididymidis as well as sperm head counts in the testis and in the cauda epididymidis no treatment-related effects were observed.

The motility of the sperm was significantly lower in males of test groups 01, 02 and 03 (20, 60 and 180 mg/kg bw/d) compared to controls. However, the lowest value (84% motile sperm) exactly matched the control value in the F1 generation and the overall span of sperm motility in this study reflects a normal range of biological variation in rat (multi)generation studies. No dose-dependency was observed. Therefore, these statistically significant differences were regarded as incidental and not treatment-related.

4.3.2. F1 generation**4.3.2.1. Hematology (cohort F1A)**

(Tables IB 20 – IB 21 Red blood cell and coagulation parameters)

(Tables IB 22 – IB 25 Total white and differential blood cell count)

At the end of the administration period, in males of test group 13 (180 mg/kg bw/d) prothrombin time (HQT, Hepatoquick's test) was prolonged. Because this was the only measured plasma coagulation parameter besides platelet counts which can be affected by a dysregulated coagulation, this alteration has to be regarded as treatment-related and adverse.

Additionally, in males of test group 13 (180 mg/kg bw/d) hemoglobin values were significantly higher compared to controls. However, this was the only changed red blood cell parameter (i.e., hemoglobin, hematocrit and red blood cell (RBC) counts). Therefore, the hemoglobin change alone, was regarded as maybe treatment-related, but non-adverse (ECETOC Technical Report No. 85, 2002).

4.3.2.2. Clinical chemistry (cohort F1A)

(Tables IB 26 – IB 27 Enzymes)

(Tables IB 28 – IB 29 Substrates)

(Tables IB 30 – IB 31 Electrolytes + minerals)

At the end of the administration period, in females of test group 13 (180 mg/kg bw/d), total protein, albumin and calcium levels were significantly increased. This was regarded as treatment-related and adverse.

In females of test groups 11, 12 and 13 (20, 60 and 180 mg/kg bw/d) sodium levels were significantly higher compared to controls. However, the mean and median values of sodium in the test groups were not changed dose-dependently and this was the only altered electrolyte parameter among these individuals. In males of test group 11 (20 mg/kg bw/d) calcium levels were significantly decreased, but again these values were not dose-dependently altered. Therefore, the mentioned alteration in this paragraph were regarded as incidental and not treatment-related.

4.3.2.3. Thyroid hormones (surplus pups PND4 PND22, cohort F1A)

(Tables IB 32 – IB 37)

In male and female PND4 pups of test groups 01, 02 and 03 (20, 60 and 180 mg/kg bw/d) not treatment-related alterations of T₄ levels were observed. TSH values were not changed in male pups, but there was a significant decrease of the TSH values in female PND4 pups of test groups 01 and 03 (20 and 180 mg/kg bw/d). However, these changes were not dose-dependent and therefore, they were regarded as incidental and not treatment-related.

In male and female PND22 pups of test groups 11, 12 and 13 (20, 60 and 180 mg/kg bw/d) no treatment-related alterations of T₄ and TSH levels were observed.

In male and female rats of the F1A cohort (test groups 11, 12 and 13; 20, 60 and 180 mg/kg bw/d) no treatment-related alterations of T₄ and TSH levels were observed.

4.3.2.4. T-cell dependent antibody response (cohort 3)

(Tables IB 38 – IB 41)

Six days after immunization, no changes in the SRBC IgM titers were found in male and female rats of the F1 generation (PND63) dosed with the test substance. SRBC titers were statistically significantly lower in male and female rats of the positive control group (dosed with Cyclophosphamide; test group 14).

4.3.2.5. Lymphocyte subpopulations in spleen (cohort F1A)

(Tables IB 42 – IB 45)

No alterations in the absolute and relative lymphocyte subpopulation cell counts in the spleen tissue (B-, T-lymphocytes, CD4-, CD8-T-lymphocytes and natural killer (NK) cells) were observed in the F1 generation at PND90 in both sexes.

4.3.2.6. Urinalyses (cohort F1A)

(Tables IB 46 – IB 49)

No treatment-related, adverse changes among urinalysis parameters were observed.

In females of test group 13 (180 mg/kg bw/d) urine volume was significantly higher and urine specific gravity was significantly lower compared to controls. These alterations reflect the physiological function of the kidneys towards higher fluid intake and therefore, without any other alterations in the urine, it was regarded as adaptive and non-adverse finding.

4.3.2.7. Spermanalysis (cohort F1A)

(Table IB 50)

Concerning motility of the sperm and the incidence of abnormal sperm in the cauda epididymidis as well as sperm head counts in the testis and in the cauda epididymidis no treatment-related effects were observed.

4.4. PATHOLOGY

Summary tables of the results are to be found in the PART C of PART I; individual tables are to be found in PART C of PART II. Abbreviations and histopathological grading used in pathology report and tables can be found in the appendix.

4.4.1. F0 generation, parental animals

4.4.1.1. Weight parameters

(Tables IC 1 – IC 10)

Absolute organ weights

When compared to the control group 00 (set to 100%), the mean absolute weights of the following organs were significantly increased in one or more test groups (statistically significant changes printed in bold):

F0	Male animals		
Test group (mg/kg bw/d)	01 (20)	02 (60)	03 (180)
Adrenal glands	104%	109%*	112%*
Kidneys	96%	104%	116%**
Thymus	113%	113%*	93%

* : p <= 0.05, **: p <= 0.01

None of the other mean absolute weight parameters in males and none of the mean absolute weight parameters in females showed significant differences.

Relative organ weights

When compared to the control group 00 (set to 100%), the mean relative weights of the following organs were significantly increased in one or more test groups (statistically significant changes printed in bold):

F0	Male animals			Female animals		
Test group (mg/kg bw/d)	01 (20)	02 (60)	03 (180)	01 (20)	02 (60)	03 (180)
Adrenal glands	106%	109%*	116%**			
Kidneys	97%	104%	120%**			
Liver				100%	102%	107%**
Thymus	116%	112%*	96%			

* : p <= 0.05, **: p <= 0.01

All other mean relative weight parameters did not show significant differences when compared to the control group 00.

In male animals, the absolute and relative weights of the adrenal glands in test groups 02 and 03 and of the kidneys in test group 03 were significantly increased, which was regarded to be treatment-related.

The increased relative liver weight in test group 03 females was assumed to be treatment-related.

The increased absolute and relative thymus weights in test group 02 males did not show a dose-response and were therefore assumed to be incidental.

4.4.1.2. Gross pathology

(Table IC 11 - IC 12)

Notable gross lesions were observed in male animals with incidences as shown in the table below:

F0	Male animals			
Test group (mg/kg bw/d)	00 (0)	01 (20)	02 (60)	03 (180)
No. of animals	24	24	24	24
Cecum				
• Enlarged	0	0	0	3
Kidneys				
• Enlarged	0	0	0	6

The finding in the kidneys was confirmed histopathologically.

The enlarged cecum in 3 animals of test group 03 could not be verified histopathologically.

All other findings occurred either individually or were biologically equally distributed over control and treatment groups. They were considered to be incidental or spontaneous in origin and without any relation to treatment.

Fertility:

The female animals (Nos. 105, 141, 145, and 183), which were not pregnant as well as the male mating partners (Nos. 5, 41, 45, and 83) did not show relevant gross lesions.

4.4.1.3. Histopathology

(Table IC 13 – IC 18)

Kidneys

Treatment-related findings were observed in kidneys of male animals of test group 03. An increased mineralization was noted in the transition from medulla to cortex. This finding is normal in females but generally not seen in control male animals. Nuclear crowding in kidney tubules was also noted. This term was used to describe an accumulation of many (often 5-10) nuclei which pile up and protrude into the tubular lumen. The nature of this finding (preneoplastic or regenerative) is at present not known.

Tubules in the outer zone of the outer medulla were dilated compared to controls. All of these findings were assumed to have contributed to the weight increase of the kidneys and to the macroscopic finding “enlarged” in test group 03.

F0	Male animals			
Test group (mg/kg bw/d)	00 (0)	01 (20)	02 (60)	03 (180)
No. of animals	24	24	24	24
Mineralization, medulla, (m)f	0	0	1	21
• Grade 1			1	11
• Grade 2				7
• Grade 3				1
• Grade 4				2
Nuclear crowding	0	0	0	22
• Grade 1				11
• Grade 2				8
• Grade 3				3
Dilation, tubular	0	0	0	13
• Grade 1				7
• Grade 2				6

There were no histopathological treatment-related findings in the cecum in animals of either sex.

All other findings occurred either individually or were biologically equally distributed over control and treatment groups. They were considered to be incidental or spontaneous in origin and without any relation to treatment.

The female animals (Nos. 105, 141, 145, and 183), which were not pregnant as well as the male mating partners (Nos. 5, 41, 45, and 83) did not show relevant histopathological findings consistent with impaired fertility.

Decedents

The female animal No. 127 was sacrificed moribund. It showed multiple lesions both macroscopically and microscopically consistent with a gavage error (macroscopically depositions on diaphragm and lungs and histopathologically inflammation with foreign material embedded in the inflammatory reaction).

4.4.2. F1 rearing animals, cohort 1A

4.4.2.1. Weight parameters

(Tables IC 19 – IC 26)

Absolute organ weights

When compared to the control group 10 (set to 100%), the mean absolute weights of the following organs were significantly increased or decreased in one or more test groups (statistically significant changes printed in bold):

F1A	Male animals		
Test group (mg/kg bw/d)	11 (20)	12 (60)	13 (180)
Kidneys	97%	103%	112%**
Liver	102%	99%	86%**
Prostate	96%	91%*	90%**
Spleen	93%	91%*	83%**
Thymus	96%	100%	81%*

*: p <= 0.05, **: p <= 0.01

Relative organ weights

When compared to the control group 10 (set to 100%), the mean relative weights of the following organs were significantly increased or decreased in one or more test groups (statistically significant changes printed in bold):

F1A	Male animals		
Test group (mg/kg bw/d)	11 (20)	12 (60)	13 (180)
Adrenal glands	98%	98%	113%**
Kidneys	98%	103%	117%**
Liver	104%	100%	91%**
Spleen	94%	92%*	87%**

*: p <= 0.05, **: p <= 0.01

None of the other mean absolute and relative weight parameters in males and none of these parameters in females showed significant differences.

In male animals, the absolute and relative weights of the kidneys and the relative weight of the adrenal glands in test group 13 were increased. This was regarded to be treatment-related.

Absolute and relative weights of the spleen in test groups 12 and 13 males were decreased. Similar changes occurred in cohort 3. There were no histopathological correlates and no findings in clinical chemistry. Therefore, this was regarded as equivocal and as not adverse.

The absolute thymus weight in males of test group 13 was significantly decreased. The relative weight (84%) was decreased without statistical significance. The thymus weights in both this cohort and in cohort 3 were decreased in a similar magnitude. There were no findings in clinical chemistry. Therefore, this was regarded to be an equivocal finding and as not adverse.

The absolute and relative liver weights were statistically significantly decreased in test group 13 males. This was regarded as possibly treatment-related as the same effect was observed in test group 13 males of cohort 1B.

The absolute weights of the prostate in test groups 12 and 13 were decreased but no significant change was seen in relative weights, therefore the decrease in absolute weights was regarded as incidental.

4.4.2.2. Gross pathology

(Tables IC 27)

All findings occurred either individually or were biologically equally distributed over control and treatment groups. They were considered to be incidental or spontaneous in origin and without any relation to treatment.

4.4.2.3. Histopathology

(Tables IC 28 – IC 32)

Treatment-related findings were observed in kidneys and mammary gland of male animals, with incidences and grading according to the tables below:

Kidneys

Findings in the kidneys of test group 13 animals were comparable with those seen in the F0 generation.

F1A	Male animals			
Test group (mg/kg bw/d)	10 (0)	11 (20)	12 (60)	13 (180)
No. of animals	20	20	20	20
Mineralization, medulla, (m)f	0	0	1	7
• Grade 1			1	2
• Grade 2				2
• Grade 3				3
Nuclear crowding	1	1	0	6
• Grade 1	1	1		5
• Grade 2				1
Dilation, tubular	0	0	2	7
• Grade 1			2	4
• Grade 2				3

Mammary gland and Mammary fat pad

Glandular atrophy was observed in the mammary gland and mammary gland fat pad in control and treated male animals. This finding was characterized by a diffuse change of the epithelium from prismatic to smaller cuboidal cells with more basophilic cytoplasm. This was consistent with the description by Rudmann et al. 2012.

In the normal male mammary gland, tubular profiles with this appearance can be found in the periphery of each lobule. This is described in Rudmann et al. as normal. Therefore, atrophy was diagnosed when a diffuse alteration of the epithelium as described above was present in all available slides.

In test group 13 males there was a clear effect compared to the control group 10.

The incidence is shown in the tables below.

Mammary gland

F1A	Male animals			
Test group (mg/kg bw/d)	10 (0)	11 (20)	12 (60)	13 (180)
No. of animals	20	18	20	20
Atrophy, (multi)focal	1	0	2	7
• Present	1	0	2	7

Mammary gland fat pad

F1A	Male animals			
Test group (mg/kg bw/d)	10 (0)	11 (20)	12 (60)	13 (180)
No. of animals	10	10	10	10
Atrophy, (multi)focal	1	0	2	7
• Present	1	0	2	7

All other findings occurred either individually or were biologically equally distributed over control and treatment groups. They were considered to be incidental or spontaneous in origin and without any relation to treatment.

Decedents

Female animal 362 (test group 13) showed a slight fibrinous inflammation in the lung, focal hyperplasia in the mammary gland and an atrophic uterus.

4.4.2.4. Differential ovarian follicle count

(Table IC 33)

The results of the differential ovarian follicle count (DOFC) – comprising the numbers of primordial and growing follicles, as well as the combined incidence of primordial plus growing follicles – did not reveal significant differences between the control group 10 and animals of test group 13:

Number of animals	Absolute values			
	Group	Primordial	Growing	Primordial + growing
20	10 (0 mg/kg bw/d)	6702	220	6922
20	13 (180 mg/kg bw/d)	7972	239	8211

Number of animals	Mean values			
	Group	Primordial	Growing	Primordial + growing
20	10 (0 mg/kg bw/d)	335.10	11	346.10
20	13 (180 mg/kg bw/d)	398.60	11.95	410.55

Wilcoxon-Test (one-sided) * = $p \leq 0.05$ ** = $p \leq 0.01$

4.4.3. F1 generation, rearing animals, cohort 1B

4.4.3.1. Weight parameters

(Tables IC 34 - IC 39)

Absolute weights

When compared to the control group 10 (set to 100%), the mean absolute weights of the following organs were significantly increased or decreased in one or more test groups (statistically significant changes printed in bold):

F1B	Male animals			Female animals		
Test group (mg/kg bw/d)	11 (20)	12 (60)	13 (180)	11 (20)	12 (60)	13 (180)
Terminal body weight				98%	104%*	106%
Adrenal glands	105%	113%**	108%			
Kidneys	102%	113%**	126%**	98%	103%	107%*
Liver	104%	99%	90%*			

* : p <= 0.05, **: p <= 0.01

Relative organ weights

When compared to the control group 10 (set to 100%), the mean relative weights of the following organs were significantly increased or decreased in one or more test groups (statistically significant changes printed in bold):

F1B	Male animals		
Test group (mg/kg bw/d)	11 (20)	12 (60)	13 (180)
Adrenal glands	105%	111%*	113%**
Kidneys	103%	110%**	132%**
Liver	105%	97%	94%*

The absolute weights of the adrenal glands were increased in male animals of test group 12 and the relative weights in test groups 12 and 13, which was regarded to be treatment-related. The absolute and relative weights of the kidneys were increased in male animals of test groups 12 and 13, which was considered to be treatment-related.

The absolute and relative liver weights were statistically significantly decreased in test group 13 males. This was regarded as possibly treatment-related as the same effect was observed in test group 13 males of cohort 1A.

In females, the terminal body weight was statistically significantly increased in test group 12 and without statistical significance in test group 13. This possibly explains the increased absolute kidney weights in test group 13 as no changes were seen in relative weights. Additionally, there were no histopathological findings in the kidneys of female animals of test group 13.

All other mean absolute and relative weight parameters did not show significant differences.

4.4.3.2. Gross pathology

(Table IC 40)

Enlarged kidneys were observed in male animals with incidences as shown in the table below:

F1B	Male animals			
Test group (mg/kg bw/d)	00 (0)	01 (20)	02 (60)	03 (180)
No. of animals	24	24	24	24
Kidneys				
• Enlarged	0	0	1	10

All other findings occurred either individually or were biologically equally distributed over control and treatment groups. They were considered to be incidental or spontaneous in origin and without any relation to treatment.

Fertility:

The female animals (Nos. 553 and 593), which were not pregnant as well as the male mating partners (Nos. 468 and 476) did not show relevant gross findings consistent with impaired fertility.

4.4.3.3. Histopathology

(Table IC 41 – IC 42)

Mammary gland and Mammary fat pad

No treatment-related effects were seen in cohort 1B male animals.

All other findings occurred either individually or were biologically equally distributed over control and treatment groups. They were considered to be incidental or spontaneous in origin and without any relation to treatment.

Fertility

The female animals (Nos. 553 and 593), which were not pregnant as well as the male mating partners (Nos. 468 and 476) did not show relevant histopathological findings consistent with impaired fertility.

Decedents

The female animal No. 362 was found dead 7 days after start of exposure. It showed a discolored lung macroscopically and correlating inflammation in the lung histopathologically which was regarded to be incidental.

4.4.4. Pathological examinations of cohort 3 animals (Immunotoxicity cohort) and animals of the positive control

4.4.4.1. Weight parameters (Tables IC 43 – IC 50)

DHDPS

Absolute weights

All mean absolute weight parameters of test groups 11, 12, and 13 did not show significant differences when compared to the control group 10.

Relative organ weights

When compared to the control group 10 (set to 100%), the mean relative weight of the thymus of test group 13 was significantly decreased (statistically significant change printed in bold):

F1 Cohort 3	Male animals		
Test group (mg/kg bw/d)	11 (20)	12 (60)	13 (180)
Spleen	94%	89%	89%
Thymus	94%	100%	81%*

The mean relative weight parameters of the spleen in test groups 11, 12, and 13 did not show significant differences when compared to the control group 10 but were similarly decreased as in cohort 1A animals. There were no correlates in clinical chemistry and there was no statistical significance, therefore, this was regarded as incidental.

The relative thymus weight in test group 13 males was decreased significantly. However, similar weight changes occurred in cohort 1A without histopathological correlates. There were no findings in clinical chemistry. Therefore, the decrease of the absolute thymus weight in test group 13 animals is regarded as an equivocal finding and as not adverse.

None of the weight parameters was significantly changed in females.

Cyclophosphamide monohydrate

Absolute and relative organ weights

When compared to the control group 10 (set to 100%), the mean absolute and relative spleen weights of test group 14 (positive control) were significantly decreased as follows (statistically significant changes printed in bold):

F1 cohort 3	Male animals		Female animals	
	Absolute	Relative	Absolute	Relative
Test group (mg/kg bw/d)	14 (4.5)	14 (4.5)	14 (4.5)	14 (4.5)
Spleen	65%**	67%**	70%**	70%**
Thymus	85%	88%	84%	85%

*p <= 0.05; **p <= 0.01

A significant decrease in absolute and relative weights of the spleen and a not statistically significant decrease of these weight parameters in the thymus occurred in the positive control male and female animals. The decreased weights of spleen and thymus were the expected result.

4.4.4.2. Gross pathology (Tables IC 51 – IC 52)

DHDPS

There were no treatment-related gross lesions.

Cyclophosphamide monohydrate

There were no treatment-related gross lesions.

4.4.4.3. Histopathology

Histopathological examination was not performed.

4.4.5. Pathological examinations of surplus F1 generation pups on PND 22 (F1 weanlings not selected for cohorts)

4.4.5.1. Weight parameters (Tables IC 53 – IC 56)

Absolute organ weights

When compared to the control group 10 (set to 100%), the mean absolute weights of the following organs were significantly increased in one or more test groups (statistically significant changes printed in bold):

Surplus F1 (PND 22)	Male animals			Female animals		
Test group (mg/kg bw/d)	11 (20)	12 (60)	13 (180)	11 (20)	12 (60)	13 (180)
Terminal body weight ¹⁾	104%	110%	109%	107%	107%	101%

¹⁾Terminal body weights included for reference, no statistically significant changes

Surplus F1 (PND 22)	Male animals		
Test group (mg/kg bw/d)	11 (20)	12 (60)	13 (180)
Brain	101%	105%**	103%
Thymus	124%**	117%*	108%

* : p <= 0.05, **: p <= 0.01

All other mean absolute weight parameters showed no significant differences.

Relative organ weights

When compared to the control group 10 (set to 100%), the mean relative weights of the following organs were significantly increased or decreased (statistically significant changes printed in bold):

Surplus F1 (PND 22)	Male animals			Female animals		
Test group (mg/kg bw/d)	11 (20)	12 (60)	13 (180)	11 (20)	12 (60)	13 (180)
Brain				95%	91%**	97%
Spleen	119%**	109%	111%			
Thymus	120%**	106%	100%			

*: p <= 0.05, **: p <= 0.01

All other mean relative weight parameters showed no significant differences.

All observed significant weight changes were assumed to be secondary to the increased terminal body weights in test group 11 and 12 (not significant) in both males and females: increased absolute brain weight in males of test group 12, increased absolute thymus weights in males of test groups 11 and 12, decreased relative brain weight in females of test group 12, increased relative spleen and thymus weights in test group 11 males.

4.4.5.2. Gross pathology

(Table IC 57)

No treatment-related gross changes were observed.

4.4.5.3. Histopathology

(Table IC 58)

There were no treatment-related histopathological findings in the mammary gland and mammary gland fat pad.

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4.5. NEUROPATHOLOGY

Summary tables of the results are to be found in Part D of PART I; individual tables are to be found in Part D of PART II. Abbreviations and histopathological grading used in pathology report and tables can be found in the appendix.

4.5.1. Cohort 2A animals (Developmental Neurotoxicity Cohort, adults)

4.5.1.1. Weight parameters

(Tables ID 1 – ID 4)

Absolute weights

When compared to the control group 10 (set to 100%), no mean absolute weights were significantly changed in any test group.

Relative weights

When compared to the control group 10 (set to 100%), no mean relative weights were significantly changed in any test group.

4.5.1.2. Length and width of brain

(Table ID 5)

All length and width measurements were without any findings.

4.5.1.3. Gross lesions

(Table ID 6)

Only one animal revealed a skin lesion, which was not treatment-related. No other gross findings were recorded.

4.5.1.4. Histopathology

(Table ID 7 – ID 8)

No treatment-related histopathological findings were seen. All lesions are regarded as incidental and/or spontaneous.

4.5.1.5. Morphometry

(Table ID 9)

All morphometric brain measurements were without any findings.

Only some single parameters in male (Nucleus caudatus width left, Corpus callosum width) or female (Nucleus caudatus width left) animals of test group 13 showed a statistically significant increase or decrease. As no other values were changed, this minimal width in-/decrease is assumed as incidental and not related to treatment.

4.5.2. Cohort 2B animals (Developmental Neurotoxicity Cohort, weanlings)**4.5.2.1. Weight parameters**

(Tables ID 10– ID 13)

Absolute weights

When compared to the control group 10 (set to 100%), no mean absolute weights were significantly changed in any test group.

Relative weights

When compared to the control group 10 (set to 100%), no mean relative weights were significantly changed in any test group.

4.5.2.2. Length and width of brain

(Table ID 14)

All length and width measurements were without any findings.

4.5.2.3. Gross lesions

(Table ID 15)

No gross findings were recorded.

4.5.2.4. Histopathology

(Table ID 16)

No treatment-related neurohistopathological findings were recorded.

5. DISCUSSION

DHDPS was administered daily to Sprague-Dawley rats as an aqueous preparation (0.5% Sodium carboxymethyl cellulose [CMC] suspension in drinking water) by stomach tube at different dosages (0, 20, 60 and 180 mg/kg body weight/day [mg/kg bw/d]) throughout the study. Control animals were daily dosed with the vehicle.

Analyses confirmed the prepared concentrations, the homogeneous distribution and the stability of the test substance in the vehicle.

There were no test substance-related **mortalities** or adverse **clinical observations** noted in any of the groups. In particular, regularly conducted detailed clinical observations revealed no test substance related effects.

Transient salivation was frequently noted at the high-dose level (180 mg/kg bw/d) across F0 parents and most F1 cohorts. This salivation was considered to be treatment-related. From the temporary, short appearance of the finding immediately after dosing it is likely, that this finding was induced by a bad taste of the test substance and/or local affection of the upper respiratory and/or digestive tract. It is, however, not considered to be a sign of systemic toxicity or an adverse effect per se.

Neither **food consumption** nor **body weights/body weight gain** were reduced in F0/F1 parental animals or F1 offspring of any treatment group. There was, however, noted an increased food consumption (and to some extent correspondingly water consumption) in the high-dose and partly also mid-dose females. Occasionally this corresponded with higher body weights. This effect proved to be rather consistent across F0 parents and F1 cohorts but was limited to the study sections when the females were non-pregnant and non-lactating. From the data of the present study neither an explanation nor the assessment of adversity for this phenomenon can be deduced at present.

Regarding **clinical pathology** no treatment-related, adverse changes were observed in the F0 generation up to a dose of 180 mg/kg bw/d. In adult rats of the F1 generation (cohort F1A), a significant prolonged prothrombin time in males of test group 13 (180 mg/kg bw/d) as well as significant higher albumin, total protein and calcium levels in females of the same test group may indicate a changed liver cell metabolism.

Regarding **pathology**, target organs were the adrenal glands and kidneys in male animals and the liver in female animals of the **F0 parental generation**.

In males, the absolute and relative weights of the adrenal glands were significantly increased in test groups 02 and 03, which was regarded to be treatment-related. No further findings were noted macroscopically or histopathologically in the adrenal glands.

This effect was regarded to be not adverse.

In male animals, the absolute and relative weights of the kidneys were significantly increased in test group 03. There were correlating macroscopic (enlarged) and histopathological findings in test group 03: increased mineralization, nuclear crowding and dilation of tubules in the outer zone of the outer medulla.

Findings in the kidney in test group 03 were assessed as treatment-related and adverse.

The increased relative liver weight in test group 03 females were assumed to be treatment-related, but in the absence of any other findings (histopathology or clinical chemistry) regarded as non-adverse.

The reproductive organs of mating pairs suspected of reduced fertility did not show histopathological findings indicative of a treatment-related effect.

All other findings occurred either individually or were biologically equally distributed over control and treatment groups. They were considered to be incidental or spontaneous in origin and without any relation to treatment.

In the **F1 rearing animals, cohort 1A**, target organs were the adrenal glands, kidneys, liver, mammary gland, and potentially spleen and thymus in male animals.

In male animals, the relative weight of the adrenal glands in test group 13 was increased. This was regarded to be treatment-related but not adverse as there was no histopathological correlate. Similar increases in relative and absolute weights of the adrenal gland were already seen in F0 male animals of test groups 02 and 03.

The absolute and relative kidney weights in test group 13 males were increased. There were correlating macroscopic (enlarged) and histopathological findings in test group 13: increased mineralization, nuclear crowding and dilation of tubules in the outer zone of the outer medulla. Findings in the kidneys of males of test group 13 were regarded as treatment-related and adverse. These findings were comparable with those of test group 03 of the F0 generation, with lower incidences in cohort 1A.

The absolute and relative liver weights were statistically significantly decreased in test group 13 males. This was regarded as possibly treatment-related as the same effect was observed in test group 13 males of cohort 1B. There were no histopathological findings in animals of cohort 1A, therefore, this finding was assessed as not adverse.

An increased incidence of atrophy was observed in the mammary gland and mammary gland fat pad in test group 13 males of cohort 1A. This finding was regarded as treatment-related and adverse.

Absolute and relative weights of the spleen in test group 12 and 13 and the absolute thymus weight in test group 13 were decreased. There were no histopathological correlates and no findings in clinical chemistry. However, similar weight changes occurred in cohort 3. Therefore, the decrease of the spleen weights in test group 12 and 13 and the absolute thymus weight in test group 13 animals is regarded as an equivocal finding and as not adverse.

In the **F1-Generation parental animals, cohort 1B**, target organs were the adrenal glands, kidneys, and liver in male animals.

The weights of the adrenal glands were increased in male animals of test group 12 and 13. This was regarded to be treatment-related as it was already seen in F0 generation and F1 generation, cohort 1A animals. This was assessed as not adverse.

The absolute and relative weights of the kidneys were increased in male animals of test groups 12 and 13, again correlating with enlarged kidneys in test group 13 males macroscopically. This was regarded to be treatment-related and adverse even though histopathology was not performed in this cohort. It was assumed that weight increase and macroscopic findings which were similar to F0 and F1, cohort 1A animals, would also correlate to the same histopathological findings seen in those groups.

The absolute and relative liver weights were statistically significantly decreased in test group 13 males. This was regarded as possibly treatment-related but not adverse. The same effect was observed in test group 13 males of cohort 1A.

In the **F1 rearing animals, cohort 3 (Immunotoxicity)**, target organs were potentially spleen and thymus in male animals.

Absolute and relative weights of the spleen in test groups 11, 12 and 13 males were decreased without statistical significance and the relative thymus weight in test group 13 males was decreased significantly. However, similar weight changes occurred in cohort 1A without histopathological correlates. There were no findings in clinical chemistry. Therefore, the decrease of the spleen weights in test groups 11, 12 and 13 and the absolute thymus weight in test group 13 animals is regarded as an equivocal finding and as non-adverse.

No findings were observed in the **surplus F1-generation pups on PND 22 (F1 weanlings not selected for cohorts)**.

There were no indications from clinical examinations as well as gross and histopathology, that **DHDPS** adversely affected the **fertility or reproductive performance** of the F0 or F1 parental animals up to and including the highest administered dose of 180 mg/kg bw/d. Estrous cycle data, mating behavior, conception, gestation, parturition, lactation and weaning as well as sexual organ weights and gross and histopathological findings of these organs (including differential ovarian follicle counts in the F1 females) were comparable between the rats of all test groups and reflect a normal range of biological variation in rat (multi)generation studies.

Estrous cycle appeared to be marginally, but statistically, prolonged in the F0 high-dose females. However, as cycle length remained unchanged in F1A and F1B cohorts and a cycle length around 4 days is common in the rat, no relationship to the treatment is assumed.

Another notable finding was a slightly lower motility of the sperm in males of test groups 01, 02 and 03 (20, 60 and 180 mg/kg bw/d) compared to controls. However, the lowest value (84% motile sperm) exactly matched the control value in the F1 generation and the overall span of sperm motility in this study reflects a normal range of biological variation in rat (multi)generation studies. No dose-dependency was observed. Therefore, this statistically significant differences were regarded as incidental and not treatment-related.

For all liveborn male and female pups of the F0 and F1B parents, no test substance-induced signs of **developmental toxicity** were noted at dose levels as high as 20 mg/kg bw/d. In the mid- and high-dose F0 parents (60 and 180 mg/kg bw/d) as well as the high-dose F1B parents prenatal development of offspring was impaired as proven by a significantly higher rate of intrauterine mortality (postimplantation losses). This is considered to be treatment-related and adverse.

On the other hand, postnatal survival, pup body weight gain as well as post-weaning development of the offspring of these test groups until puberty remained unaffected by the test substance up to the high-dose level of 180 mg/kg bw/d. Furthermore, clinical and/or gross necropsy examinations of the F1 and F2 pups revealed no toxicologically relevant adverse findings.

Measurement of thyroid hormones revealed no effect caused by the test item, neither in the F0 parental animals nor in the F1 offspring.

Anogenital distance and anogenital index of all test substance treated F1 and F2 pups (20, 60 and 180 mg/kg bw/d) did not exhibit any effect related to the treatment. In addition, the check for the presence of nipples/areolas, also a very sensitive marker of potential endocrine-mediated imbalances, revealed no test substance-related effects at all.

Vaginal opening and preputial separation are commonly used developmental markers for **onset of puberty** in laboratory rats. No delays beyond a normal range of biological variation in rat (multi)generation studies which might be attributable to the treatment were noted in any of the test substance-treated groups.

There was no evidence that the test substance impaired **neuronal development and function** in the F1 offspring as demonstrated by the absence of relevant effects in a functional observation battery as well as automated motor activity, auditory startle and learning/memory testing. This is in good correlation to assessment of **neuropathology**, where brain weight determination, brain length and width measurements as well as brain morphometry and neuropathology examination by light microscopy did not reveal any neuropathological treatment-related adverse findings in Cohort 2A animals (adults, PND 77) and in Cohort 2B (weanlings, PND 22).

There was no evidence that the test substance produced any **developmental immunotoxicity**. Neither T-cell dependent anti-SRBC IgM antibody response, nor absolute and relative lymphocyte subpopulation cell counts in the spleen tissue (B-, T-lymphocytes, CD4-, CD8-T-lymphocytes and natural killer (NK) cells) displayed any treatment-related changes.

6. CONCLUSION

Under the conditions of the present modified extended 1-generation reproduction toxicity study the **NOAEL** (no observed adverse effect level) for **general, systemic toxicity** is 60 mg/kg bw/d for the F0 and F1 parental as well as adolescent animals, based on evidence for kidney toxicity, as well as corresponding effects on clinical-pathological parameters, which were observed at the LOAEL (Lowest Observed Adverse Effect Level) of 180 mg/kg bw/d.

The **NOAEL** for **fertility** and **reproductive performance** for the F0 and F1 parental rats is 180 mg/kg bw/d, the highest dose tested.

The **NOAEL** for **developmental toxicity** in the F1 and F2 progeny is 20 mg/kg bw/d, based on increased postimplantation loss in the F1 progeny, which was observed at the LOAEL (Lowest Observed Adverse Effect Level) of 60 mg/kg bw/d.

The **NOAEL** for **developmental neurotoxicity** for the F1 progeny is 180 mg/kg bw/d, the highest dose tested.

The **NOAEL** for **developmental immunotoxicity** for the F1 progeny is 180 mg/kg bw/d, the highest dose tested. Lower mean and median anti-SRBC IgM antibody titers of the positive control group (4.5 mg/kg bw/d cyclophosphamide, oral) demonstrated that the test system worked properly.

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8. APPENDIX

The following list contains abbreviations and definitions generally used in reports for this study type.

This report will not necessarily use all expressions listed below.

8.1. LIST OF ABBREVIATIONS USED IN TABLES IA AND IIA

DAY 0 GD	= day when sperm was detected in the vaginal smear of a mated female for the first time within a mating period
MEAN/M	= mean value
MG/KG BW/D	= milligram per kilogram body weight per day
N/#/No.	= number
F	= female
M	= male
P	= significance level
PPM	= parts per million
S.D.	= standard deviation
TOTAL	= total number
%	= per cent
Deviation Vs Control	= deviation versus control in percent
G	= gram
0	= no such finding / observation
-	= no animals examined
ms	= Milliseconds

All other abbreviations used are explained in the tables.

8.2. LIST OF ABBREVIATIONS USED IN TABLES IB AND IIB**CLINICAL PATHOLOGY:**

S.d.	= standard deviation
N	= number of values

HEMATOLOGY:

RBC	= red blood cells (erythrocytes)
HGB	= hemoglobin
HCT	= hematocrit
MCV	= mean corpuscular volume
MCH	= mean corpuscular hemoglobin
MCHC	= mean corpuscular hemoglobin concentration
RET	= reticulocytes
PLT	= platelets
HQT	= prothrombin time (Hepato Quick's test)
PTT	= activated partial thromboplastin time
QT	= prothrombin time (Quick's test)
WBC	= white blood cells (leukocytes)
NEUTA	= polymorphonuclear neutrophils (absolute)
LYMPHA	= lymphocytes (absolute)
MONOA	= monocytes (absolute)
EOSA	= eosinophils (absolute)
BASOA	= basophils (absolute)
LUCA	= large unstained cells (absolute)
NEUT	= polymorphonuclear neutrophils
LYMPH	= lymphocytes
MONO	= monocytes
EOS	= eosinophils
BASO	= basophils
LUC	= large unstained cells

CLINICAL CHEMISTRY:

ALT	= alanine aminotransferase
AST	= aspartate aminotransferase
ALP	= alkaline phosphatase
GGT_C	= serum- γ -glutamyltransferase
UREA	= urea
CREA	= creatinine
GLUC	= glucose
TBIL	= total bilirubin

TBA	=	bile acids
TPROT	=	total protein
ALB	=	albumin
GLOB	=	globulins
TRIG	=	triglycerides
CHOL	=	cholesterol
NA	=	sodium
K	=	potassium
CL	=	chloride
INP	=	inorganic phosphate
CA	=	Calcium

HORMONES:

T4	=	total thyroxine
TSH	=	thyroid-stimulating hormone

URINALYSIS:

pH/pH_C	=	pH value
PRO	=	protein
0	=	negative 0.25 g/L
1	=	0.75 g/L
2	=	1.5 g/L
3	=	5.00 g/L
PRO_C	=	for statistical calculation grade 0 + 1 is set grade 1
GLU	=	glucose
0	=	normal
1	=	3 mmol/L
2	=	6 mmol/L
3	=	17 mmol/L, 56 mmol/L
GLU_C	=	glucose
KET	=	ketones
0	=	negative
1	=	0.5 mmol/L, 1.5 mmol/L
2	=	5 mmol/L
3	=	15 mmol/L
KET_C	=	for statistical calculation grade 0 + 1 is set grade 1

UBG = urobilinogen
0 = normal
1 = 17 $\mu\text{mol/L}$
2 = 68 $\mu\text{mol/L}$
3 = 135 $\mu\text{mol/L}$, 203 $\mu\text{mol/L}$
UBG_C = for statistical calculation grade 0 + 1 is set grade 1

BIL = bilirubin
0 = negative
1 = 17 $\mu\text{mol/L}$
2 = 50 $\mu\text{mol/L}$
3 = 100 $\mu\text{mol/L}$
BIL_C = for statistical calculation grade 0 + 1 is set grade 1

BLOOD = blood (erythrocytes)
0 = negative
1 = 10 ery/ μL
2 = 25 ery/ μL , 50 ery/ μL
3 = 150 ery/ μL , 250 ery/ μL
BLOOD_C = for statistical calculation grade 0 + 1 is set grade 1

VOL = volume
SP.GR._C = specific gravity calculated with dilution factor

TURB = turbidity
c = clear
cl = cloudy

COL = color
y = yellow
dyl = dark yellow
ly = light yellow

SEDIMENT:

CRYST	= crystals
RENAL EC	= renal epithelial cells
TRANS EC	= transitional epithelial cells
SQUAM EC	= squamous epithelial cells
CASTS	= casts
ERY	= erythrocytes
LEUCO	= lymphocytes

0	= none
1	= few
2	= many
3	= masses

CRYST_C	= for statistical calculation grade 0 - 2 is set grade 2
RENAL EC_C	= for statistical calculation grade 0 + 1 is set grade 1
TRANS EC_C	= for statistical calculation grade 0 + 1 is set grade 1
SQUAM EC_C	= for statistical calculation grade 0 + 1 is set grade 1
CASTS_C	= casts
ERY_C	= for statistical calculation grade 0 + 1 is set grade 1
LEUCO_C	= for statistical calculation grade 0 + 1 is set grade 1

P	= triple phosphates
O	= calcium oxalates
C	= crystals of unknown origin
T	= tyrosine-like crystals
GCE	= granulated casts/epithelial casts
CE	= epithelial casts
V	= clusters

a	= macrohematuria
b	= slight macrohematuria
c	= epithelial scaling
d	= atypical epithelial cells
e	= degenerated epithelial cells
f	= squamous epithelial cells with some nuclei
g	= transitional epithelial cells with some nuclei
h	= caudate epithelial cells with some nuclei

HORMONES:

T4 = total thyroxine
TSH = thyroid stimulating hormone

LOQ = lowest quantifiable value

SPERM PARAMETERS:

MOTILE_C = motile sperms
TS/gT = total spermatids/gram testis
TS/gC = total sperms/gram cauda epididymis
ABNORMAL = abnormal sperms
_C

T-CELL DEPENDENT ANTIBODY RESPONSE:

SRBC = sheep red blood cell

SPLENIC LYMPHOCYTES SUBPOPULATIONS:

B_SPL = B lymphocytes in spleen
T_SPL = T lymphocytes in spleen
B/T_SPL = ratio B/T- lymphocytes in spleen
CD4_SPL = CD4+ lymphocytes in spleen
CD8_SPL = CD8+ lymphocytes in spleen
CD4/CD8_S = ratio CD4+/CD8+ lymphocytes in spleen
PL
NK_SPL = natural killer cells in spleen
BA_SPL = B lymphocytes in spleen (absolute)
TA_SPL = T lymphocytes in spleen (absolute)
CD4A_SPL = CD4+ lymphocytes in spleen (absolute)
CD8A_SPL = CD8+ lymphocytes in spleen (absolute)
NKA_SPL = natural killer cells in spleen (absolute)

UNITS:

mmol/L	= millimole/liter
μmol/L	= micromole/liter
nmol/L	= nanomole/liter
g/L	= gram/liter
μg/L	= microgram/liter
L/L	= liter/liter
%	= per cent
fmol	= femtomole = 10^{-15} mole
fL	= femtoliter = 10^{-15} liter
tera/L	= tera/liter = 10^{12} /liter
giga/L	= giga/liter = 10^9 /liter
μkat/L	= microkatal/liter
μkat/L E.	= microkatal/gram protein
μkat/g P.	= microkatal/liter
nkat/L	= nanokatal/liter
PPM	= parts per million
mg/kg	= mg/kilogram
mL	= milliliter
Mio/g	= millions/gram
U/mL	= units/milliliter

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8.3. LIST OF ABBREVIATIONS USED IN TABLES IC AND IIC

AI	=	Apoptotic index
A.-no.	=	animal number
BrdU	=	2'bromo-5-deoxyuridine
dev	=	deviation
exam	=	examined
F	=	female animals
F1	=	final sacrifice group
g	=	weight determination in grams
I1, I2 ...	=	satellite groups; animals selected for perfusion fixation in neurotoxicology studies
l	=	left
LI	=	Labeling index
M	=	male animals (under sex); mean value (on weight level)
mg	=	weight determination in milligrams
mg/m ³	=	milligram per cubic meter
mg/kg bw/day	=	milligram per kilogram body weight and day
ml	=	milliliter
n	=	number of values measured for the determination of mean value and standard deviation
ppm	=	parts per million
r	=	right
R1, R2 ...	=	recovery groups
s	=	suspect weight (not included in the mean values)
SD	=	standard deviation
TUNEL	=	Terminal deoxynucleotidyl transferase-mediated dUTP nick end-labelling
u	=	unilaterally weighed
u/a	=	not measureable
%	=	percentage related to the reference weight in relative organ weight calculations
.	=	for incidences of gross lesions: no gross finding in that organ

for incidences of microscopic findings:

- on organ level: not examined
- on finding level: no such finding observed

Codes for the status at necropsy:

- 1 (P) = planned sacrifice
2 (K) = killed moribund
3 (S) = spontaneous death

Codes used at finding level:

The codes are used for a grading system that takes into consideration either the severity or the number or the size of a microscopic finding.

	Severity	Number	Size
Grade 1	Minimal	Very few	Very small
Grade 2	Slight, mild	Few	Small
Grade 3	Moderate	Moderate number	Moderate size
Grade 4	Marked; severe	Many	Large
Grade 5	Massive; extreme	Extensive number	Extensive size

Whenever a grading was not used, the microscopic finding was indicated to be present (P).

IA- 1
04-Dec-2018 10:13
Ascentos™ 1.3

Study 90R0066/05R034

Summary - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 00/M 0 mg/kg bw/d	Test Group 01/M 20 mg/kg bw/d	Test Group 02/M 60 mg/kg bw/d	Test Group 03/M 180 mg/kg bw/d
Animals examined	N 24	24	24	24
Animals with signs	N 0	0	0	14
head	N 0	0	0	13
salivation				
normal	N 24	24	24	24
NAD				
eye	N 0	0	0	1
discolored				

day 0 [00:00 - 24:00] -> day 69 [00:00 - 24:00]

IA- 2
04-Dec-2018 10:16
Ascentos™ 1.3

Study 90R0066/05R034

Summary - Clinical Observation

Sex: Female - Phase: In-life

	Test Group 00/F		Test Group 01/F		Test Group 02/F		Test Group 03/F	
	0 mg/kg bw/d	24	20 mg/kg bw/d	24	60 mg/kg bw/d	24	180 mg/kg bw/d	24
Animals examined	N	24	N	24	N	24	N	24
Animals with signs	N	0	N	1	N	0	N	6
gait	N	0	N	1	N	0	N	0
unsteady gait	N	0	N	1	N	0	N	0
head	N	0	N	0	N	0	N	6
salivation	N	0	N	0	N	0	N	0
dead	N	0	N	1	N	0	N	0
sacrificed moribund	N	0	N	1	N	0	N	0
normal	N	24	N	24	N	24	N	24
NAD	N	24	N	24	N	24	N	24
eye	N	0	N	1	N	0	N	0
closed eyelid	N	0	N	1	N	0	N	0
nose	N	0	N	1	N	0	N	0
encrusted	N	0	N	1	N	0	N	0
skin	N	0	N	1	N	0	N	0
pale	N	0	N	1	N	0	N	0
general condition	N	0	N	1	N	0	N	0
hypothermia	N	0	N	1	N	0	N	0
poor	N	0	N	1	N	0	N	0
respiration	N	0	N	1	N	0	N	0
labored	N	0	N	1	N	0	N	0
abdominal	N	0	N	1	N	0	N	0
fur	N	0	N	1	N	0	N	0
piloerection	N	0	N	1	N	0	N	0

day 0 [00:00 - 24:00] -> day 69 [00:00 - 24:00]

IA- 3
04-Dec-2018 10:23
Ascentos™ 1.3

Study 90R0066/05R034

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 00/M 0 mg/kg bw/d	Test Group 01/M 20 mg/kg bw/d	Test Group 02/M 60 mg/kg bw/d	Test Group 03/M 180 mg/kg bw/d
Animals examined	N 24	24	24	24
Animals with signs	N 0	0	0	1
head	N 0	0	0	0
salivation				
normal	N 24	24	24	24
NAD				
eye	N 0	0	0	1
discolored				

day 0 -> 69
[-03:00-00:00]

IA- 4

04-Dec-2018 10:25

Ascentos™ 1.3

Study 90R0066/05R034

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 00/M 0 mg/kg bw/d	Test Group 01/M 20 mg/kg bw/d	Test Group 02/M 60 mg/kg bw/d	Test Group 03/M 180 mg/kg bw/d
Animals examined	N 24	24	24	24
Animals with signs	N 0	0	0	14
head	N 0	0	0	13
salivation				
normal	N 24	24	24	24
NAD				
eye	N 0	0	0	1
discolored				

day 0 -> 69
[00:00-02:00]

IA- 5
04-Dec-2018 10:25
Ascentos™ 1.3

Study 90R0066/05R034

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 00/M 0 mg/kg bw/d	Test Group 01/M 20 mg/kg bw/d	Test Group 02/M 60 mg/kg bw/d	Test Group 03/M 180 mg/kg bw/d
Animals examined	N 24	24	24	24
Animals with signs	N 0	0	0	1
head	N 0	0	0	0
salivation				
normal	N 24	24	24	24
NAD				
eye	N 0	0	0	1
discolored				

day 0 -> 69
[02:00-05:00]

IA- 6
04-Dec-2018 10:28
Ascentos™ 1.3

Study 90R0066/05R034

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: Female - Phase: In-life

		Test Group 00/F 0 mg/kg bw/d	Test Group 01/F 20 mg/kg bw/d	Test Group 02/F 60 mg/kg bw/d	Test Group 03/F 180 mg/kg bw/d
		N	24	24	24
	Animals examined	N			
	Animals with signs	N	1	0	0
	head	N	0	0	0
	salivation				
	normal	N	24	24	24
	NAD				
	respiration	N	1	0	0
	labored	N	0	0	0
	abdominal	N	1	0	0
	fur				
	piloerection	N	1	0	0

day 0 -> 69
[-03:00-00:00]

IA- 7
04-Dec-2018 10:30
Ascentos™ 1.3

Study 90R0066/05R034

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Female** - Phase: **In-life**

	Test Group 00/F 0 mg/kg bw/d	Test Group 01/F 20 mg/kg bw/d	Test Group 02/F 60 mg/kg bw/d	Test Group 03/F 180 mg/kg bw/d
Animals examined	N 24	24	24	24
Animals with signs	N 0	1	0	6
head	N 0	0	0	6
salivation				
normal	N 24	24	24	24
NAD				
respiration	N 0	1	0	0
labored	N 0	0	0	0
abdominal	N 0	1	0	0
fur				
piloerection	N 0	1	0	0

day 0 -> 69
[00:00-02:00]

IA- 8
04-Dec-2018 10:30
Ascentos™ 1.3

Study 90R0066/05R034

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Female** - Phase: **In-life**

	Test Group 00/F 0 mg/kg bw/d	Test Group 01/F 20 mg/kg bw/d	Test Group 02/F 60 mg/kg bw/d	Test Group 03/F 180 mg/kg bw/d
Animals examined	N 24	24	24	24
Animals with signs	N 0	1	0	0
head	N 0	0	0	0
salivation	N 0	0	0	0
normal	N 24	24	24	24
NAD	N 0	1	0	0
respiration	N 0	0	0	0
labored	N 0	0	0	0
abdominal	N 0	1	0	0
fur	N 0	1	0	0
piloerection	N 0	1	0	0

day 0 -> 69
[02:00-05:00]

4-DEC-18 05R034M0 MALES 009

TABLE : 1A-
PROJ. NO. 90R0066/05R034: MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - F0 MALES
SUMMARY OF MALE CLINICAL OBSERVATIONS

	GROUP#	WEEK OF STUDY					5. TOTAL
		0	1	2	3	4	
# OF ANIMALS EXAMINED	00	24	24	24	24	24	24
	01	24	24	24	24	24	24
	02	24	24	24	24	24	24
	03	24	24	24	24	24	24
NORMAL							
NOTHING ABNORMAL DETECTED	00	0	0	0	0	0	24 24
	01	0	0	0	0	0	24 24
	02	0	0	0	0	0	24 24
	03	0	0	0	0	0	23 23
NOTHING ABNORMAL DETECTED	00	24	24	24	24	16	24
BEFORE TREATMENT	01	24	24	24	24	16	24
	02	24	24	24	24	16	24
	03	23	23	23	23	15	23
NOTHING ABNORMAL DETECTED	00	24	24	24	24	16	24
AFTER TREATMENT (<2H)	01	24	24	24	24	16	24
	02	24	24	24	24	16	24
	03	23	22	22	23	13	23
NOTHING ABNORMAL DETECTED	00	24	24	24	24	16	24
AFTER TREATMENT (>2H<5H)	01	24	24	24	24	16	24
	02	24	24	24	24	16	24
	03	23	23	23	23	15	23
DEAD							
SCHEDULED SACRIFICE	00	0	0	0	0	0	24 24
	01	0	0	0	0	0	24 24
	02	0	0	0	0	0	24 24
	03	0	0	0	0	0	24 24
EYES							
EYE(S) DISCOLORED	00	0	0	0	0	0	0 0
	01	0	0	0	0	0	0 0
	02	0	0	0	0	0	0 0
	03	0	0	0	0	0	1 1

4-DEC-18	05R034M0	MALES	PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - F0 MALES SUMMARY OF MALE CLINICAL OBSERVATIONS										TABLE : 1A-	010
			GROUP#	WEEK OF STUDY					5 TOTAL					
				0	1	2	3	4						
# OF ANIMALS EXAMINED			00	24	24	24	24	24	24	24				
			01	24	24	24	24	24	24	24				
			02	24	24	24	24	24	24	24				
			03	24	24	24	24	24	24	24				
EYE(S) DISCOLORED BEFORE TREATMENT			00	0	0	0	0	0	0	0				
			01	0	0	0	0	0	0	0				
			02	0	0	0	0	0	0	0				
			03	1	1	1	1	1	1	1				
EYE(S) DISCOLORED AFTER TREATMENT (<2H)			00	0	0	0	0	0	0	0				
			01	0	0	0	0	0	0	0				
			02	0	0	0	0	0	0	0				
			03	1	1	1	1	1	1	1				
EYE(S) DISCOLORED AFTER TREATMENT (>2H<5H)			00	0	0	0	0	0	0	0				
			01	0	0	0	0	0	0	0				
			02	0	0	0	0	0	0	0				
			03	1	1	1	1	1	1	1				
ORAL-BUCCAL SALIVATION AFTER TREATMENT (<2H)			00	0	0	0	0	0	0	0				
			01	0	0	0	0	0	0	0				
			02	0	0	0	0	0	0	0				
			03	18	15	17	13	13	2	19				

4-DEC-18 05R034F0 PROJ. NO. 90R0066/05R034: MOD. EXTENDED ONE-GENERATION REPRODUCTION TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - F0 FEMALES
TABLE : 1A- 011

FEMALES SUMMARY OF FEMALE CLINICAL OBSERVATIONS (EXCEPT GESTATION AND LACTATION PERIODS)

	GROUP#	WEEK OF STUDY							TOTAL
		0	1	2	3	4	5	6	
# OF ANIMALS EXAMINED	00	24	0	0	0	1	1	24	24
	01	23	0	0	0	2	2	23	23
	02	24	0	0	0	0	0	24	24
	03	24	0	0	0	1	1	24	24
NORMAL									
NOTHING ABNORMAL DETECTED	00	0	-	-	-	0	0	0	24
	01	0	-	-	-	0	0	0	23
	02	0	-	-	-	-	0	0	24
	03	0	-	-	-	0	0	0	24
NOTHING ABNORMAL DETECTED BEFORE TREATMENT	00	13	-	-	-	1	1	24	24
	01	17	-	-	-	2	2	23	23
	02	18	-	-	-	-	-	24	24
	03	18	-	-	-	1	1	24	24
NOTHING ABNORMAL DETECTED AFTER TREATMENT (<2H)	00	13	-	-	-	1	1	24	24
	01	17	-	-	-	2	2	23	23
	02	18	-	-	-	-	-	24	24
	03	17	-	-	-	1	1	24	24
NOTHING ABNORMAL DETECTED AFTER TREATMENT (>2H<5H)	00	13	-	-	-	1	1	24	24
	01	17	-	-	-	2	2	23	23
	02	18	-	-	-	-	-	24	24
	03	18	-	-	-	1	1	24	24
DEAD									
SCHEDULED SACRIFICE	00	0	-	-	-	0	0	0	24
	01	0	-	-	-	0	0	0	23
	02	0	-	-	-	-	0	0	24
	03	0	-	-	-	0	0	0	24
MISCELLANEOUS									
SPERM IN VAGINAL SMEAR (DAY 0 P.C. FOR F1)	00	24	-	-	-	0	0	0	0
	01	23	-	-	-	0	0	0	23
	02	24	-	-	-	-	-	0	0
	03	24	-	-	-	0	0	0	24

4-DEC-18 05R034F0 012
TABLE : 1A-

PROJ. NO. 90R0066/05R034: MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - FO FEMALES
SUMMARY OF FEMALE CLINICAL OBSERVATIONS (EXCEPT GESTATION AND LACTATION PERIODS)

	GROUP#	WEEK OF STUDY							TOTAL
		0	1	2	3	4	5	6	
# OF ANIMALS EXAMINED	00	24	0	0	0	1	1	24	24
	01	23	0	0	0	2	2	23	23
	02	24	0	0	0	0	0	24	24
	03	24	0	0	0	1	1	24	24
ORAL-BUCAL									
SALIVATION AFTER TREATMENT (<2H)	00	0	-	-	-	0	0	0	0
	01	0	-	-	-	0	0	0	0
	02	0	-	-	-	-	-	0	0
	03	1	-	-	-	0	0	0	3
SKIN/FUR									
SKIN LESION: GROIN REGION BEFORE TREATMENT	00	1	-	-	-	0	0	0	1
	01	0	-	-	-	0	0	0	0
	02	0	-	-	-	-	-	0	0
	03	0	-	-	-	0	0	0	0
SKIN LESION: GROIN REGION AFTER TREATMENT (<2H)	00	1	-	-	-	0	0	0	1
	01	0	-	-	-	0	0	0	0
	02	0	-	-	-	-	-	0	0
	03	0	-	-	-	0	0	0	0
SKIN LESION: GROIN REGION AFTER TREATMENT (>2H<5H)	00	1	-	-	-	0	0	0	1
	01	0	-	-	-	0	0	0	0
	02	0	-	-	-	-	-	0	0
	03	0	-	-	-	0	0	0	0

4-DEC-18

05R034L1

TABLE : IA-013

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX.STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF MATERNAL CLINICAL OBSERVATIONS DURING GESTATION

DAY OF GESTATION

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	TOTAL
--	---	---	---	---	---	---	---	---	---	---	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	-------

OF FEMALES EXAMINED

NORMAL

Category	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99
NOTHING DETECTED	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99
NOTHING ABNORMAL	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99
BEFORE TREATMENT	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99

Category	Count
NOTHING ABNORMAL DETECTED	00
AFTER TREATMENT (<2H)	01

	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99
NOTHING ABNORMAL DETECTED	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99
AFTER TREATMENT (>2H<5H)	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99

MISCELLANEOUS

[illegible]

ORAL-BUCCAL

[illegible]

SKIN/FUR

[illegible]

4-DEC-18

05R034L1

TABLE : 1A- 014

PROJ.NO.: 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF MATERNAL CLINICAL OBSERVATIONS DURING GESTATION

GROUP#	DAY OF GESTATION																										
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	TOTAL
# OF FEMALES EXAMINED	00	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	22	2	1	1	1	1
	01	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	22	3	2	2	2	2
	02	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	23	1	0	0	0	0
	03	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	23	2	1	1	1	1
SKIN LESION: GROIN REGION AFTER TREATMENT (<2H)	00	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	1
	01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SKIN LESION: GROIN REGION AFTER TREATMENT (>2H<5H)	00	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	1
	01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	03	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

4-DEC-18

05R034I1

TABLE : IA- 015

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF MATERNAL/POP CLINICAL OBSERVATIONS DURING LACTATION

	GROUP#	DAY OF LACTATION																					TOTAL	
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		21
# OF FEMALES EXAMINED	00	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	
	01	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	
	02	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	
	03	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	
NORMAL																								
NOTHING ABNORMAL DETECTED	00	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	
	01	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	
	02	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	
	03	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	
NOTHING ABNORMAL DETECTED BEFORE TREATMENT	00	22	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	
	01	16	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	
	02	22	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	
	03	19	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	
NOTHING ABNORMAL DETECTED AFTER TREATMENT (<2H)	00	22	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	
	01	16	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	
	02	22	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	
	03	18	21	22	22	21	22	22	22	23	23	23	21	23	22	22	23	23	23	22	22	22	23	
NOTHING ABNORMAL DETECTED AFTER TREATMENT (>2H<5H)	00	22	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	
	01	16	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	21	
	02	22	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	
	03	19	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	
ORAL-BUCCAL																								
SALIVATION AFTER TREATMENT (<2H)	00	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	03	1	2	1	1	2	1	0	1	1	0	0	0	2	0	1	1	0	0	0	1	1	1	3

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04-Dec-2018 11:11
Ascentos™ 1.3

Study 90R0066/05R034

Summary Water Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 00/M 0 mg/kg bw/d	Test Group 01/M 20 mg/kg bw/d	Test Group 02/M 60 mg/kg bw/d	Test Group 03/M 180 mg/kg bw/d
d 0 -> 3	Mean [g]	24.5 n	24.8	24.5	26.3
	S.d.	1.5	1.0	1.7	1.9
	N	8	8	8	8
	Deviation Vs Control [%]		1.1	0.0	7.3
d 7 -> 10	Mean [g]	28.4 n	28.0	28.9	32.7 **
	S.d.	2.0	2.5	2.0	2.5
	N	8	8	8	8
	Deviation Vs Control [%]		-1.5	1.7	14.8
d 14 -> 17	Mean [g]	29.5 n	30.0	31.4	35.4 **
	S.d.	2.3	2.7	3.5	2.4
	N	8	8	8	8
	Deviation Vs Control [%]		1.9	6.6	20.2
d 21 -> 24	Mean [g]	29.7 n	30.6	31.1	36.2 **
	S.d.	2.6	3.2	3.5	3.9
	N	8	8	8	8
	Deviation Vs Control [%]		2.8	4.6	21.7
d 28 -> 31	Mean [g]	30.2 n	31.6	33.3	36.7 **
	S.d.	1.8	4.2	3.7	3.1
	N	8	8	8	8
	Deviation Vs Control [%]		4.4	10.0	21.5

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Ascentos™ 1.3

Study 90R0066/05R034

Summary Water Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 00/M 0 mg/kg bw/d	Test Group 01/M 20 mg/kg bw/d	Test Group 02/M 60 mg/kg bw/d	Test Group 03/M 180 mg/kg bw/d
d 35 -> 38	Mean [g]	31.0 n	31.9	32.4	35.9
	S.d.	2.1	3.6	6.2	3.1
	N	8	8	8	8
	Deviation Vs Control [%]		3.0	4.5	15.7
d 42 -> 45	Mean [g]	31.7 n	31.7	33.8	36.0
	S.d.	4.2	4.1	3.9	2.2
	N	8	8	8	8
	Deviation Vs Control [%]		-0.1	6.5	13.4
d 49 -> 52	Mean [g]	32.7 n	33.8	35.3	37.2
	S.d.	3.6	3.7	4.2	3.1
	N	8	8	8	8
	Deviation Vs Control [%]		3.4	7.9	13.7
d 56 -> 59	Mean [g]	31.7 n	33.0	33.8	37.1 *
	S.d.	4.1	3.5	3.5	2.7
	N	8	8	8	8
	Deviation Vs Control [%]		4.3	6.6	17.1
d 63 -> 66	Mean [g]	32.1 n	35.0	35.0	37.8 *
	S.d.	4.6	3.4	4.7	2.7
	N	8	8	8	8
	Deviation Vs Control [%]		9.2	9.2	18.0

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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Ascentos™ 1.3

Study 90R0066/05R034

Summary Water Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 00/F 0 mg/kg bw/d	Test Group 01/F 20 mg/kg bw/d	Test Group 02/F 60 mg/kg bw/d	Test Group 03/F 180 mg/kg bw/d
d 0 -> 3	Mean [g]	15.0 n	16.3	16.6	16.6 *
	S.d.	0.9	1.4	0.7	1.7
	N	8	8	8	8
	Deviation Vs Control [%]		8.3	10.3	10.6
d 7 -> 10	Mean [g]	17.5 n	19.2	19.1	19.5
	S.d.	1.0	2.1	0.8	2.3
	N	8	8	8	8
	Deviation Vs Control [%]		10.3	9.4	11.5
d 14 -> 17	Mean [g]	17.9 n	19.4	19.4	20.7 *
	S.d.	1.5	1.9	0.9	2.5
	N	8	8	8	8
	Deviation Vs Control [%]		8.7	8.5	15.9
d 21 -> 24	Mean [g]	18.6 n	21.0	20.0	22.0 **
	S.d.	1.5	2.2	1.6	2.9
	N	8	8	8	8
	Deviation Vs Control [%]		12.9	7.3	18.1
d 28 -> 31	Mean [g]	18.7 n	21.0	20.9	22.8 **
	S.d.	1.4	2.3	1.7	3.1
	N	8	8	8	8
	Deviation Vs Control [%]		12.6	11.7	21.9

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Ascentos™ 1.3

Study 90R0066/05R034

Summary Water Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 00/F 0 mg/kg bw/d	Test Group 01/F 20 mg/kg bw/d	Test Group 02/F 60 mg/kg bw/d	Test Group 03/F 180 mg/kg bw/d
d 35 -> 38	Mean [g]	20.4 n	22.3	21.4	23.6 *
	S.d.	1.4	2.8	1.9	3.4
	N	8	8	8	8
	Deviation Vs Control [%]		9.4	4.9	15.8
d 42 -> 45	Mean [g]	20.2 n	22.4	21.9	23.6 *
	S.d.	1.5	3.1	1.1	2.8
	N	8	8	8	8
	Deviation Vs Control [%]		10.6	8.2	16.9
d 49 -> 52	Mean [g]	21.6 n	23.5	22.4	24.6
	S.d.	1.5	3.9	0.9	3.6
	N	8	8	8	8
	Deviation Vs Control [%]		8.8	3.7	14.1
d 56 -> 59	Mean [g]	20.0 n	23.1	23.2	24.9 *
	S.d.	1.3	3.9	2.0	4.3
	N	8	8	8	8
	Deviation Vs Control [%]		15.8	16.2	24.5
d 63 -> 66	Mean [g]	21.7 n	23.7	23.7	25.4 *
	S.d.	1.8	3.1	1.3	3.5
	N	8	8	8	8
	Deviation Vs Control [%]		9.2	9.2	17.1

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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05R034I1

TABLE : IA- 020

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
MEAN MATERNAL WATER CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

DAYS	0 TO 1	TEST GROUP 00			TEST GROUP 01			TEST GROUP 02			TEST GROUP 03		
		0 MG/KG BW/D			20 MG/KG BW/D			60 MG/KG BW/D			180 MG/KG BW/D		
DAYS 0 TO 1		MEAN	18.2 D		18.3			19.1			19.2		
		S.D.	3.78		3.65			4.50			6.09		
		N	23		21			24			23		
DAYS 3 TO 4		MEAN	24.3 D		27.7			27.0			29.6*		
		S.D.	5.51		3.95			4.18			4.65		
		N	12		8			8			9		
DAYS 7 TO 8		MEAN	24.4 D		23.3			26.7			26.8		
		S.D.	5.53		4.57			4.03			7.29		
		N	23		21			24			23		
DAYS 10 TO 11		MEAN	28.0 D		29.1			29.7			30.4		
		S.D.	5.68		7.40			6.29			8.05		
		N	23		21			23			23		
DAYS 14 TO 15		MEAN	28.8 D		29.4			33.2			35.8**		
		S.D.	4.72		6.24			5.79			8.60		
		N	22		21			24			22		
DAYS 17 TO 18		MEAN	35.6 D		40.5*			43.6**			45.7**		
		S.D.	5.10		7.02			7.38			6.82		
		N	23		21			24			23		
DAYS 19 TO 20		MEAN	34.8 D		37.3			40.7**			42.5**		
		S.D.	5.00		7.08			7.74			5.71		
		N	23		21			24			23		

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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05R034I1

TABLE : IA- 021

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
MEAN MATERNAL WATER CONSUMPTION DURING LACTATION -- GRAMS/ANIMAL/DAY

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
DAYS 1 TO 2	MEAN	40.3 D	35.8	43.0	40.5
	S.D.	6.27	10.69	10.20	8.74
	N	23	21	24	23
DAYS 4 TO 5	MEAN	55.7 D	55.1	62.2	62.9
	S.D.	9.66	10.58	12.88	10.44
	N	23	21	24	23
DAYS 7 TO 8	MEAN	70.7 D	68.9	73.1	70.2
	S.D.	12.55	16.07	16.06	12.57
	N	23	19	24	23
DAYS 10 TO 11	MEAN	70.5 D	64.6	75.6	73.4
	S.D.	13.20	14.84	14.94	14.08
	N	23	21	24	22
DAYS 14 TO 15	MEAN	81.1 D	81.0	85.1	77.8
	S.D.	13.28	14.94	17.65	14.27
	N	23	21	24	23
DAYS 17 TO 18	MEAN	84.7 D	87.6	96.5	87.8
	S.D.	12.92	23.22	21.99	20.20
	N	23	21	24	23
DAYS 20 TO 21	MEAN	123.3 D	132.1	134.6	127.7
	S.D.	15.64	27.58	22.85	20.86
	N	23	21	24	23

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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Study 90R0066/05R034

Summary Food Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 00/M 0 mg/kg bw/d	Test Group 01/M 20 mg/kg bw/d	Test Group 02/M 60 mg/kg bw/d	Test Group 03/M 180 mg/kg bw/d
d 0 -> 7	Mean [g]	23.6 n	23.5	23.9	24.7
	S.d.	0.9	1.2	1.3	1.6
	N	8	8	8	8
	Deviation Vs Control [%]		-0.5	1.3	4.6
d 7 -> 14	Mean [g]	26.2 n	25.6	26.7	27.8
	S.d.	1.2	1.8	1.5	1.4
	N	8	8	8	8
	Deviation Vs Control [%]		-2.3	1.9	6.1
d 14 -> 21	Mean [g]	27.7 n	28.0	28.8	30.0
	S.d.	1.4	2.6	1.4	2.0
	N	8	8	8	8
	Deviation Vs Control [%]		1.3	3.8	8.3
d 21 -> 28	Mean [g]	28.8 n	29.5	30.9	29.9
	S.d.	2.8	3.0	4.9	2.5
	N	8	8	8	8
	Deviation Vs Control [%]		2.3	7.4	3.8

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Study 90R0066/05R034

Summary Food Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 00/M 0 mg/kg bw/d	Test Group 01/M 20 mg/kg bw/d	Test Group 02/M 60 mg/kg bw/d	Test Group 03/M 180 mg/kg bw/d
d 28 -> 35	Mean [g]	28.3 n	29.1	29.4	30.7
	S.d.	1.4	3.2	1.5	2.4
	N	8	8	8	8
	Deviation Vs Control [%]		2.9	3.9	8.4
d 35 -> 42	Mean [g]	28.5 n	29.2	30.2	30.9
	S.d.	2.0	3.5	3.0	2.7
	N	8	8	8	8
	Deviation Vs Control [%]		2.5	5.9	8.5
d 42 -> 49	Mean [g]	28.3 n	29.5	30.6	29.4
	S.d.	2.0	3.8	2.9	2.3
	N	8	8	8	8
	Deviation Vs Control [%]		4.3	8.0	4.0
d 49 -> 56	Mean [g]	28.3 n	29.3	30.8	30.6
	S.d.	1.6	2.7	2.7	3.2
	N	8	8	8	8
	Deviation Vs Control [%]		3.4	8.8	8.0

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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Ascentos™ 1.3

Study 90R0066/05R034

Summary Food Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 00/M 0 mg/kg bw/d	Test Group 01/M 20 mg/kg bw/d	Test Group 02/M 60 mg/kg bw/d	Test Group 03/M 180 mg/kg bw/d
d 56 -> 63	Mean [g]	28.6 n	29.1	30.1	29.9
	S.d.	2.2	3.4	2.8	2.8
	N	8	8	8	8
	Deviation Vs Control [%]		1.7	5.0	4.4
d 63 -> 69	Mean [g]	28.5 n	29.9	31.3	30.8
	S.d.	1.6	3.8	3.9	3.0
	N	8	8	8	8
	Deviation Vs Control [%]		5.1	9.8	8.2
d 0 -> 69	Mean [g]	27.7 n	28.3	29.2	29.5
	S.d.	1.5	2.5	2.1	2.1
	N	8	8	8	8
	Deviation Vs Control [%]		2.1	5.6	6.4

Statistic Profile = Dunnett test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
n=DUNNETT; d = day

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Study 90R0066/05R034

Summary Food Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 00/F 0 mg/kg bw/d	Test Group 01/F 20 mg/kg bw/d	Test Group 02/F 60 mg/kg bw/d	Test Group 03/F 180 mg/kg bw/d
d 0 -> 7	Mean [g]	14.1 n	14.7	15.3 *	14.9
	S.d.	0.4	0.9	0.8	1.1
	N	8	8	8	8
	Deviation Vs Control [%]		4.3	8.8	6.2
d 7 -> 14	Mean [g]	15.1 n	15.6	16.2	16.0
	S.d.	0.6	0.8	1.0	1.5
	N	8	8	8	8
	Deviation Vs Control [%]		2.8	7.1	5.8
d 14 -> 21	Mean [g]	16.3 n	16.9	17.3	19.7 *
	S.d.	0.8	0.9	0.9	5.1
	N	8	8	8	8
	Deviation Vs Control [%]		3.5	5.8	20.7
d 21 -> 28	Mean [g]	16.8 n	17.4	18.2	21.7 *
	S.d.	1.4	0.9	1.6	6.3
	N	8	8	8	8
	Deviation Vs Control [%]		3.6	7.9	28.8

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Study 90R0066/05R034

Summary Food Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 00/F 0 mg/kg bw/d	Test Group 01/F 20 mg/kg bw/d	Test Group 02/F 60 mg/kg bw/d	Test Group 03/F 180 mg/kg bw/d
d 28 -> 35	Mean [g]	16.7 n	17.9	19.2 *	21.2 **
	S.d.	1.1	1.3	1.5	3.2
	N	8	8	8	7
	Deviation Vs Control [%]		7.1	14.4	26.8
d 35 -> 42	Mean [g]	18.6 n	17.8	20.4	20.5
	S.d.	2.3	1.3	4.2	2.1
	N	8	8	8	8
	Deviation Vs Control [%]		-4.5	9.3	10.3
d 42 -> 49	Mean [g]	17.4 n	18.0	19.1	22.6 **
	S.d.	1.1	1.4	1.5	3.6
	N	8	8	8	8
	Deviation Vs Control [%]		3.3	9.9	29.9
d 49 -> 56	Mean [g]	17.9 n	18.6	19.5	21.7
	S.d.	1.3	2.1	3.2	5.2
	N	8	8	8	8
	Deviation Vs Control [%]		4.1	9.4	21.7

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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Study 90R0066/05R034

Summary Food Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 00/F 0 mg/kg bw/d	Test Group 01/F 20 mg/kg bw/d	Test Group 02/F 60 mg/kg bw/d	Test Group 03/F 180 mg/kg bw/d
d 56 -> 63	Mean [g]	18.3 n	18.4	20.2	21.6 *
	S.d.	2.4	1.9	1.9	1.9
	N	8	8	8	6
	Deviation Vs Control [%]		0.4	10.3	18.3
d 63 -> 69	Mean [g]	17.8 n	18.7	19.5	24.3 **
	S.d.	1.6	1.8	2.0	5.1
	N	8	8	8	8
	Deviation Vs Control [%]		4.8	9.7	36.2
d 0 -> 69	Mean [g]	16.9 n	17.4	18.5	19.8 **
	S.d.	0.9	1.2	1.5	1.7
	N	8	8	8	6
	Deviation Vs Control [%]		2.8	9.3	17.2

Statistic Profile = Dunnett test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
n=DUNNETT; d = day

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05R034I1

TABLE : IA- 028

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
DAYS 0 TO 7	MEAN	21.8 D	22.7	22.5	21.8
	S.D.	2.06	2.77	1.93	2.87
	N	23	21	24	23
DAYS 7 TO 14	MEAN	23.2 D	23.9	23.7	23.6
	S.D.	2.12	2.32	1.95	2.32
	N	23	21	24	23
DAYS 14 TO 20	MEAN	25.2 D	26.1	26.6*	27.1**
	S.D.	1.83	2.02	2.28	2.08
	N	23	21	24	23
DAYS 0 TO 20	MEAN OF MEANS	23.4	24.2	24.3	24.2
	S.D.	1.70	1.75	2.13	2.67
	N	3	3	3	3

Statistics: D=Dunnnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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TABLE : IA- 029

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
MEAN MATERNAL FOOD CONSUMPTION DURING LACTATION -- GRAMS/ANIMAL/DAY

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
DAYS 1 TO 4	MEAN	40.8 D	37.7	42.0	39.3
	S.D.	4.85	6.20	6.27	6.37
	N	23	21	24	23
DAYS 4 TO 7	MEAN	51.3 D	49.9	53.5	52.5
	S.D.	4.22	5.50	5.72	4.75
	N	23	21	24	23
DAYS 7 TO 10	MEAN	61.4 D	58.7	62.7	60.8
	S.D.	5.13	7.62	7.43	7.78
	N	23	21	24	23
DAYS 10 TO 14	MEAN	66.9 D	65.5	68.7	66.7
	S.D.	5.33	7.67	7.04	7.37
	N	23	21	24	23
DAYS 14 TO 17	MEAN	68.4 D	68.2	69.7	68.5
	S.D.	4.95	9.24	9.83	7.73
	N	23	21	24	23
DAYS 17 TO 19	MEAN	72.2 D	73.6	77.8	75.3
	S.D.	5.54	10.44	9.54	9.41
	N	23	21	24	23
DAYS 19 TO 21	MEAN	90.5 D	93.4	93.9	92.6
	S.D.	7.12	15.21	11.81	11.85
	N	23	21	24	23
DAYS 1 TO 21	MEAN OF MEANS	64.5	63.9	66.9	65.1
	S.D.	15.83	17.78	16.70	16.93
	N	7	7	7	7

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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Ascentos™ 1.3

Study 90R0066/05R034

Summary Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

		Test Group 00/M 0 mg/kg bw/d	Test Group 01/M 20 mg/kg bw/d	Test Group 02/M 60 mg/kg bw/d	Test Group 03/M 180 mg/kg bw/d
day 0	Mean	188.4 n	187.9	188.6	190.0
	S.d.	8.7	10.4	9.0	8.6
	N	24	24	24	24
	Deviation Vs Control [%]		-0.3	0.1	0.9
day 7	Mean	251.3 n	248.3	252.1	255.9
	S.d.	13.5	15.4	13.3	13.5
	N	24	24	24	24
	Deviation Vs Control [%]		-1.2	0.3	1.8
day 14	Mean	309.1 n	305.0	312.0	316.3
	S.d.	20.8	22.3	15.3	19.1
	N	24	24	24	24
	Deviation Vs Control [%]		-1.3	0.9	2.3
day 21	Mean	350.9 n	347.2	357.1	358.8
	S.d.	27.4	38.4	17.4	27.5
	N	24	24	24	24
	Deviation Vs Control [%]		-1.1	1.8	2.2
day 28	Mean	383.1 n	378.1	389.0	389.2
	S.d.	32.3	40.9	21.1	35.5
	N	24	24	24	24
	Deviation Vs Control [%]		-1.3	1.5	1.6

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

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04-Dec-2018 11:49
Ascentos™ 1.3

Study 90R0066/05R034

Summary Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

		Test Group 00/M 0 mg/kg bw/d	Test Group 01/M 20 mg/kg bw/d	Test Group 02/M 60 mg/kg bw/d	Test Group 03/M 180 mg/kg bw/d
day 35	Mean	408.1n	401.8	409.9	410.8
	S.d.	36.7	47.6	23.5	40.5
	N	24	24	24	24
	Deviation Vs Control [%]		-1.5	0.4	0.7
day 42	Mean	433.4n	426.7	435.5	434.4
	S.d.	39.5	52.4	27.0	44.1
	N	24	24	24	24
	Deviation Vs Control [%]		-1.5	0.5	0.2
day 49	Mean	453.1n	444.3	454.7	450.2
	S.d.	43.9	56.6	29.5	45.3
	N	24	24	24	24
	Deviation Vs Control [%]		-1.9	0.3	-0.6
day 56	Mean	472.0n	460.5	471.6	465.2
	S.d.	44.9	59.9	32.3	46.7
	N	24	24	24	24
	Deviation Vs Control [%]		-2.4	-0.1	-1.4
day 63	Mean	490.9n	482.5	487.1	479.1
	S.d.	45.1	63.6	33.6	51.3
	N	24	24	24	24
	Deviation Vs Control [%]		-1.7	-0.8	-2.4

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

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04-Dec-2018 11:50

Ascentos™ 1.3

Study 90R0066/05R034

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 00/F 0 mg/kg bw/d	Test Group 01/F 20 mg/kg bw/d	Test Group 02/F 60 mg/kg bw/d	Test Group 03/F 180 mg/kg bw/d
day 0	Mean	115.3 n	115.9	116.5	115.3
	S.d.	5.1	6.4	6.1	5.7
	N	24	24	24	24
	Deviation Vs Control [%]		0.5	1.0	0.0
day 7	Mean	141.3 n	144.8	148.3 *	145.2
	S.d.	6.2	9.1	10.2	8.6
	N	24	24	24	24
	Deviation Vs Control [%]		2.5	5.0	2.8
day 14	Mean	162.8 n	169.9	172.4 *	169.6
	S.d.	11.7	12.7	12.0	11.7
	N	24	24	24	24
	Deviation Vs Control [%]		4.3	5.9	4.2
day 21	Mean	184.5 n	192.6	193.3	190.7
	S.d.	14.9	15.9	14.2	13.1
	N	24	24	24	24
	Deviation Vs Control [%]		4.4	4.8	3.4
day 28	Mean	199.7 n	208.0	209.5	208.5
	S.d.	16.1	18.0	16.4	16.2
	N	24	24	24	24
	Deviation Vs Control [%]		4.2	4.9	4.4

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

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04-Dec-2018 11:51

Ascentos™ 1.3

Study 90R0066/05R034

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 00/F 0 mg/kg bw/d	Test Group 01/F 20 mg/kg bw/d	Test Group 02/F 60 mg/kg bw/d	Test Group 03/F 180 mg/kg bw/d
day 35	Mean	209.5 n	218.3	218.8	214.7
	S.d.	17.3	20.8	17.3	17.1
	N	24	24	24	24
	Deviation Vs Control [%]		4.2	4.5	2.5
day 42	Mean	225.5 n	234.0	235.2	233.2
	S.d.	21.8	23.2	18.3	18.5
	N	24	24	24	24
	Deviation Vs Control [%]		3.8	4.3	3.4
day 49	Mean	233.2 n	242.0	240.6	238.6
	S.d.	20.1	22.3	18.5	18.7
	N	24	24	24	24
	Deviation Vs Control [%]		3.8	3.1	2.3
day 56	Mean	240.5 n	249.5	246.4	245.6
	S.d.	19.6	23.8	18.2	19.7
	N	24	24	24	24
	Deviation Vs Control [%]		3.7	2.4	2.1
day 63	Mean	249.1 n	259.0	258.1	256.4
	S.d.	22.1	25.5	19.4	19.4
	N	24	24	24	24
	Deviation Vs Control [%]		4.0	3.6	2.9

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

4-DEC-18
05R034M0
TABLE : IA- 034

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - F0 MALES
MEAN PARENTAL BODY WEIGHTS -- GRAMS

WEEK		TEST GROUP 00			TEST GROUP 01			TEST GROUP 02			TEST GROUP 03		
		0 MG/KG BW/D			20 MG/KG BW/D			60 MG/KG BW/D			180 MG/KG BW/D		
		MEAN			MEAN			MEAN			MEAN		
		S.D.			S.D.			S.D.			S.D.		
		N			N			N			N		
WEEK	0		492.5 D		487.2			488.4			478.7		
			47.15		63.18			36.06			47.75		
			24		24			24			24		
WEEK	1		512.6 D		505.2			508.4			497.6		
			50.67		66.89			37.40			50.00		
			24		24			24			24		
WEEK	2		523.0 D		513.9			520.1			506.9		
			51.13		68.50			38.88			52.06		
			24		24			24			24		
WEEK	3		535.6 D		524.5			532.9			519.8		
			54.14		72.05			40.59			54.86		
			24		24			24			24		
WEEK	4		545.2 D		538.2			548.8			532.7		
			55.70		75.22			41.42			56.26		
			24		24			24			24		
WEEK	5		544.1 D		535.9			563.7			551.7		
			61.23		76.02			44.08			60.36		
			16		16			16			16		

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034I1

TABLE : IA- 035

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
MEAN MATERNAL BODY WEIGHTS DURING GESTATION -- GRAMS

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
DAY 0	MEAN	256.2 D	262.9	261.9	257.5
	S.D.	22.97	23.32	18.42	21.51
	N	23	21	24	23
DAY 7	MEAN	289.2 D	295.8	295.5	288.8
	S.D.	24.88	25.89	18.32	22.29
	N	23	21	24	23
DAY 14	MEAN	323.6 D	329.9	329.5	323.4
	S.D.	25.68	27.40	20.90	24.03
	N	23	21	24	23
DAY 20	MEAN	402.4 D	403.6	405.6	398.0
	S.D.	30.60	34.67	26.89	30.36
	N	23	21	24	23

Statistics: D=Dunnett-test (two-sided)
* : $p \leq 0.05$ ** : $p \leq 0.01$

4-DEC-18

05R034I1

TABLE : IA- 036

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
MEAN MATERNAL BODY WEIGHTS DURING LACTATION -- GRAMS

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
DAY 0	MEAN	300.8 D	310.9	310.2	304.7
	S.D.	23.61	23.24	22.94	30.07
	N	23	21	24	23
DAY 1	MEAN	300.8 D	305.4	307.7	296.9
	S.D.	24.57	26.65	15.97	25.54
	N	23	21	24	23
DAY 4	MEAN	316.7 D	318.3	326.1	319.3
	S.D.	25.67	24.99	15.87	22.00
	N	23	21	24	23
DAY 7	MEAN	319.0 D	323.4	327.7	324.8
	S.D.	24.09	22.84	25.12	20.37
	N	23	21	24	23
DAY 10	MEAN	336.2 D	337.4	344.2	340.9
	S.D.	22.21	23.52	16.16	23.84
	N	23	21	24	23
DAY 14	MEAN	333.4 D	340.1	344.0	336.3
	S.D.	20.91	17.95	18.64	21.57
	N	23	21	24	23
DAY 17	MEAN	330.0 D	334.6	333.9	334.8
	S.D.	20.70	27.82	23.82	20.86
	N	23	21	24	23
DAY 19	MEAN	320.7 D	327.9	332.7	331.2
	S.D.	18.79	19.62	18.25	20.98
	N	23	21	24	23
DAY 21	MEAN	316.6 D	324.8	327.8	322.5
	S.D.	20.98	20.58	19.54	19.67
	N	23	21	24	23

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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04-Dec-2018 12:02

Ascentos™ 1.3

Study 90R0066/05R034

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

	Test Group 00/M			Test Group 01/M			Test Group 02/M			Test Group 03/M		
	0 mg/kg bw/d			20 mg/kg bw/d			60 mg/kg bw/d			180 mg/kg bw/d		
d 0 -> 7	Mean	62.9 n		60.4			63.5			65.9		
	S.d.	7.9		7.5			5.4			7.2		
	N	24		24			24			24		
d 7 -> 14	Mean	57.8 n		56.6			59.8			60.4		
	S.d.	10.0		8.2			6.3			8.1		
	N	24		24			24			24		
d 14 -> 21	Mean	41.8 n		42.2			45.1			42.5		
	S.d.	7.9		13.1			7.7			12.3		
	N	24		24			24			24		
d 21 -> 28	Mean	32.2 n		30.9			32.0			30.5		
	S.d.	7.3		9.2			6.7			11.0		
	N	24		24			24			24		
d 28 -> 35	Mean	24.9 n		23.8			20.9			21.5		
	S.d.	6.4		9.3			5.4			7.3		
	N	24		24			24			24		
d 35 -> 42	Mean	25.3 n		24.9			25.7			23.6		
	S.d.	5.2		7.5			6.3			7.5		
	N	24		24			24			24		
d 42 -> 49	Mean	19.7 n		17.6			19.2			15.8		
	S.d.	7.3		6.6			6.4			5.8		
	N	24		24			24			24		

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Ascentos™ 1.3

Study 90R0066/05R034

Summary Changes Body Weights - BW / Body Weights [g]

Sex: **Male** - Phase: **In-life**

		Test Group 00/M		Test Group 01/M		Test Group 02/M		Test Group 03/M	
		0 mg/kg bw/d		20 mg/kg bw/d		60 mg/kg bw/d		180 mg/kg bw/d	
d 49 -> 56	Mean	18.9 n		16.2		16.9		15.0	
	S.d.	5.1		5.7		6.3		6.3	
	N	24		24		24		24	
d 56 -> 63	Mean	18.9 n		22.0		15.4		13.9 *	
	S.d.	3.9		6.5		6.2		8.8	
	N	24		24		24		24	
d 0 -> 63	Mean	302.5 n		294.6		298.4		289.1	
	S.d.	41.1		58.1		31.5		48.8	
	N	24		24		24		24	

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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04-Dec-2018 12:05

Ascentos™ 1.3

Study 90R0066/05R034

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 00/F 0 mg/kg bw/d	Test Group 01/F 20 mg/kg bw/d	Test Group 02/F 60 mg/kg bw/d	Test Group 03/F 180 mg/kg bw/d
d 0 -> 7	Mean	26.0 n	29.0	31.8 **	29.9
	S.d.	5.0	6.7	7.0	7.6
	N	24	24	24	24
d 7 -> 14	Mean	21.6 n	25.1	24.1	24.4
	S.d.	8.3	5.7	5.7	7.1
	N	24	24	24	24
d 14 -> 21	Mean	21.6 n	22.7	20.8	21.1
	S.d.	4.3	4.8	4.4	4.7
	N	24	24	24	24
d 21 -> 28	Mean	15.2 n	15.3	16.2	17.8
	S.d.	4.8	4.9	5.6	5.7
	N	24	24	24	24
d 28 -> 35	Mean	9.8 n	10.4	9.3	6.2
	S.d.	6.7	5.9	5.6	5.8
	N	24	24	24	24
d 35 -> 42	Mean	16.0 n	15.7	16.4	18.5
	S.d.	7.1	7.3	5.2	5.9
	N	24	24	24	24
d 42 -> 49	Mean	7.7 n	8.0	5.3	5.4
	S.d.	5.6	5.5	6.0	5.1
	N	24	24	24	24

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Ascentos™ 1.3

Study 90R0066/05R034

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 00/F 0 mg/kg bw/d	Test Group 01/F 20 mg/kg bw/d	Test Group 02/F 60 mg/kg bw/d	Test Group 03/F 180 mg/kg bw/d
d 49 -> 56	Mean	7.3 n	7.4	5.8	6.9
	S.d.	6.3	7.1	5.5	6.1
	N	24	24	24	24
d 56 -> 63	Mean	8.6 n	9.5	11.7	10.8
	S.d.	8.0	5.2	5.7	5.5
	N	24	24	24	24
d 0 -> 63	Mean	133.8 n	143.1	141.6	141.0
	S.d.	21.3	22.6	17.6	19.2
	N	24	24	24	24

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

4-DEC-18
05R034M0
TABLE : IA- 041

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - F0 MALES
MEAN PARENTAL BODY WEIGHT CHANGE -- GRAMS

MALES

		TEST GROUP 00		TEST GROUP 01		TEST GROUP 02		TEST GROUP 03	
		0 MG/KG BW/D		20 MG/KG BW/D		60 MG/KG BW/D		180 MG/KG BW/D	
WEEK	0 TO 1	MEAN	20.0 D	MEAN	18.0	MEAN	20.0	MEAN	19.0
		S.D.	7.06	S.D.	7.25	S.D.	9.14	S.D.	7.71
		N	24	N	24	N	24	N	24
WEEK	1 TO 2	MEAN	10.5 D	MEAN	8.7	MEAN	11.8	MEAN	9.2
		S.D.	5.38	S.D.	5.45	S.D.	6.74	S.D.	9.32
		N	24	N	24	N	24	N	24
WEEK	2 TO 3	MEAN	12.6 D	MEAN	10.6	MEAN	12.8	MEAN	12.9
		S.D.	5.59	S.D.	6.02	S.D.	6.31	S.D.	6.13
		N	24	N	24	N	24	N	24
WEEK	3 TO 4	MEAN	9.6 D	MEAN	13.7	MEAN	15.9**	MEAN	12.9
		S.D.	6.67	S.D.	6.82	S.D.	5.78	S.D.	6.32
		N	24	N	24	N	24	N	24
WEEK	4 TO 5	MEAN	7.2 D	MEAN	6.0	MEAN	5.7	MEAN	10.6
		S.D.	4.68	S.D.	5.67	S.D.	5.56	S.D.	7.43
		N	16	N	16	N	16	N	16
WEEK	0 TO 5	MEAN	58.1 D	MEAN	56.7	MEAN	68.3	MEAN	66.6
		S.D.	15.87	S.D.	15.95	S.D.	15.67	S.D.	18.07
		N	16	N	16	N	16	N	16

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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05R034I1

TABLE : IA- 042

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
DAYS 0 TO 7	MEAN	33.0 D	32.8	33.6	31.3
	S.D.	8.38	7.19	6.43	6.27
	N	23	21	24	23
DAYS 7 TO 14	MEAN	34.4 D	34.1	34.0	34.6
	S.D.	7.74	5.50	5.35	4.89
	N	23	21	24	23
DAYS 14 TO 20	MEAN	78.7 D	73.7	76.1	74.6
	S.D.	9.59	14.24	12.60	14.63
	N	23	21	24	23
DAYS 0 TO 20	MEAN	146.1 D	140.6	143.8	140.5
	S.D.	13.13	19.34	16.80	19.39
	N	23	21	24	23

Statistics: D=Dunnett-test (two-sided)
* : $p \leq 0.05$ ** : $p \leq 0.01$

4-DEC-18

05R034I1

TABLE : IA- 043

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
MEAN MATERNAL BODY WEIGHT CHANGE DURING LACTATION -- GRAMS

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
DAYS 0 TO 1	MEAN	0.0 D	-5.5	-2.5	-7.8
	S.D.	7.43	11.57	14.92	12.94
	N	23	21	24	23
DAYS 1 TO 4	MEAN	15.8 D	12.9	18.4	22.5
	S.D.	6.61	8.81	6.35	14.20
	N	23	21	24	23
DAYS 4 TO 7	MEAN	2.3 D	5.2	1.6	5.4
	S.D.	13.36	16.14	17.38	14.36
	N	23	21	24	23
DAYS 7 TO 10	MEAN	17.3 D	13.9	16.5	16.1
	S.D.	13.73	13.27	17.18	17.47
	N	23	21	24	23
DAYS 10 TO 14	MEAN	-2.9 D	2.7	-0.3	-4.6
	S.D.	10.95	17.17	10.43	14.84
	N	23	21	24	23
DAYS 14 TO 17	MEAN	-3.3 D	-5.4	-10.1	-1.5
	S.D.	11.87	16.32	22.28	12.97
	N	23	21	24	23
DAYS 17 TO 19	MEAN	-9.4 D	-6.8	-1.2	-3.6
	S.D.	10.65	17.75	18.97	11.67
	N	23	21	24	23
DAYS 19 TO 21	MEAN	-4.1 D	-3.1	-5.0	-8.7
	S.D.	11.15	15.48	10.78	12.04
	N	23	21	24	23
DAYS 0 TO 21	MEAN	15.8 D	13.9	17.6	17.8
	S.D.	16.58	17.06	19.26	19.38
	N	23	21	24	23

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034DC

MALES

TABLE : 1A-

044

PROJ. NO. 90R0066/05R034:MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - DCO (MALE AND FEMALE)
SUMMARY OF MALE CLINICAL OBSERVATIONS

	GROUP#	WEEK OF STUDY														TOTAL
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	
# OF ANIMALS EXAMINED	00	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	01	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	02	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	03	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
NORMAL																
NOTHING ABNORMAL DETECTED	00	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	01	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	02	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	03	24	24	24	24	24	24	24	24	24	24	23	23	23	23	24
EYES																
EYE(S) DISCOLORED	00	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	01	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	02	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	03	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1

4-DEC-18		TABLE : 1A-															045	
05R034DC		PROJ. NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - DCO (MALE AND FEMALE) SUMMARY OF FEMALE CLINICAL OBSERVATIONS																
FEMALES																		

4-DEC-18

05R034F0

TABLE : 1A- 046

PROJ.NO. 90R0066/05R034:MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - F0 FEMALES
SUMMARY OF MEAN ESTROUS CYCLE DURATION

	TEST GROUP 00 0 MG/KG BW/D	TEST GROUP 01 20 MG/KG BW/D	TEST GROUP 02 60 MG/KG BW/D	TEST GROUP 03 180 MG/KG BW/D
MEAN# OF DAYS FROM ESTRUS TO ESTRUS	3.9 D	3.9	3.9	4.1*
S.D.	0.10	0.26	0.14	0.22
N	24	24	24	24

Statistics: D=Dunnett-test (two-sided)
* : $p \leq 0.05$ ** : $p \leq 0.01$

4-DEC-18

05R034I1

TABLE : 1A- 047

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)

SUMMARY OF COHABITATION DATA

	TEST GROUP 00 0 MG/KG BW/D	TEST GROUP 01 20 MG/KG BW/D	TEST GROUP 02 60 MG/KG BW/D	TEST GROUP 03 180 MG/KG BW/D
Males placed with females	N 24	23	24	24
mated (A)	N 24 F	23	24	24
male mating index (B)	% 100	100	100	100
did not mate	N 0 F	0	0	0
	% 0.0	0.0	0.0	0.0
with females pregnant (C)	N 23 F	21	24	23
male fertility index (D)	% 96	91	100	96
without females pregnant	N 1 F	2	0	1
	% 4.2	8.7	0.0	4.2

Statistics: F=Fisher's exact test (two-sided)

* : p<=0.05 ** : p<=0.01

(A) DEFINED BY A FEMALE WITH VAGINAL SPERM, OR THAT GAVE BIRTH TO A LITTER, OR WITH PUPS/IMPLANTATIONS IN UTERO

(B) MALE MATING INDEX = NUMBER OF MALES WITH CONFIRMED MATINGS

NUMBER OF MALES PLACED WITH FEMALES X 100

(C) DEFINED BY A FEMALE GIVING BIRTH TO A LITTER, OR WITH PUPS/IMPLANTATIONS IN UTERO

(D) MALE FERTILITY INDEX = NUMBER OF MALES PROVING THEIR FERTILITY X 100

NUMBER OF MALES PLACED WITH FEMALES

4-DEC-18

05R034I1

TABLE : IA- 048

PROJ.NO.: 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF FEMALE REPRODUCTION AND DELIVERY DATA

		TEST GROUP 00 0 MG/KG BW/D	TEST GROUP 01 20 MG/KG BW/D	TEST GROUP 02 60 MG/KG BW/D	TEST GROUP 03 180 MG/KG BW/D
Females on Study	N	24	23	24	24
Females Mated	N	24Fi	23	24	24
Female Mating Index	%	100	100	100	100
Mating days until day 0 pc	MEAN	2.0 D	2.3	2.2	2.3
	S.D.	1.00	1.06	0.93	1.04
	N	24	23	24	24
days 1 to 4	N	24	23	24	24
	%	100	100	100	100
days 5 to 8	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
days 9 to 14	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
days 15 to 21	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Females Pregnant	N	23Fi	21	24	23
Female Fertility Index	%	96	91	100	96
Duration of Gestation (Days)	MEAN	22.0 D	22.0	22.0	22.0
	S.D.	0.37	0.32	0.29	0.30
Implantation sites	TOTAL	353	310	357	328
	MEAN	15.3 D	14.8	14.9	14.3
	S.D.	1.90	3.56	2.68	3.14
	N	23	21	24	23
Postimplantation Loss	TOTAL	11	16	32	35
	MEAN	0.5 D	0.8	1.3*	1.5**
	S.D.	0.67	0.89	0.92	1.62
	N	23	21	24	23
% Postimplantation Loss	MEAN	3.1 D	5.9	9.4*	10.5**
	S.D.	4.31	7.70	7.23	10.86
	N	23	21	24	23

Statistics: D=Dunnett-test (two-sided) Fi =Fisher's exact test (one-sided)

* : p<=0.05 ** : p<=0.01

THE INDICES ARE DEFINED IN THE TEXT

4-DEC-18

05R034I1

TABLE : IA- 049

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF FEMALE REPRODUCTION AND DELIVERY DATA

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
Females with Liveborn Gestation Index	N %	23Fi 100	21 100	24 100	23 100
with Stillborn Pups	N %	2Fi 8.7	4 19	2 8.3	4 17
with all Stillborn	N %	0Fi 0.0	0 0.0	0 0.0	0 0.0
Pups Delivered	MEAN	14.9 D	14.0	13.5	12.7
	S.D.	1.94	3.66	2.86	3.33
	TOTAL	342	294	325	293
Liveborn	N	340Fi	289	322	285*
Live Birth Index	%	99	98	99	97
Stillborn	N	2Fi	5	3	8*
	%	0.6	1.7	0.9	2.7

Statistics: D=Dunnett-test (two-sided) Fi =Fisher's exact test (one-sided)

* : p<=0.05 ** : p<=0.01

THE INDICES ARE DEFINED IN THE TEXT

4-DEC-18

05R034I1

TABLE : IA- 050

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)

SUMMARY OF LITTER DATA

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
(Total Number of) Litters	N	23	21	24	23
Litters with Liveborn Pups	N	23Fi	21	24	23
	%	100	100	100	100
Litters with Stillborn Pups	N	2Fi	4	2	4
	%	8.7	19	8.3	17
Litters with all Stillborn Pups	N	0Fi	0	0	0
	%	0.0	0.0	0.0	0.0
Pups Delivered	TOTAL	342	294	325	293
	MEAN	14.9 D	14.0	13.5	12.7
	S.D.	1.94	3.66	2.86	3.33
Pups Liveborn	N	340Fi	289	322	285*
	%	99	98	99	97
Pups Stillborn	N	2Fi	5	3	8*
	%	0.6	1.7	0.9	2.7
Pups Died	N	3Fi	6	1	4
	%	0.9	2.0	0.3	1.4
Pups Sacrificed Moribund	N	0Fi	0	0	0
	%	0.0	0.0	0.0	0.0
Pups Cannibalized	N	2Fi	4	3	0
	%	0.6	1.4	0.9	0.0
Pups Accidental Death	N	0	0	1	0
	%	0.0	0.0	0.3	0.0
Pups Sacrificed, Maternal Death	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Pups Culled day 4	N	106	83	86	62
	%	31	28	26	21

Statistics: D=Dunnett-test (two-sided) Fi =Fisher's exact test (one-sided)

* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034I1

TABLE : 1A- 051

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF LITTER DATA

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
Pups dead day 0	N %	1 0.3	1 0.3	0 0.0	0 0.0
days 1 to 4	N %	3 0.9	8 2.8	3 0.9	2 0.7
days 5 to 7	N %	0 0.0	0 0.0	0 0.0	0 0.0
days 8 to 14	N %	0 0.0	0 0.0	0 0.0	0 0.0
days 15 to 21	N %	1 0.3	0 0.0	1 0.3	1 0.4
Pups Surviving days 0 to 4	N	336Fi	280	319	283
Viability Index	%	99	97	99	99
Pups Surviving days 4 to 21	N	229Fi	197	232	220
Lactation Index	%	100	100	100	100

Statistics: Fi = Fisher's exact test (one-sided)

* : p<=0.05 ** : p<=0.01

THE INDICES ARE DEFINED IN THE TEXT. Pups Dead = Pups Died + Sacrificed Moribund + Cannibalized

4-DEC-18	05R034L1	TABLE : 1A-				052
PROJ. NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER) SUMMARY OF LITTER DATA						
		TEST GROUP 00 0 MG/KG BW/D	TEST GROUP 01 20 MG/KG BW/D	TEST GROUP 02 60 MG/KG BW/D	TEST GROUP 03 180 MG/KG BW/D	
Live Pups/Litter						
day 1	MEAN	14.7	13.5	13.4	12.4	
	S.D.	1.92	3.66	2.89	3.29	
	TOTAL	338	283	321	285	
day 4 (preculling)	MEAN	14.6	13.3	13.3	12.3	
	S.D.	1.92	3.67	2.88	3.21	
	TOTAL	336	280	319	283	
day 4 (postculling)	MEAN	10.0	9.4	9.7	9.6	
	S.D.	0.00	1.83	1.04	1.47	
	TOTAL	230	197	233	221	
day 7	MEAN	10.0	9.4	9.7	9.6	
	S.D.	0.00	1.83	1.04	1.47	
	TOTAL	230	197	233	221	
day 14	MEAN	10.0	9.4	9.7	9.6	
	S.D.	0.00	1.83	1.04	1.47	
	TOTAL	230	197	233	221	
day 21	MEAN	10.0	9.4	9.7	9.6	
	S.D.	0.21	1.83	1.05	1.47	
	TOTAL	229	197	232	220	
Sex Ratio						
day 0	%					
- live Males	%	53.8	51.6	46.9	47.7	
- live Females	%	46.2	48.4	53.1	52.3	
day 21	%					
- live Males	%	50.2	50.3	47.4	49.1	
- live Females	%	49.8	49.7	52.6	50.9	
SELECTED AS PARENT/RAISED						
males	N	74	64	64	64	
females	N	74	64	63	63	

4-DEC-18

05R034I1

TABLE : IA- 053

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY - PRESENCE OF AREOLAS/NIPPLES

	TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
	0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
AREOLAS/NIPPLES				
Litters tested	23	21	24	23
Pups tested	116	99	111	109
Pups reaching criteria	77	71	76	70
%	66	72	68	64
Pups reaching criteria/litter	67.8W	71.4	67.8	65.9
MEAN%				
S.D.	30.26	31.69	32.16	27.63

Statistics: Wt =Wilcoxon-test (one-sided)

* : p<=0.05 ** : p<=0.01

4-DEC-18 05R034L1 TABLE : IA- 054

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY - PRESENCE OF AREOLAS/NIPPLES

	TEST GROUP 00 0 MG/KG BW/D	TEST GROUP 01 20 MG/KG BW/D	TEST GROUP 02 60 MG/KG BW/D	TEST GROUP 03 180 MG/KG BW/D
AREOLAS/NIPPLES - SECOND OBS				
Litters tested	23	21	24	23
Pups tested	116	99	110	108
Pups reaching criteria	0	0	0	0
%	0.0	0.0	0.0	0.0
Pups reaching criteria/litter	0.071	0.0	0.0	0.0
MEAN%	0.00	0.00	0.00	0.00
S.D.				

Statistics: Wt =Wilcoxon-test (one-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034I1

TABLE : IA- 055

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF PUP BODY WEIGHTS -- GRAMS

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
day 1 males	MEAN	7.1 D	7.4	7.7*	7.7
	S.D.	0.52	0.76	0.74	0.76
	N	23	21	24	23
day 1 females	MEAN	6.7 D	7.0	7.2*	7.3*
	S.D.	0.46	0.83	0.69	0.74
	N	23	21	24	23
day 1 males+females	MEAN	6.9 D	7.2	7.5*	7.5*
	S.D.	0.49	0.78	0.69	0.75
	N	23	21	24	23
day 4 males preculling	MEAN	10.3 D	10.8	11.5**	11.3*
	S.D.	0.84	1.55	1.24	1.16
	N	23	21	24	23
day 4 females preculling	MEAN	9.8 D	10.2	10.9*	10.8*
	S.D.	0.83	1.77	1.12	1.17
	N	23	21	24	23
day 4 males+females preculling	MEAN	10.1 D	10.5	11.1*	11.1*
	S.D.	0.83	1.67	1.13	1.19
	N	23	21	24	23
day 4 males postculling	MEAN	10.5 D	10.9	11.5*	11.4*
	S.D.	0.80	1.53	1.19	1.15
	N	23	21	24	23
day 4 females postculling	MEAN	9.9 D	10.3	10.9*	10.9*
	S.D.	0.83	1.71	1.13	1.11
	N	23	21	24	23
day 4 males+females postculling	MEAN	10.2 D	10.6	11.2*	11.2*
	S.D.	0.80	1.62	1.11	1.14
	N	23	21	24	23

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034I1

TABLE : IA- 056

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF PUP BODY WEIGHTS -- GRAMS

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
day 7 males	MEAN	16.9 D	17.5	18.3*	17.7
	S.D.	1.31	2.23	1.52	1.17
	N	23	21	24	23
day 7 females	MEAN	16.1 D	16.6	17.3*	16.8
	S.D.	1.29	2.55	1.40	1.04
	N	23	21	24	23
day 7 males+females	MEAN	16.5 D	17.1	17.8*	17.3
	S.D.	1.28	2.39	1.39	1.09
	N	23	21	24	23
day 14 males	MEAN	33.4 D	34.5	35.3	33.8
	S.D.	2.52	4.31	2.24	1.60
	N	23	21	24	23
day 14 females	MEAN	32.1 D	33.2	33.9	32.9
	S.D.	2.32	4.61	2.12	1.82
	N	23	21	24	23
day 14 males+females	MEAN	32.8 D	33.8	34.5	33.5
	S.D.	2.38	4.44	2.07	1.68
	N	23	21	24	23
day 21 males	MEAN	54.0 D	56.8	57.4*	55.7
	S.D.	4.13	6.25	3.19	3.06
	N	23	21	24	23
day 21 females	MEAN	52.0 D	54.3	54.8*	53.7
	S.D.	3.55	5.67	2.95	3.31
	N	23	21	24	23
day 21 males+females	MEAN	53.0 D	55.5	56.0*	54.7
	S.D.	3.74	5.77	2.88	3.09
	N	23	21	24	23

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18		TABLE : IA-		057	
05R034L1		PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION TOX.STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) FO FEMALES (L1 LITTER) SUMMARY OF PUP BODY WEIGHT CHANGES -- GRAMS			
		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
DAYS 1 TO 4					
males	MEAN	3.2 D	3.4	3.8*	3.7*
	S.D.	0.49	0.90	0.69	0.62
	N	23	21	24	23
females	MEAN	3.1 D	3.2	3.6*	3.5
	S.D.	0.49	1.07	0.61	0.61
	N	23	21	24	23
males+females	MEAN	3.1 D	3.3	3.7*	3.6
	S.D.	0.48	0.99	0.62	0.61
	N	23	21	24	23
DAYS 4 TO 7					
males	MEAN	6.4 D	6.6	6.8	6.2
	S.D.	0.80	0.89	0.65	0.50
	N	23	21	24	23
females	MEAN	6.2 D	6.3	6.4	6.0
	S.D.	0.81	0.98	0.67	0.54
	N	23	21	24	23
males+females	MEAN	6.3 D	6.5	6.6	6.1
	S.D.	0.79	0.93	0.67	0.49
	N	23	21	24	23
DAYS 7 TO 14					
males	MEAN	16.5 D	17.0	17.0	16.2
	S.D.	1.54	2.32	1.16	1.45
	N	23	21	24	23
females	MEAN	16.1 D	16.5	16.5	16.1
	S.D.	1.52	2.27	1.11	1.27
	N	23	21	24	23
males+females	MEAN	16.3 D	16.8	16.7	16.2
	S.D.	1.50	2.26	1.09	1.21
	N	23	21	24	23
Statistics: D=Dunnett-test (two-sided) * : p<=0.05 ** : p<=0.01					

Statistics: D=Punnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034I1

TABLE : 1A- 058

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF PUP BODY WEIGHT CHANGES -- GRAMS

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
DAYS 14 TO 21	males	MEAN	20.6 D	22.3	22.1
		S.D.	2.11	2.48	1.85
		N	23	21	24
					23
	females	MEAN	19.8 D	21.2*	21.0
		S.D.	1.63	1.98	1.78
		N	23	21	24
					23
	males+females	MEAN	20.3 D	21.7*	21.2
		S.D.	1.75	2.04	1.69
		N	23	21	24
					23
DAYS 4 TO 21	males	MEAN	43.7 D	45.9	44.4
		S.D.	3.72	4.92	2.69
		N	23	21	24
					23
	females	MEAN	42.2 D	44.1	43.9
		S.D.	3.19	4.14	2.45
		N	23	21	24
					23
	males+females	MEAN	43.0 D	45.0	43.6
		S.D.	3.33	4.31	2.74
		N	23	21	24
					23

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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05R034L1
TABLE : IA- 059

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF PUP ANOGENITAL DISTANCE

AG DIST DAY 1 of Male Pups	UNITS: MM	TEST GROUP 00 0 MG/KG BW/D			TEST GROUP 01 20 MG/KG BW/D			TEST GROUP 02 60 MG/KG BW/D			TEST GROUP 03 180 MG/KG BW/D		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
		3.59	0.240	23	3.67	0.298	21	3.61	0.305	24	3.63	0.256	23

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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05R034L1

TABLE : IA- 060

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF PUP ANOGENITAL DISTANCE

AG DIST DAY 1	UNITS: MM	TEST GROUP 00			TEST GROUP 01			TEST GROUP 02			TEST GROUP 03		
		0 MG/KG BW/D			20 MG/KG BW/D			60 MG/KG BW/D			180 MG/KG BW/D		
of Female Pups	MEAN	1.72 D			1.78			1.78			1.79		
	S.D.	0.129			0.221			0.118			0.133		
	N	23			21			24			23		

Statistics: D=Dunnett-test (two-sided)
* : $p \leq 0.05$ ** : $p \leq 0.01$

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05R034I1

TABLE : IA- 061

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF POP ANOGENITAL INDEX (FORMULA WITH CUBIC ROOT)

AG DIST DAY 1 of Male Pups	to BODY WEIGHT RATIO (AG Index)	TEST GROUP 00 0 MG/KG BW/D			TEST GROUP 01 20 MG/KG BW/D			TEST GROUP 02 60 MG/KG BW/D			TEST GROUP 03 180 MG/KG BW/D		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
		1.87 D	0.102	23	1.88	0.128	21	1.83	0.141	24	1.85	0.149	23

Statistics: D=Dunnett-test (two-sided)
* : $p \leq 0.05$ ** : $p \leq 0.01$

4-DEC-18

05R034I1

TABLE : IA- 062

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF POP ANOGENITAL INDEX (FORMULA WITH CUBIC ROOT)

AG DIST DAY 1 of Female Pups	TEST GROUP 00 0 MG/KG BW/D		TEST GROUP 01 20 MG/KG BW/D		TEST GROUP 02 60 MG/KG BW/D		TEST GROUP 03 180 MG/KG BW/D	
	MEAN	N	MEAN	N	MEAN	N	MEAN	N
	0.91 D	23	0.93	21	0.92	24	0.93	23
	0.068		0.091		0.068		0.068	

Statistics: D=Dunnett-test (two-sided)
* : $p \leq 0.05$ ** : $p \leq 0.01$

4-DEC-18

05R034I1

TABLE : IA- 063

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)

SUMMARY OF PUP NECROPSY OBSERVATIONS

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
Litters Evaluated	N	23	20	24	23
Pups Evaluated	N	152	122	154	125
Live	N	150	117	151	117
Stillborn	N	2	5	3	8
POST MORTEM AUTOLYSIS					
Pup Incidence	N	0	1	0	1
	%	0.0	0.8	0.0	0.8
Litter Incidence	N	0Fi	1	0	1
	%	0.0	5.0	0.0	4.3
Affected Pups/Litter	MEAN%	0.0Wi	1.0	0.0	1.4
	S.D.	0.00	4.47	0.00	6.95
EYE(S) DISCOLORED					
Pup Incidence	N	0	0	1	0
	%	0.0	0.0	0.6	0.0
Litter Incidence	N	0Fi	0	1	0
	%	0.0	0.0	4.2	0.0
Affected Pups/Litter	MEAN%	0.0Wi	0.0	0.7	0.0
	S.D.	0.00	0.00	3.40	0.00
EMPTY STOMACH					
Pup Incidence	N	2	1	0	0
	%	1.3	0.8	0.0	0.0
Litter Incidence	N	2Fi	1	0	0
	%	8.7	5.0	0.0	0.0
Affected Pups/Litter	MEAN%	1.3Wi	0.6	0.0	0.0
	S.D.	4.25	2.48	0.00	0.00

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)

* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034L1

TABLE : IA- 064

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)

SUMMARY OF PUP NECROPSY OBSERVATIONS

		TEST GROUP 00	TEST GROUP 01	TEST GROUP 02	TEST GROUP 03
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
Litters Evaluated	N	23	20	24	23
Pups Evaluated	N	152	122	154	125
Live	N	150	117	151	117
Stillborn	N	2	5	3	8
HEMORRHAGIC TESTIS					
Pup Incidence	N	0	0	1	0
	%	0.0	0.0	0.6	0.0
Litter Incidence	N	0Fi	0	1	0
	%	0.0	0.0	4.2	0.0
Affected Pups/Litter	MEAN%	0.0Wi	0.0	0.4	0.0
	S.D.	0.00	0.00	1.86	0.00
TOTAL PUP NECROPSY OBSERVATIONS					
Pup Incidence	N	2	2	2	1
	%	1.3	1.6	1.3	0.8
Litter Incidence	N	2Fi	2	2	1
	%	8.7	10	8.3	4.3
Affected Pups/Litter	MEAN%	1.3Wi	1.6	1.1	1.4
	S.D.	4.25	5.00	3.80	6.95

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)

* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034I1

TABLE : IA- 065

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF SEXUAL MATURATION DATA (CUMULATED VALUE)

		TEST GROUP 00 0 MG/KG BW/D	TEST GROUP 01 20 MG/KG BW/D	TEST GROUP 02 60 MG/KG BW/D	TEST GROUP 03 180 MG/KG BW/D
VAGINAL OPENING	Pups reaching criteria				
Pups tested	N	64	64	64	64
day 28	N %	0 F 0.0	0 0.0	0 0.0	4 6.3
day 29	N %	6 F 9.4	1 1.6	4 6.3	6 9.4
day 30	N %	10 F 16	8 13	8 13	15 23
day 31	N %	22 F 34	18 28	22 34	28 44
day 32	N %	37 F 58	31 48	39 61	43 67
day 33	N %	52 F 81	34** 53	45 70	51 80
day 34	N %	57 F 89	43** 67	54 84	56 88
day 35	N %	59 F 92	57 89	60 94	59 92
day 36	N %	62 F 97	59 92	62 97	63 98
day 37	N %	63 F 98	61 95	63 98	63 98
day 38	N %	64 F 100	63 98	63 98	63 98
day 40	N %	64 F 100	64 100	63 98	63 98

Statistics: F=Fisher's exact test (two-sided)

* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034I1

TABLE : IA- 066

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF SEXUAL MATURATION DATA (CUMULATED VALUE)

	TEST GROUP 00 0 MG/KG BW/D	TEST GROUP 01 20 MG/KG BW/D	TEST GROUP 02 60 MG/KG BW/D	TEST GROUP 03 180 MG/KG BW/D
days to criterion	32.3 D MEAN 1.95 S.D. 64 N	33.2* 2.34 S.D. 64 N	32.3 1.85 S.D. 63 N	31.8 2.00 S.D. 63 N
body weight at criterion	105.8 D MEAN 9.00 S.D. 23 N	112.6* 11.05 S.D. 21 N	113.4* 8.84 S.D. 24 N	109.9 8.19 S.D. 23 N

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18
05R034I1
TABLE : IA-
067

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF SEXUAL MATURATION DATA (CUMULATED VALUE)

		TEST GROUP 00 0 MG/KG BW/D	TEST GROUP 01 20 MG/KG BW/D	TEST GROUP 02 60 MG/KG BW/D	TEST GROUP 03 180 MG/KG BW/D
PREPUTIAL SEPARATION	Pups reaching criteria				
Pups tested	N	64	64	64	64
day 38	N %	0 F 0.0	1 1.6	2 3.1	0 0.0
day 39	N %	5 F 7.8	5 7.8	8 13	1 1.6
day 40	N %	17 F 27	11 17	20 31	8 13
day 41	N %	26 F 41	21 33	26 41	22 34
day 42	N %	30 F 47	29 45	32 50	29 45
day 43	N %	34 F 53	35 55	39 61	38 59
day 44	N %	45 F 70	49 77	50 78	45 70
day 45	N %	54 F 84	54 84	55 86	50 78
day 46	N %	58 F 91	59 92	61 95	58 91
day 47	N %	59 F 92	60 94	62 97	60 94
day 48	N %	60 F 94	62 97	62 97	60 94
day 49	N %	60 F 94	62 97	64 100	62 97

Statistics: F=Fisher's exact test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034L1

TABLE : 1A-

068

PROJ. NO. 90R0066/05R034:MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F0 FEMALES (L1 LITTER)
SUMMARY OF SEXUAL MATURATION DATA (CUMULATED VALUE)

		TEST GROUP 00 0 MG/KG BW/D	TEST GROUP 01 20 MG/KG BW/D	TEST GROUP 02 60 MG/KG BW/D	TEST GROUP 03 180 MG/KG BW/D
PREPUTIAL SEPARATION Pups reaching criteria					
day 50	N %	62 F 97	62 97	64 100	63 98
day 51	N %	62 F 97	63 98	64 100	63 98
day 52	N %	62 F 97	64 100	64 100	63 98
day 54	N %	63 F 98	64 100	64 100	64 100
day 55	N %	64 F 100	64 100	64 100	64 100
days to criterion	MEAN S.D. N	43.1 D 3.37 64	43.0 2.76 64	42.5 2.64 64	43.3 2.84 64
body weight at criterion	MEAN S.D. N	221.1 D 20.03 23	222.8 21.83 21	223.3 18.77 24	222.5 19.19 23

Statistics: D=Dunnett-test (two-sided) F=Fisher's exact test (two-sided)
* : p<=0.05 ** : p<=0.01

IA- 69

04-Dec-2018 14:29

Ascentos™ 1.3

Study 90R0066/05R034_1A

Summary - Clinical Observation

Sex: **Male** - Phase: **In-life**

		Test Group 10/M	Test Group 11/M	Test Group 12/M	Test Group 13/M
		0 mg/kg bw/d	20 mg/kg bw/d	60 mg/kg bw/d	180 mg/kg bw/d
Animals examined	N	20	20	20	20
Animals with signs	N	0	0	0	12
head	N	0	0	0	12
salivation					
dead	N	20	20	20	20
sacrificed scheduled					
normal	N	20	20	20	20
NAD					

day 0 [00:00 - 24:00] -> day 65 [00:00 - 24:00]

IA- 70

04-Dec-2018 14:31

Ascentos™ 1.3

Study

90R0066/05R034_1A

Summary - Clinical Observation

Sex: **Female** - Phase: **In-life**

	Test Group 10/F		Test Group 11/F		Test Group 12/F		Test Group 13/F	
	0 mg/kg bw/d	20 mg/kg bw/d	0 mg/kg bw/d	20 mg/kg bw/d	60 mg/kg bw/d	180 mg/kg bw/d	0 mg/kg bw/d	20 mg/kg bw/d
Animals examined	N	20	N	20	20	20	N	20
Animals with signs	N	0	N	0	0	0	N	15
head	N	0	N	0	0	0	N	14
salivation	N	0	N	0	0	0	N	14
dead	N	20	N	20	20	20	N	20
found dead	N	0	N	0	0	0	N	1
sacrificed scheduled	N	20	N	20	20	20	N	19
normal	N	20	N	20	20	20	N	20
NAD	N	20	N	20	20	20	N	20
respiration	N	0	N	0	0	0	N	1
gasp	N	0	N	0	0	0	N	1
posture	N	0	N	0	0	0	N	1
abdominal position	N	0	N	0	0	0	N	1

day 0 [00:00 - 24:00] -> day 65 [00:00 - 24:00]

IA- 71
04-Dec-2018 14:35
Ascentos™ 1.3

Study

90R0066/05R034_1A

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
day 0 -> 64 [-03:00-00:00]	Animals examined	N 20	20	20	20
	Animals with signs	N 0	0	0	0
	head	N 0	0	0	0
	salivation	N 0	0	0	0
	normal NAD	N 20	20	20	20

IA- 72

04-Dec-2018 14:37

Ascentos™ 1.3

Study 90R0066/05R034_1A

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
Animals examined	N 20	20	20	20
Animals with signs	N 0	0	0	12
head	N 0	0	0	12
salivation				
normal	N 20	20	20	20
NAD				

day 0 -> 64
[00:00-02:00]

IA- 73

04-Dec-2018 14:37

Ascentos™ 1.3

Study 90R0066/05R034_1A

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
Animals examined	N 20	20	20	20
Animals with signs	N 0	0	0	0
head	N 0	0	0	0
salivation	N 0	0	0	0
normal	N 20	20	20	20
NAD	N 20	20	20	20

day 0 -> 64
[02:00-05:00]

IA- 74

04-Dec-2018 14:40

Ascentos™ 1.3

Study 90R0066/05R034_1A

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Female** - Phase: **In-life**

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
Animals examined	N 20	20	20	20
Animals with signs	N 0	0	0	0
head	N	0	0	0
salivation	N	0	0	0
dead	N 0	0	0	0
found dead	N 0	0	0	0
sacrificed scheduled	N 0	0	0	0
normal	N 20	20	20	20
NAD	N	0	0	0
respiration	N 0	0	0	0
gasping	N	0	0	0
posture	N 0	0	0	0
abdominal position	N	0	0	0

day 0 -> 64
[-03:00-00:00]

IA- 75

04-Dec-2018 14:41

Ascentos™ 1.3

Study 90R0066/05R034_1A

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: Female - Phase: In-life

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
Animals examined	N 20	20	20	20
Animals with signs	N 0	0	0	15
head	N 0	0	0	14
salivation	N 0	0	0	0
dead	N 0	0	0	0
found dead	N 0	0	0	0
sacrificed scheduled	N 0	0	0	0
normal	N 20	20	20	19
NAD				
respiration	N 0	0	0	1
gasping				
posture	N 0	0	0	1
abdominal position				

day 0 -> 64
[00:00-02:00]

IA- 76
04-Dec-2018 14:41
Ascentos™ 1.3

Study

90R0066/05R034_1A

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: Female - Phase: In-life

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
Animals examined	N 20	20	20	20
Animals with signs	N 0	0	0	0
head	N 0	0	0	0
salivation	N 0	0	0	0
dead	N 0	0	0	1
found dead	N 0	0	0	1
sacrificed scheduled	N 0	0	0	0
normal	N 20	20	20	19
NAD				
respiration	N 0	0	0	0
gasping				
posture	N 0	0	0	0
abdominal position				

day 0 -> 64
[02:00-05:00]

IA- 77

04-Dec-2018 14:48

Ascentos™ 1.3

Study 90R0066/05R034_1A

Summary Water Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 0 -> 3	Mean [g]	18.1 n	17.7	18.7	18.4
	S.d.	1.7	1.0	1.5	2.0
	N	10	10	10	10
	Deviation Vs Control [%]		-2.2	3.4	1.6
d 7 -> 10	Mean [g]	26.0 n	24.4	26.3	25.3
	S.d.	2.3	1.8	2.3	3.3
	N	10	10	10	10
	Deviation Vs Control [%]		-6.0	1.2	-2.5
d 14 -> 17	Mean [g]	30.2 n	29.6	30.8	28.8
	S.d.	2.4	2.2	2.1	6.2
	N	10	10	10	10
	Deviation Vs Control [%]		-2.2	1.8	-4.8
d 21 -> 24	Mean [g]	31.5 n	30.1	32.5	32.8
	S.d.	2.7	3.3	2.4	3.3
	N	10	10	10	10
	Deviation Vs Control [%]		4.6	3.1	4.0
d 28 -> 31	Mean [g]	34.7 n	34.4	36.8	35.9
	S.d.	2.8	4.3	2.0	3.3
	N	10	10	10	10
	Deviation Vs Control [%]		-0.7	6.1	3.5

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

IA- 78

04-Dec-2018 14:49

Ascentos™ 1.3

Study 90R0066/05R034_1A

Summary Water Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 35 -> 38	Mean [g]	35.0 n	34.1	37.2	35.2
	S.d.	4.3	5.8	2.3	3.4
	N	10	10	10	10
	Deviation Vs Control [%]		-2.6	6.2	0.4
d 42 -> 45	Mean [g]	35.3 n	34.7	36.6	36.2
	S.d.	3.9	4.6	2.7	3.9
	N	10	10	10	10
	Deviation Vs Control [%]		-1.8	3.5	2.3
d 49 -> 52	Mean [g]	34.7 n	34.1	37.3	36.5
	S.d.	4.9	4.3	3.9	3.9
	N	10	10	10	10
	Deviation Vs Control [%]		-1.8	7.3	5.2

Statistic Profile = Dunnett test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
n=DUNNETT; d = day

IA- 79

04-Dec-2018 14:53

Ascentos™ 1.3

Study 90R0066/05R034_1A

Summary Water Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 0 -> 3	Mean [g]	15.6 n	16.6	17.4	16.9
	S.d.	1.1	1.6	1.8	2.4
	N	10	10	10	10
	Deviation Vs Control [%]		6.5	11.6	8.6
d 7 -> 10	Mean [g]	19.1 n	21.0	22.7 *	23.4 **
	S.d.	1.3	3.0	2.9	4.1
	N	10	10	10	10
	Deviation Vs Control [%]		10.1	18.9	22.8
d 14 -> 17	Mean [g]	20.2 n	21.9	24.2 *	24.7 **
	S.d.	1.7	3.6	2.4	3.9
	N	10	10	10	10
	Deviation Vs Control [%]		8.2	19.4	22.3
d 21 -> 24	Mean [g]	19.7 n	21.5	23.0	24.1 **
	S.d.	2.3	3.4	2.2	4.3
	N	10	10	10	10
	Deviation Vs Control [%]		9.0	16.6	22.3
d 28 -> 31	Mean [g]	21.9 n	24.6	25.1	27.5 **
	S.d.	2.6	4.6	1.6	3.9
	N	10	10	10	10
	Deviation Vs Control [%]		12.1	14.6	25.4

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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04-Dec-2018 14:54

Ascentos™ 1.3

Study 90R0066/05R034_1A

Summary Water Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 35 -> 38	Mean [g]	22.3 n	24.6	25.2	28.0 **
	S.d.	2.9	3.2	1.7	5.4
	N	10	10	10	10
	Deviation Vs Control [%]		10.0	13.0	25.3
d 42 -> 45	Mean [g]	24.4 n	26.0	28.1	28.3 *
	S.d.	3.1	4.5	2.0	3.6
	N	10	10	10	10
	Deviation Vs Control [%]		6.6	15.3	16.0
d 49 -> 52	Mean [g]	23.4 n	26.0	26.2	28.4 **
	S.d.	2.8	3.8	1.4	4.7
	N	10	10	10	10
	Deviation Vs Control [%]		11.2	11.9	21.4

Statistic Profile = Dunnett test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
n=DUNNETT; d = day

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04-Dec-2018 14:59
Ascentos™ 1.3

Study

90R0066/05R034_1A

Summary Food Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 0 -> 7	Mean [g]	16.1 n	14.9	15.1	15.4
	S.d.	2.5	1.3	1.4	1.2
	N	10	10	10	10
	Deviation Vs Control [%]		-7.6	-5.9	-4.1
d 7 -> 14	Mean [g]	22.4 n	21.8	22.5	21.8
	S.d.	1.1	1.5	1.3	1.5
	N	9	10	10	10
	Deviation Vs Control [%]		-2.4	0.5	-2.5
d 14 -> 21	Mean [g]	25.9 n	25.0	25.9	24.0
	S.d.	1.3	1.7	1.0	5.1
	N	10	10	10	10
	Deviation Vs Control [%]		-3.2	0.1	-7.0
d 21 -> 28	Mean [g]	27.9 n	27.7	29.7	28.2
	S.d.	1.3	2.1	3.4	2.2
	N	10	10	10	10
	Deviation Vs Control [%]		-0.8	6.3	1.0
d 28 -> 35	Mean [g]	29.8 n	30.0	31.5	31.0
	S.d.	1.9	2.6	3.0	2.9
	N	10	10	10	10
	Deviation Vs Control [%]		0.9	5.8	4.3

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Ascentos™ 1.3

Study

90R0066/05R034_1A

Summary Food Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 35 -> 42	Mean [g]	29.7 n	29.2	31.0	30.5
	S.d.	1.9	2.5	2.6	3.3
	N	10	10	9	10
	Deviation Vs Control [%]		-1.6	4.4	2.8
d 42 -> 49	Mean [g]	30.1 n	30.0	31.0	31.5
	S.d.	1.8	2.3	2.0	3.0
	N	10	10	10	9
	Deviation Vs Control [%]		-0.3	3.2	4.6
d 49 -> 56	Mean [g]	29.6 n	29.7	31.4	30.7
	S.d.	1.7	2.6	2.7	2.2
	N	10	10	10	9
	Deviation Vs Control [%]		0.2	6.0	3.5
d 0 -> 56	Mean [g]	26.2 n	26.0	26.9	26.4
	S.d.	1.2	1.9	1.2	1.9
	N	9	10	9	9
	Deviation Vs Control [%]		-0.6	2.8	0.8

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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Ascentos™ 1.3

Study

90R0066/05R034_1A

Summary Food Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 0 -> 7	Mean [g]	12.5 n	12.9	13.7	13.3
	S.d.	0.4	0.8	1.3	1.6
	N	10	10	10	10
	Deviation Vs Control [%]		3.0	9.2	6.4
d 7 -> 14	Mean [g]	15.4 n	16.0	17.0	18.0 **
	S.d.	1.1	1.3	1.3	2.2
	N	10	10	10	10
	Deviation Vs Control [%]		4.0	10.7	17.0
d 14 -> 21	Mean [g]	16.4 n	16.6	17.6	18.5 *
	S.d.	1.1	1.7	1.5	2.3
	N	10	10	10	10
	Deviation Vs Control [%]		0.9	7.5	12.7
d 21 -> 28	Mean [g]	16.9 n	17.2	18.0	18.7 *
	S.d.	1.0	1.3	1.2	2.1
	N	10	10	10	10
	Deviation Vs Control [%]		2.0	6.5	10.6
d 28 -> 35	Mean [g]	18.8 n	19.3	19.5	22.1 *
	S.d.	2.0	1.9	1.3	4.2
	N	10	10	10	10
	Deviation Vs Control [%]		2.8	3.9	17.7

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Ascentos™ 1.3

Study

90R0066/05R034_1A

Summary Food Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 35 -> 42	Mean [g]	19.5 n	19.5	20.4	22.3
	S.d.	4.2	2.4	1.4	4.0
	N	10	10	10	9
	Deviation Vs Control [%]		0.1	4.5	14.3
d 42 -> 49	Mean [g]	19.0 n	19.8	20.1	22.2
	S.d.	2.2	2.3	1.1	5.0
	N	10	10	10	10
	Deviation Vs Control [%]		4.4	6.1	17.1
d 49 -> 56	Mean [g]	19.3 n	19.8	20.0	23.3 *
	S.d.	2.0	1.8	1.3	6.0
	N	10	10	10	10
	Deviation Vs Control [%]		2.6	3.8	20.8
d 0 -> 56	Mean [g]	17.2 n	17.6	18.3	19.7 *
	S.d.	1.5	1.5	1.0	3.0
	N	10	10	10	9
	Deviation Vs Control [%]		2.4	6.3	14.3

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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Study

90R0066/05R034_1A

Summary Body Weights - BW / Body Weights [g]

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
day 0	Mean	86.8n	86.8	85.5	85.9
	S.d.	7.3	8.9	5.5	8.1
	N	20	20	20	20
	Deviation Vs Control [%]		0.0	-1.5	-1.0
day 7	Mean	141.0n	139.9	139.6	139.3
	S.d.	10.5	15.3	8.9	12.5
	N	20	20	20	20
	Deviation Vs Control [%]		-0.7	-1.0	-1.2
day 14	Mean	208.0n	203.0	204.9	203.7
	S.d.	13.9	22.8	11.3	17.3
	N	20	20	20	20
	Deviation Vs Control [%]		-2.4	-1.5	-2.0
day 21	Mean	266.4n	262.7	263.9	254.0
	S.d.	16.0	28.5	11.4	28.0
	N	20	20	20	20
	Deviation Vs Control [%]		-1.4	-1.0	-4.7
day 28	Mean	326.7n	322.0	323.5	315.5
	S.d.	17.6	35.8	12.7	30.7
	N	20	20	20	20
	Deviation Vs Control [%]		-1.4	-1.0	-3.4

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

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Study 90R0066/05R034_1A

Summary Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
day 35	Mean	366.7 n	363.1	364.9	355.6
	S.d.	21.8	43.0	14.8	30.7
	N	20	20	20	20
	Deviation Vs Control [%]		-1.0	-0.5	-3.0
day 42	Mean	408.4 n	404.1	408.4	394.1
	S.d.	27.0	47.3	16.9	34.2
	N	20	20	20	20
	Deviation Vs Control [%]		-1.0	0.0	-3.5
day 49	Mean	444.1 n	439.3	443.2	425.1
	S.d.	31.6	52.8	19.8	36.6
	N	20	20	20	20
	Deviation Vs Control [%]		-1.1	-0.2	-4.3
day 56	Mean	468.0 n	463.3	470.3	452.3
	S.d.	35.8	56.1	22.0	40.0
	N	20	20	20	20
	Deviation Vs Control [%]		-1.0	0.5	-3.4
day 63	Mean	488.3 n	490.6	472.9	459.2
	S.d.	29.6	69.2	21.3	38.1
	N	10	10	10	10
	Deviation Vs Control [%]		0.5	-3.2	-6.0

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

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Study 90R0066/05R034_1A

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
day 0	Mean	77.5 n	78.4	79.9	78.2
	S.d.	6.2	5.9	6.2	6.0
	N	20	20	20	20
	Deviation Vs Control [%]		1.2	3.1	0.9
day 7	Mean	115.5 n	118.4	121.6	119.7
	S.d.	8.0	9.2	10.1	9.9
	N	20	20	20	19
	Deviation Vs Control [%]		2.5	5.2	3.7
day 14	Mean	149.0 n	153.4	159.6 *	159.6 *
	S.d.	10.7	12.2	14.0	12.7
	N	20	20	20	19
	Deviation Vs Control [%]		3.0	7.1	7.1
day 21	Mean	173.9 n	176.1	184.2	183.2
	S.d.	14.8	14.0	16.3	11.6
	N	20	20	20	19
	Deviation Vs Control [%]		1.3	5.9	5.4
day 28	Mean	193.5 n	196.0	207.3 *	207.1 *
	S.d.	17.5	16.6	18.2	14.9
	N	20	20	20	19
	Deviation Vs Control [%]		1.3	7.2	7.0

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

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Study 90R0066/05R034_1A

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
day 35	Mean	210.5 n	213.4	220.8	224.1
	S.d.	20.0	19.3	19.1	15.1
	N	20	20	20	19
	Deviation Vs Control [%]		1.4	4.9	6.5
day 42	Mean	226.9 n	228.4	237.6	241.0
	S.d.	22.4	19.3	19.6	16.9
	N	20	20	20	19
	Deviation Vs Control [%]		0.7	4.7	6.2
day 49	Mean	245.6 n	244.0	255.5	257.9
	S.d.	25.3	21.1	22.3	15.1
	N	20	20	20	19
	Deviation Vs Control [%]		-0.6	4.0	5.0
day 56	Mean	250.4 n	250.7	264.0	267.2
	S.d.	27.4	23.1	22.5	15.7
	N	20	20	20	19
	Deviation Vs Control [%]		0.1	5.4	6.7
day 63	Mean	264.1 n	256.3	265.1	277.0
	S.d.	22.9	26.9	24.8	20.6
	N	10	10	10	10
	Deviation Vs Control [%]		-3.0	0.4	4.9

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

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Study

90R0066/05R034_1A

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

	Test Group 10/M			Test Group 11/M			Test Group 12/M			Test Group 13/M		
	0 mg/kg bw/d			20 mg/kg bw/d			60 mg/kg bw/d			180 mg/kg bw/d		
d 0 -> 7	Mean	54.2 n		53.1			54.1			53.3		
	S.d.	4.2		7.7			5.3			5.3		
	N	20		20			20			20		
d 7 -> 14	Mean	67.0 n		63.1			65.3			64.5		
	S.d.	4.8		8.8			4.1			6.3		
	N	20		20			20			20		
d 14 -> 21	Mean	58.4 n		59.7			59.0			50.3		
	S.d.	6.5		6.9			4.1			20.8		
	N	20		20			20			20		
d 21 -> 28	Mean	60.3 n		59.3			59.7			61.5		
	S.d.	6.6		9.1			4.8			8.3		
	N	20		20			20			20		
d 28 -> 35	Mean	40.0 n		41.1			41.4			40.1		
	S.d.	9.0		9.2			6.3			8.8		
	N	20		20			20			20		
d 35 -> 42	Mean	41.7 n		41.0			43.5			38.5		
	S.d.	7.7		7.4			5.1			7.5		
	N	20		20			20			20		
d 42 -> 49	Mean	35.7 n		35.2			34.8			31.0		
	S.d.	7.0		7.8			5.8			7.4		
	N	20		20			20			20		

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Ascentos™ 1.3

Study

90R0066/05R034_1A

Summary Changes Body Weights - BW / Body Weights [g]

Sex: **Male** - Phase: **In-life**

		Test Group 10/M		Test Group 11/M		Test Group 12/M		Test Group 13/M	
		0 mg/kg bw/d		20 mg/kg bw/d		60 mg/kg bw/d		180 mg/kg bw/d	
d 49 -> 56	Mean	24.0 n		24.0		27.0		27.2	
	S.d.	7.3		6.5		5.6		7.7	
	N	20		20		20		20	
d 56 -> 63	Mean	16.2 n		16.6		11.1		7.8**	
	S.d.	3.4		5.2		6.1		7.3	
	N	10		10		10		10	
d 0 -> 63	Mean	396.7 n		402.2		383.6		368.2	
	S.d.	26.6		61.9		20.6		33.8	
	N	10		10		10		10	

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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Ascentos™ 1.3

Study

90R0066/05R034_1A

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 0 -> 7	Mean	38.0 n	39.9	41.6 *	41.4
	S.d.	4.3	4.2	5.1	5.0
	N	20	20	20	19
d 7 -> 14	Mean	33.5 n	35.1	38.0	39.8 *
	S.d.	7.7	6.1	7.1	5.3
	N	20	20	20	19
d 14 -> 21	Mean	24.9 n	22.7	24.6	23.6
	S.d.	7.6	6.7	7.2	4.7
	N	20	20	20	19
d 21 -> 28	Mean	19.6 n	19.9	23.1	23.9
	S.d.	6.0	6.5	5.3	7.0
	N	20	20	20	19
d 28 -> 35	Mean	17.0 n	17.4	13.5	17.1
	S.d.	7.7	7.1	4.9	7.4
	N	20	20	20	19
d 35 -> 42	Mean	16.4 n	15.0	16.8	16.9
	S.d.	6.5	3.0	5.7	6.3
	N	20	20	20	19
d 42 -> 49	Mean	18.7 n	15.6	17.9	16.9
	S.d.	7.2	6.6	7.3	5.1
	N	20	20	20	19

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Ascentos™ 1.3

Study

90R0066/05R034_1A

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 49 -> 56	Mean	4.8 n	6.7	8.4	9.3
	S.d.	6.1	7.7	6.5	7.3
	N	20	20	20	19
d 56 -> 63	Mean	11.9 n	12.5	3.4 *	8.2
	S.d.	4.9	4.0	9.8	8.3
	N	10	10	10	10
d 0 -> 63	Mean	183.8 n	177.6	182.0	195.1
	S.d.	22.6	24.2	19.5	19.0
	N	10	10	10	10

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

4-DEC-18
05R034DA
TABLE : 1A- 093

PROJ. NO. 90R0066/05R034: MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - DCO (COHORT 1A)
MALES SUMMARY OF MALE CLINICAL OBSERVATIONS

GROUP#	WEEK OF STUDY								TOTAL	
	0	1	2	3	4	5	6	7		
10	20	20	20	20	20	20	20	20	20	20
11	20	20	20	20	20	20	20	20	20	20
12	20	20	20	20	20	20	20	20	20	20
13	20	20	20	20	20	20	20	20	20	20

OF ANIMALS EXAMINED

NORMAL

NOTHING ABNORMAL DETECTED 10
11
12
13

4-DEC-18
05R034DA
FEMALES
TABLE : 1A-
094

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - DCO (COHORT 1A)
SUMMARY OF FEMALE CLINICAL OBSERVATIONS

	GROUP#	WEEK OF STUDY							
		0	1	2	3	4	5	6	7 8 TOTAL
# OF ANIMALS EXAMINED	10	20	20	20	20	20	20	20	20 20
	11	20	20	20	20	20	20	20	20 20
	12	20	20	20	20	20	20	20	20 20
	13	20	19	19	19	19	19	19	19 19
NORMAL									
NOTHING ABNORMAL DETECTED	10	20	20	20	20	20	20	20	20 20
	11	20	20	20	20	20	20	20	20 20
	12	20	20	20	20	20	20	20	20 20
	13	19	19	19	19	19	19	19	19 19
DEAD									
FOUND DEAD	10	0	0	0	0	0	0	0	0 0
	11	0	0	0	0	0	0	0	0 0
	12	0	0	0	0	0	0	0	0 0
	13	1	0	0	0	0	0	0	1 0

4-DEC-18

05R034ZA

TABLE : 1A- 095

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - COHORT 1A CYCLUS
SUMMARY OF MEAN ESTROUS CYCLE DURATION

	TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
MEAN# OF DAYS FROM ESTRUS TO ESTRUS	4.1 D	4.1	4.1	4.1
S.D.	0.23	0.23	0.21	0.23
N	20	20	20	19

Statistics: D=Dunnett-test (two-sided)
* : $p \leq 0.05$ ** : $p \leq 0.01$

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04-Dec-2018 16:58

Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
Animals examined	N 24	24	24	24
Animals with signs	N 0	0	0	11
head	N 0	0	0	11
salivation	N 0	0	0	11
normal	N 24	24	24	24
NAD	N 24	24	24	24

day 0 [00:00 - 24:00] -> day 76 [00:00 - 24:00]

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06-Dec-2018 12:05
Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary - Clinical Observation

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
Animals examined	N	24	24	24	24
Animals with signs	N	0	0	0	9
head	N	0	0	0	9
salivation	N	0	0	0	9
dead	N	0	0	1	0
found dead	N	24	24	24	24
normal	N	24	24	24	24
NAD	N	24	24	24	24

day 0 [00:00 - 24:00] -> day 76 [00:00 - 24:00]

IA- 98
04-Dec-2018 17:04
Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
Animals examined	N 24	24	24	24
Animals with signs	N 0	0	0	0
head	N 0	0	0	0
salivation	N 0	0	0	0
normal	N 24	24	24	24
NAD	N 24	24	24	24

day 0 -> 76
[-03:00-00:00]

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04-Dec-2018 17:07
Ascentos™ 1.3

Study

90R0066/05R034_F1

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
Animals examined	N 24	24	24	24
Animals with signs	N 0	0	0	11
head	N 0	0	0	11
salivation				
normal	N 24	24	24	24
NAD				

day 0 -> 76
[00:00-02:00]

IA- 100
04-Dec-2018 17:07
Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
Animals examined	N 24	24	24	24
Animals with signs	N 0	0	0	0
head	N 0	0	0	0
salivation	N 0	0	0	0
normal	N 24	24	24	24
NAD	N 24	24	24	24

day 0 -> 76
[02:00-05:00]

IA- 101
04-Dec-2018 17:07
Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Female** - Phase: **In-life**

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
	N 24	24	24	24
Animals examined	N	0	0	0
Animals with signs	N	0	0	0
head	N	0	0	0
salivation	N	0	0	0
normal	N	24	24	24
NAD	N	24	24	24

day 0 -> 76
[-03:00-00:00]

IA- 102
04-Dec-2018 17:09
Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Female** - Phase: **In-life**

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
Animals examined	N 24	24	24	24
Animals with signs	N 0	0	0	9
head	N 0	0	0	9
salivation	N 0	0	0	9
normal	N 24	24	24	24
NAD				

day 0 -> 76
[00:00-02:00]

IA- 103
04-Dec-2018 17:09
Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: Female - Phase: In-life

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
Animals examined	N 24	24	24	24
Animals with signs	N 0	0	0	0
head	N 0	0	0	0
salivation	N 0	0	0	0
normal	N 24	24	24	24
NAD				

day 0 -> 76
[02:00-05:00]

4-DEC-18
05R034M1
MALES
TABLE : 1A-
104

PROJ. NO. 90R0066/05R034: MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - F1 MALES
SUMMARY OF MALE CLINICAL OBSERVATIONS

WEEK OF STUDY
0 1 2 3 4 5 TOTAL

OF ANIMALS EXAMINED
10 24 24 24 24 24 24
11 24 24 24 24 24 24
12 24 24 24 24 24 24
13 24 24 24 24 24 24

NORMAL

NOTHING ABNORMAL DETECTED 10 0 0 0 0 0 24 24
11 0 0 0 0 0 24 24
12 0 0 0 0 0 24 24
13 0 0 0 0 0 24 24

NOTHING ABNORMAL DETECTED 10 24 24 24 24 24 24
BEFORE TREATMENT 11 24 24 24 24 24 24
12 24 24 24 24 24 24
13 24 24 24 24 24 24

NOTHING ABNORMAL DETECTED 10 24 24 24 24 24 24
AFTER TREATMENT (<2H) 11 24 24 24 24 24 24
12 24 24 24 24 24 24
13 24 24 23 24 23 24

NOTHING ABNORMAL DETECTED 10 24 24 24 24 24 24
AFTER TREATMENT (>2H<5H) 11 24 24 24 24 24 24
12 24 24 24 24 24 24
13 24 24 24 24 24 24

DEAD

SCHEDULED SACRIFICE 10 0 0 0 0 0 24 24
11 0 0 0 0 0 24 24
12 0 0 0 0 0 24 24
13 0 0 0 0 0 24 24

ORAL-BUCCAL

SALIVATION AFTER 10 0 0 0 0 0 0 0
TREATMENT (<2H) 11 0 0 0 0 0 0 0
12 0 0 0 0 0 0 0
13 12 12 14 15 12 6 17

4-DEC-18 05R034F1 105

PROJ. NO. 90R0066/05R034: MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - F1 FEMALES

TABLE : 1A-

SUMMARY OF FEMALE CLINICAL OBSERVATIONS (EXCEPT GESTATION AND LACTATION PERIODS)

	GROUP#	WEEK OF STUDY							TOTAL
		0	1	2	3	4	5	6	
# OF ANIMALS EXAMINED	10	24	0	0	0	0	0	24	24
	11	24	0	0	0	0	0	24	24
	12	23	1	1	2	2	2	23	23
	13	24	1	0	2	3	3	23	24
NORMAL									
NOTHING ABNORMAL DETECTED	10	0	-	-	-	-	-	0	24
	11	0	-	-	-	-	-	0	24
	12	0	0	0	0	0	0	0	23
	13	0	0	-	0	0	0	0	24
NOTHING ABNORMAL DETECTED BEFORE TREATMENT									
	10	21	-	-	-	-	-	24	24
	11	18	-	-	-	-	-	24	24
	12	17	1	1	2	2	2	23	23
	13	18	1	-	2	2	3	23	24
NOTHING ABNORMAL DETECTED AFTER TREATMENT (<2H)									
	10	21	-	-	-	-	-	24	24
	11	18	-	-	-	-	-	24	24
	12	17	1	1	2	2	2	23	23
	13	17	1	-	2	2	3	23	24
NOTHING ABNORMAL DETECTED AFTER TREATMENT (>2H<5H)									
	10	21	-	-	-	-	-	24	24
	11	18	-	-	-	-	-	24	24
	12	17	1	1	2	2	2	23	23
	13	18	1	-	2	3	3	23	24
DEAD									
SCHEDULED SACRIFICE	10	0	-	-	-	-	-	0	24
	11	0	-	-	-	-	-	0	24
	12	0	0	0	0	0	0	0	23
	13	0	0	-	0	0	0	0	24
MISCELLANEOUS									
SPERM IN VAGINAL SMEAR (DAY 0 P.C. FOR F2)	10	24	-	-	-	-	-	0	0
	11	24	-	-	-	-	-	0	0
	12	22	0	0	0	0	0	0	0
	13	23	1	-	0	0	0	0	0

4-DEC-18 05R034F1 106
TABLE : 1A-

PROJ. NO. 90R0066/05R034: MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - F1 FEMALES
SUMMARY OF FEMALE CLINICAL OBSERVATIONS (EXCEPT GESTATION AND LACTATION PERIODS)

	GROUP#	WEEK OF STUDY							TOTAL
		0	1	2	3	4	5	6	
# OF ANIMALS EXAMINED	10	24	0	0	0	0	0	24	24
	11	24	0	0	0	0	0	24	24
	12	23	1	1	2	2	2	23	23
	13	24	1	0	2	3	3	23	24
NO SPERM IN VAGINAL SMEAR (NO DAY 0 P.C. FOR F2)	10	0	-	-	-	-	-	0	0
	11	0	-	-	-	-	-	0	0
	12	0	1	0	0	0	0	1	1
	13	0	0	-	0	0	0	0	0
NO SPERM IN VAGINAL SMEAR DETECTED (BUT F2 PUPS)	10	0	-	-	-	-	-	0	0
	11	0	-	-	-	-	-	0	0
	12	0	0	0	1	0	0	1	1
	13	0	0	-	0	0	0	0	0
VAGINAL HEMORRHAGE BEFORE TREATMENT	10	0	-	-	-	-	-	0	0
	11	0	-	-	-	-	-	0	0
	12	0	0	0	0	0	0	0	0
	13	0	0	-	0	1	1	0	1
VAGINAL HEMORRHAGE AFTER TREATMENT (<2H)	10	0	-	-	-	-	-	0	0
	11	0	-	-	-	-	-	0	0
	12	0	0	0	0	0	0	0	0
	13	0	0	-	0	1	1	0	1
VAGINAL HEMORRHAGE AFTER TREATMENT (>2H<5H)	10	0	-	-	-	-	-	0	0
	11	0	-	-	-	-	-	0	0
	12	0	0	0	0	0	0	0	0
	13	0	0	-	0	0	1	0	1
ORAL-BUCCAL SALIVATION AFTER TREATMENT (<2H)	10	0	-	-	-	-	-	0	0
	11	0	-	-	-	-	-	0	0
	12	0	0	0	0	0	0	0	0
	13	8	0	-	0	0	0	0	1

4-DEC-18

05R034L2

TABLE : IA-107

PROJ. NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY OF MATERNAL CLINICAL OBSERVATIONS DURING GESTATION

[illegible]

OF FEMALES EXAMINED

NORMAL

Category	Count	Percentage
Nothing abnormal detected	10	24
Before treatment	11	24
After treatment	11	24
Nothing abnormal detected	10	24
Before treatment	11	24
After treatment	11	24

[illegible][illegible]

MISCELLANEOUS

[illegible][illegible]

ORAL-BUCCAL

[illegible]

4-DEC-18

05R034L2

TABLE : IA-108

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX.STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY OF MATERNAL/PUP CLINICAL OBSERVATIONS DURING LACTATION

[illegible]

IA- 109
04-Dec-2018 17:17
Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Water Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 0 -> 3	Mean [g]	16.8 n	17.3	19.1 **	16.9
	S.d.	1.0	0.8	1.4	1.8
	N	8	8	8	8
	Deviation Vs Control [%]		3.1	13.6	0.7
d 7 -> 10	Mean [g]	22.7 n	23.6	26.6 **	23.6
	S.d.	1.4	1.4	2.2	2.1
	N	8	8	8	8
	Deviation Vs Control [%]		3.8	17.1	4.0
d 14 -> 17	Mean [g]	28.3 n	30.3	33.3 **	30.8
	S.d.	1.3	1.8	3.4	3.0
	N	8	8	8	8
	Deviation Vs Control [%]		7.1	17.9	8.9
d 21 -> 24	Mean [g]	29.9 n	31.0	33.7	33.1
	S.d.	2.3	1.7	4.3	3.6
	N	8	8	8	8
	Deviation Vs Control [%]		3.5	12.7	10.6
d 28 -> 31	Mean [g]	33.8 n	34.6	36.5	36.6
	S.d.	2.8	2.3	2.9	3.1
	N	8	8	8	8
	Deviation Vs Control [%]		2.3	7.9	8.3

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

IA- 110
04-Dec-2018 17:18
Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Water Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 35 -> 38	Mean [g]	34.7 n	35.0	38.2	37.4
	S.d.	2.1	2.4	4.3	3.9
	N	8	8	8	8
	Deviation Vs Control [%]		0.9	10.1	8.0
d 42 -> 45	Mean [g]	34.1 n	33.2	37.0	36.1
	S.d.	3.6	1.7	3.1	4.1
	N	8	8	8	8
	Deviation Vs Control [%]		-2.6	8.5	6.0
d 49 -> 52	Mean [g]	32.6 n	32.5	35.0	35.7
	S.d.	3.6	2.3	3.2	3.1
	N	8	8	7	8
	Deviation Vs Control [%]		-0.4	7.3	9.2
d 56 -> 59	Mean [g]	34.2 n	33.9	38.3	36.2
	S.d.	3.5	2.4	5.0	3.1
	N	8	8	8	8
	Deviation Vs Control [%]		-0.9	12.2	5.9
d 63 -> 66	Mean [g]	33.0 n	33.7	37.0	35.2
	S.d.	3.5	2.1	6.1	2.9
	N	8	8	8	8
	Deviation Vs Control [%]		1.9	11.9	6.6

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

IA- 111
04-Dec-2018 17:19
Ascentos™ 1.3

Study

90R0066/05R034_F1

Summary Water Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 0 -> 3	Mean [g]	15.4 n	15.2	17.0	16.1
	S.d.	1.5	1.1	1.2	1.9
	N	8	8	8	8
	Deviation Vs Control [%]		-1.0	10.4	4.9
d 7 -> 10	Mean [g]	18.7 n	19.0	20.9	21.2 *
	S.d.	1.8	1.8	1.6	2.5
	N	8	8	8	8
	Deviation Vs Control [%]		1.9	12.2	13.8
d 14 -> 17	Mean [g]	20.1 n	20.1	23.0 *	23.5 **
	S.d.	1.8	1.0	1.6	3.4
	N	8	8	8	8
	Deviation Vs Control [%]		-0.2	14.2	17.0
d 21 -> 24	Mean [g]	21.2 n	20.9	22.9	25.4 *
	S.d.	2.6	2.5	2.0	4.5
	N	8	8	8	8
	Deviation Vs Control [%]		-1.3	7.9	19.6
d 28 -> 31	Mean [g]	22.4 n	22.5	25.0	28.2 **
	S.d.	2.4	1.9	2.6	5.4
	N	8	8	8	8
	Deviation Vs Control [%]		0.8	11.8	26.2

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

IA- 112

04-Dec-2018 17:20

Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Water Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 35 -> 38	Mean [g]	22.9 n	22.6	25.2	27.5 **
	S.d.	1.7	1.8	3.0	2.1
	N	8	8	8	7
	Deviation Vs Control [%]		-1.5	10.0	19.8
d 42 -> 45	Mean [g]	22.3 n	22.1	25.6 **	27.3 **
	S.d.	2.2	1.8	1.8	1.9
	N	8	8	8	7
	Deviation Vs Control [%]		-0.9	14.7	22.1
d 49 -> 52	Mean [g]	22.8 n	23.2	25.0	26.9 *
	S.d.	3.1	2.9	2.8	2.1
	N	8	8	8	7
	Deviation Vs Control [%]		1.8	9.5	18.1
d 56 -> 59	Mean [g]	24.1 n	24.2	26.7	27.0
	S.d.	3.1	2.4	2.4	1.5
	N	8	8	8	7
	Deviation Vs Control [%]		0.2	10.7	12.1
d 63 -> 66	Mean [g]	23.4 n	23.0	25.1	25.8
	S.d.	2.8	2.5	3.4	1.4
	N	8	8	8	7
	Deviation Vs Control [%]		-1.3	7.6	10.3

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

4-DEC-18
05R034L2
TABLE : IA-
113

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
MEAN MATERNAL WATER CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

DAYS	0 TO 1		TEST GROUP 10			TEST GROUP 11			TEST GROUP 12			TEST GROUP 13		
			0 MG/KG BW/D			20 MG/KG BW/D			60 MG/KG BW/D			180 MG/KG BW/D		
DAYS	0 TO 1	MEAN	25.5	D		24.3			24.9			21.3		
		S.D.	6.63			5.86			5.22			7.70		
		N	24			24			21			23		
DAYS	3 TO 4	MEAN	28.7	D		26.7			27.9			30.5		
		S.D.	7.61			5.12			6.28			7.88		
		N	24			24			21			23		
DAYS	7 TO 8	MEAN	28.2	D		26.9			27.5			31.4		
		S.D.	6.44			6.30			6.82			7.16		
		N	24			24			21			23		
DAYS	10 TO 11	MEAN	30.1	D		29.8			33.1			34.5		
		S.D.	6.13			4.76			7.63			7.50		
		N	24			24			21			23		
DAYS	14 TO 15	MEAN	32.7	D		32.4			34.8			36.7		
		S.D.	7.88			5.22			7.32			11.24		
		N	24			24			21			23		
DAYS	17 TO 18	MEAN	39.4	D		40.9			43.7			43.8		
		S.D.	9.42			6.64			7.16			10.89		
		N	24			24			21			23		
DAYS	19 TO 20	MEAN	39.3	D		39.1			41.4			43.6		
		S.D.	6.26			6.15			7.73			12.94		
		N	24			24			21			23		

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034L2

TABLE : IA- 114

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
MEAN MATERNAL WATER CONSUMPTION DURING LACTATION -- GRAMS/ANIMAL/DAY

		TEST GROUP 10	TEST GROUP 11	TEST GROUP 12	TEST GROUP 13
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
DAYS 1 TO 2	MEAN	43.3 D	43.8	43.8	40.4
	S.D.	9.39	12.03	8.70	11.69
	N	24	24	20	21
DAYS 4 TO 5	MEAN	63.4 D	61.8	61.0	55.0*
	S.D.	9.72	13.36	7.74	13.26
	N	24	24	20	21
DAYS 7 TO 8	MEAN	70.2 D	66.5	68.2	69.2
	S.D.	9.92	9.55	18.19	14.06
	N	24	24	20	21
DAYS 10 TO 11	MEAN	76.9 D	82.2	78.3	69.5
	S.D.	9.80	15.56	12.97	23.65
	N	24	24	20	21
DAYS 14 TO 15	MEAN	94.6 D	86.5	93.8	81.4
	S.D.	16.48	25.65	12.95	22.82
	N	24	24	20	21
DAYS 17 TO 18	MEAN	96.8 D	100.4	94.3	93.6
	S.D.	26.59	16.40	14.96	20.21
	N	24	24	20	21
DAYS 20 TO 21	MEAN	130.6 D	130.8	136.8	130.1
	S.D.	20.02	22.68	13.33	30.79
	N	24	24	20	21

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

IA- 115

04-Dec-2018 17:29

Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Food Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 0 -> 7	Mean [g]	13.4 n	14.0	14.5	14.1
	S.d.	0.7	0.4	1.2	1.8
	N	8	8	8	8
	Deviation Vs Control [%]		4.6	7.7	4.9
d 7 -> 14	Mean [g]	20.3 n	19.2	19.0	18.7 *
	S.d.	1.4	1.3	1.3	1.1
	N	8	8	8	8
	Deviation Vs Control [%]		-5.8	-6.8	-8.0
d 14 -> 21	Mean [g]	25.1 n	25.6	26.3	25.6
	S.d.	2.1	1.5	1.9	1.3
	N	8	8	8	8
	Deviation Vs Control [%]		2.1	5.0	2.0
d 21 -> 28	Mean [g]	27.8 n	27.6	28.9	28.4
	S.d.	2.1	1.3	2.0	1.9
	N	8	8	8	8
	Deviation Vs Control [%]		-0.8	3.9	2.3

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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04-Dec-2018 17:29

Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Food Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 28 -> 35	Mean [g]	32.0 n	30.7	31.0	29.8
	S.d.	4.8	2.0	2.3	2.0
	N	8	8	8	8
	Deviation Vs Control [%]		-3.8	-2.9	-6.6
d 35 -> 42	Mean [g]	31.0 n	29.0	31.9	30.5
	S.d.	4.2	1.1	3.4	2.2
	N	8	8	8	8
	Deviation Vs Control [%]		-6.4	2.9	-1.5
d 42 -> 49	Mean [g]	29.4 n	28.4	31.1	29.6
	S.d.	2.1	0.7	2.6	2.9
	N	8	8	8	8
	Deviation Vs Control [%]		-3.5	5.6	0.4
d 49 -> 56	Mean [g]	29.9 n	28.8	30.6	31.9
	S.d.	2.7	1.3	0.7	4.2
	N	8	8	7	8
	Deviation Vs Control [%]		-3.9	2.3	6.6

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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04-Dec-2018 17:29
Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Food Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 56 -> 63	Mean [g]	30.2 n	31.6	32.8	30.8
	S.d.	2.7	4.3	3.5	2.4
	N	8	8	8	8
	Deviation Vs Control [%]		4.5	8.7	1.8
d 63 -> 70	Mean [g]	29.9 n	31.2	32.9	31.2
	S.d.	3.2	4.6	2.5	2.5
	N	8	8	8	8
	Deviation Vs Control [%]		4.2	9.8	4.4
d 0 -> 70	Mean [g]	26.9 n	26.6	27.4	27.1
	S.d.	2.3	0.9	0.6	1.8
	N	8	8	7	8
	Deviation Vs Control [%]		-1.1	1.9	0.6

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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Study

90R0066/05R034_F1

Summary Food Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 0 -> 7	Mean [g]	11.7 n	11.6	12.2	12.7
	S.d.	0.7	0.4	0.5	1.3
	N	8	8	8	8
	Deviation Vs Control [%]		-1.1	4.5	8.4
d 7 -> 14	Mean [g]	15.9 n	16.2	17.9 *	17.1
	S.d.	1.3	1.4	2.1	0.6
	N	8	8	8	8
	Deviation Vs Control [%]		2.2	12.9	7.8
d 14 -> 21	Mean [g]	17.4 n	17.8	20.0	18.8
	S.d.	3.4	4.4	5.3	1.6
	N	8	8	8	8
	Deviation Vs Control [%]		1.9	14.9	7.7
d 21 -> 28	Mean [g]	17.9 n	18.4	19.2	19.4
	S.d.	2.0	2.4	1.6	1.4
	N	8	8	7	8
	Deviation Vs Control [%]		2.7	6.8	8.2

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Study 90R0066/05R034_F1

Summary Food Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 28 -> 35	Mean [g]	19.5 n	19.6	22.3	23.2 *
	S.d.	2.6	1.9	3.7	2.6
	N	8	7	7	7
	Deviation Vs Control [%]		0.1	14.2	18.6
d 35 -> 42	Mean [g]	18.6 n	18.9	20.7	22.2 *
	S.d.	1.4	2.5	2.5	2.8
	N	8	8	7	7
	Deviation Vs Control [%]		2.1	11.8	19.9
d 42 -> 49	Mean [g]	17.9 n	18.3	20.3	21.9 **
	S.d.	1.6	1.5	1.2	3.6
	N	8	7	6	8
	Deviation Vs Control [%]		1.9	13.1	22.0
d 49 -> 56	Mean [g]	18.4 n	19.8	20.7	20.6
	S.d.	2.0	2.1	1.5	1.9
	N	8	8	6	7
	Deviation Vs Control [%]		7.5	12.5	12.3

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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Study 90R0066/05R034_F1

Summary Food Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 56 -> 63	Mean [g]	19.5 n	21.5	21.8	22.7
	S.d.	2.1	3.9	1.3	3.8
	N	8	8	6	8
	Deviation Vs Control [%]		10.3	11.8	16.1
d 63 -> 70	Mean [g]	20.0 n	20.7	20.0	23.2
	S.d.	2.9	3.4	0.6	3.6
	N	8	8	6	8
	Deviation Vs Control [%]		3.8	0.1	16.1
d 0 -> 70	Mean [g]	17.7 n	17.7	19.1	19.9*
	S.d.	1.8	1.2	1.0	1.5
	N	8	7	6	7
	Deviation Vs Control [%]		0.2	7.7	12.5

Statistic Profile = Dunnett test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
n=DUNNETT; d = day

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05R034L2

TABLE : IA- 121

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

DAYS	0 TO 7	TEST GROUP 10			TEST GROUP 11			TEST GROUP 12			TEST GROUP 13		
		0 MG/KG BW/D			20 MG/KG BW/D			60 MG/KG BW/D			180 MG/KG BW/D		
DAYS	0 TO 7	MEAN	23.7	D	23.3			23.5			23.3		
		S.D.	2.53		2.42			2.00			3.52		
		N	24		24			21			23		
DAYS	7 TO 14	MEAN	25.0	D	24.2			25.0			26.0		
		S.D.	2.62		2.15			2.01			2.65		
		N	24		24			21			23		
DAYS	14 TO 20	MEAN	28.3	D	27.3			28.5			28.9		
		S.D.	2.84		2.61			1.84			3.04		
		N	24		24			21			23		
DAYS	0 TO 20	MEAN OF MEANS	25.7		24.9			25.6			26.1		
		S.D.	2.34		2.12			2.54			2.81		
		N	3		3			3			3		

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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TABLE : IA-122

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
MEAN MATERNAL FOOD CONSUMPTION DURING LACTATION -- GRAMS/ANIMAL/DAY

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
DAYS 1 TO 4	MEAN S.D. N	43.7 D 5.01 24	41.4 6.50 24	42.9 4.63 21	39.3 7.78 21
DAYS 4 TO 7	MEAN S.D. N	60.1 D 4.51 24	58.9 7.06 24	59.0 4.09 21	55.0* 8.42 21
DAYS 7 TO 10	MEAN S.D. N	67.4 D 5.17 24	65.7 6.73 24	67.6 3.96 21	63.7 10.63 21
DAYS 10 TO 14	MEAN S.D. N	71.9 D 5.83 24	72.5 5.37 24	74.0 4.28 21	68.7 10.42 21
DAYS 14 TO 17	MEAN S.D. N	78.6 D 6.97 24	77.6 7.97 24	78.5 6.81 21	73.3 11.47 21
DAYS 17 TO 19	MEAN S.D. N	83.0 D 7.66 24	84.3 8.46 24	82.4 6.35 21	78.2 12.31 21
DAYS 19 TO 21	MEAN S.D. N	96.7 D 8.99 24	95.3 6.39 24	101.2 8.32 21	91.2 17.58 21
DAYS 1 TO 21	MEAN OF MEANS S.D. N	71.6 17.02 7	70.8 17.61 7	72.3 18.44 7	67.1 16.72 7

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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Study 90R0066/05R034_F1

Summary Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
day 0	Mean	79.8n	80.1	82.3	78.9
	S.d.	6.3	7.8	6.7	7.6
	N	24	24	24	24
	Deviation Vs Control [%]		0.4	3.1	-1.2
day 7	Mean	128.4n	128.5	133.8	127.7
	S.d.	9.9	12.0	12.2	12.6
	N	24	24	24	24
	Deviation Vs Control [%]		0.1	4.2	-0.5
day 14	Mean	190.0n	179.2	177.6*	173.7**
	S.d.	14.1	14.4	15.2	19.0
	N	24	24	24	24
	Deviation Vs Control [%]		-5.7	-6.5	-8.6
day 21	Mean	253.9n	250.3	260.4	248.4
	S.d.	17.4	19.0	16.5	27.5
	N	24	24	24	24
	Deviation Vs Control [%]		-1.4	2.5	-2.2

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
n=DUNNETT

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Study 90R0066/05R034_F1

Summary Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
day 28	Mean	311.0n	308.1	321.6	304.5
	S.d.	20.7	23.9	21.2	33.9
	N	24	24	24	24
	Deviation Vs Control [%]		-0.9	3.4	-2.1
day 35	Mean	357.8n	354.5	370.1	349.2
	S.d.	24.2	26.4	25.2	37.8
	N	24	24	24	24
	Deviation Vs Control [%]		-0.9	3.4	-2.4
day 42	Mean	392.3n	390.0	410.2	382.4
	S.d.	27.5	31.9	29.6	41.6
	N	24	24	24	24
	Deviation Vs Control [%]		-0.6	4.6	-2.5
day 49	Mean	422.2n	416.4	437.7	405.5
	S.d.	30.5	35.3	33.6	44.0
	N	24	24	24	24
	Deviation Vs Control [%]		-1.4	3.7	-4.0

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

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Study

90R0066/05R034_F1

Summary Body Weights - BW / Body Weights [g]

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
day 56	Mean	451.4 n	447.5	465.0	433.1
	S.d.	33.3	38.6	31.6	45.4
	N	24	24	21	24
	Deviation Vs Control [%]		-0.9	3.0	-4.0
day 63	Mean	472.2 n	466.1	485.4	454.5
	S.d.	38.1	40.7	36.5	46.9
	N	24	24	24	24
	Deviation Vs Control [%]		-1.3	2.8	-3.8
day 70	Mean	489.2 n	481.8	502.7	466.8
	S.d.	38.9	42.3	39.5	46.2
	N	24	24	24	24
	Deviation Vs Control [%]		-1.5	2.8	-4.6

Statistic Profile = Dunnett test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
n=DUNNETT

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Study

90R0066/05R034_F1

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
day 0	Mean	73.4 n	71.5	75.4	73.6
	S.d.	5.9	6.0	7.1	8.3
	N	24	24	24	24
	Deviation Vs Control [%]		-2.6	2.8	0.4
day 7	Mean	109.7 n	108.1	115.0	113.5
	S.d.	8.4	7.5	9.5	11.8
	N	24	24	23	24
	Deviation Vs Control [%]		-1.5	4.8	3.4
day 14	Mean	145.4 n	144.6	155.3 *	154.8 *
	S.d.	12.0	8.6	11.3	13.5
	N	24	24	23	24
	Deviation Vs Control [%]		-0.6	6.8	6.4
day 21	Mean	170.9 n	170.7	185.8 **	184.7 **
	S.d.	13.9	11.0	14.3	16.1
	N	24	24	23	24
	Deviation Vs Control [%]		-0.1	8.7	8.1

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

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Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
day 28	Mean	192.9 n	193.1	207.1 *	209.8 **
	S.d.	17.6	12.8	16.4	19.3
	N	24	24	23	24
	Deviation Vs Control [%]		0.1	7.3	8.7
day 35	Mean	210.9 n	211.1	226.6 *	229.7 **
	S.d.	19.3	15.3	18.1	20.2
	N	24	24	23	24
	Deviation Vs Control [%]		0.1	7.4	8.9
day 42	Mean	226.4 n	223.1	240.3	245.6 **
	S.d.	21.8	16.9	18.9	23.0
	N	24	24	23	24
	Deviation Vs Control [%]		-1.5	6.1	8.5
day 49	Mean	237.6 n	233.0	252.7 *	258.4 **
	S.d.	22.6	17.6	20.1	23.8
	N	24	24	23	24
	Deviation Vs Control [%]		-1.9	6.3	8.8

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

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Study 90R0066/05R034_F1

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
day 56	Mean	252.1 n	250.8	267.9 *	276.7 **
	S.d.	24.8	18.8	21.0	24.1
	N	24	24	23	24
	Deviation Vs Control [%]		-0.5	6.3	9.8
day 63	Mean	258.8 n	257.8	276.2 *	279.3 *
	S.d.	26.8	21.8	21.9	26.7
	N	24	24	23	24
	Deviation Vs Control [%]		-0.4	6.7	7.9
day 70	Mean	265.6 n	260.9	280.9	284.4 *
	S.d.	28.0	21.6	21.6	25.7
	N	24	24	23	24
	Deviation Vs Control [%]		-1.8	5.8	7.1

Statistic Profile = Dunnett test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
n=DUNNETT

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TABLE : 1A-
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PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - F1 MALES
MEAN PARENTAL BODY WEIGHTS -- GRAMS

WEEK	0	TEST GROUP 10			TEST GROUP 11			TEST GROUP 12			TEST GROUP 13		
		0 MG/KG BW/D			20 MG/KG BW/D			60 MG/KG BW/D			180 MG/KG BW/D		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
WEEK	0	503.0 D	39.60	24	498.2	41.74	24	517.7	42.79	24	479.7	51.09	24
WEEK	1	520.2 D	42.16	24	514.8	44.06	24	531.2	45.78	24	492.3	49.49	24
WEEK	2	530.6 D	45.61	24	523.5	44.87	24	542.1	48.83	24	505.0	50.77	24
WEEK	3	539.1 D	46.95	24	532.7	45.25	24	549.0	52.31	24	512.4	50.22	24
WEEK	4	552.1 D	47.66	24	546.5	46.61	24	566.4	52.64	24	529.0	51.34	24
WEEK	5	564.3 D	48.62	24	559.2	47.86	24	579.7	54.81	24	541.6	51.02	24

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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TABLE : IA-

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PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
MEAN MATERNAL BODY WEIGHTS DURING GESTATION -- GRAMS

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
DAY 0	MEAN	276.8 D	270.5	292.2	291.4
	S.D.	27.58	23.30	20.66	26.15
	N	24	24	21	23
DAY 7	MEAN	312.7 D	304.9	324.2	323.5
	S.D.	29.57	25.33	21.04	31.93
	N	24	24	21	23
DAY 14	MEAN	345.9 D	335.1	356.3	355.7
	S.D.	28.36	27.02	22.51	30.82
	N	24	24	21	23
DAY 20	MEAN	426.0 D	412.3	436.5	415.7
	S.D.	35.65	35.06	32.36	37.28
	N	24	24	21	23

Statistics: D=Dunnett-test (two-sided)
* : $p \leq 0.05$ ** : $p \leq 0.01$

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TABLE : IA-

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PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
MEAN MATERNAL BODY WEIGHTS DURING LACTATION -- GRAMS

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
DAY 0	MEAN	330.6 D	323.8	343.8	341.3
	S.D.	33.26	28.38	22.02	20.23
	N	24	24	21	21
DAY 1	MEAN	325.8 D	312.6	334.4	328.4
	S.D.	29.73	26.60	17.15	22.84
	N	24	24	21	21
DAY 4	MEAN	342.7 D	329.5	351.3	346.3
	S.D.	30.13	27.00	18.08	21.72
	N	24	24	21	21
DAY 7	MEAN	353.9 D	343.2	359.6	354.9
	S.D.	27.90	26.68	17.64	20.08
	N	24	24	21	21
DAY 10	MEAN	359.3 D	350.6	371.4	367.0
	S.D.	26.70	22.68	17.98	18.79
	N	24	24	21	21
DAY 14	MEAN	350.3 D	349.2	371.8*	366.3
	S.D.	35.33	23.96	14.81	17.54
	N	24	24	21	21
DAY 17	MEAN	358.8 D	346.4	368.1	359.3
	S.D.	25.84	24.41	23.07	15.42
	N	24	24	21	21
DAY 19	MEAN	350.5 D	343.2	362.6	359.9
	S.D.	28.31	22.39	18.55	18.20
	N	24	24	21	21
DAY 21	MEAN	342.3 D	332.9	356.6	353.0
	S.D.	25.56	25.07	17.47	19.31
	N	24	24	21	21

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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Study 90R0066/05R034_F1

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

	Test Group 10/M			Test Group 11/M			Test Group 12/M			Test Group 13/M		
	0 mg/kg bw/d			20 mg/kg bw/d			60 mg/kg bw/d			180 mg/kg bw/d		
d 0 -> 7	Mean	48.6 n		48.4			51.5			48.8		
	S.d.	5.0		5.2			6.4			7.2		
	N	24		24			24			24		
d 7 -> 14	Mean	61.6 n		50.7 **			43.8 **			46.0 **		
	S.d.	6.7		9.9			11.4			12.4		
	N	24		24			24			24		
d 14 -> 21	Mean	63.8 n		71.1			82.7 **			74.7 **		
	S.d.	7.5		10.9			12.1			12.5		
	N	24		24			24			24		
d 21 -> 28	Mean	57.1 n		57.8			61.2			56.1		
	S.d.	7.0		6.7			8.1			9.0		
	N	24		24			24			24		
d 28 -> 35	Mean	46.9 n		46.4			48.4			44.7		
	S.d.	6.8		7.6			9.1			7.5		
	N	24		24			24			24		
d 35 -> 42	Mean	34.5 n		35.5			40.1 *			33.1		
	S.d.	5.6		7.9			7.9			7.5		
	N	24		24			24			24		
d 42 -> 49	Mean	29.9 n		26.4			27.5			23.1 **		
	S.d.	6.4		5.8			6.9			5.8		
	N	24		24			24			24		

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Changes Body Weights - BW / Body Weights [g]

Sex: **Male** - Phase: **In-life**

	Test Group 10/M			Test Group 11/M			Test Group 12/M			Test Group 13/M		
	0 mg/kg bw/d			20 mg/kg bw/d			60 mg/kg bw/d			180 mg/kg bw/d		
d 49 -> 56	Mean	29.1 n		31.1			30.7			27.7		
	S.d.	4.8		6.1			4.2			6.6		
	N	24		24			21			24		
d 56 -> 63	Mean	20.8 n		18.6			21.4			21.4		
	S.d.	7.4		6.6			5.3			6.7		
	N	24		24			21			24		
d 63 -> 70	Mean	17.0 n		15.7			17.3			12.4 *		
	S.d.	4.3		5.0			8.2			5.4		
	N	24		24			24			24		
d 0 -> 70	Mean	409.3 n		401.7			420.4			387.9		
	S.d.	37.3		38.1			36.3			44.5		
	N	24		24			24			24		

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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12-Dec-2018 11:55

Ascentos™ 1.3

Study 90R0066/05R034_F1

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

	Test Group 10/F 0 mg/kg bw/d			Test Group 11/F 20 mg/kg bw/d			Test Group 12/F 60 mg/kg bw/d			Test Group 13/F 180 mg/kg bw/d		
	Mean	S.d.	N	Mean	S.d.	N	Mean	S.d.	N	Mean	S.d.	N
d 0 -> 7	36.4 n	4.8	24	36.6	3.0	24	39.8 *	3.9	23	39.8 *	5.2	24
d 7 -> 14	35.7 n	6.7	24	36.6	4.2	24	40.2 *	4.4	23	41.3 **	6.0	24
d 14 -> 21	25.4 n	5.7	24	26.1	5.1	24	30.5 *	5.8	23	29.9 *	6.7	24
d 21 -> 28	22.1 n	7.4	24	22.4	4.8	24	21.3	6.1	23	25.1	6.9	24
d 28 -> 35	18.0 n	6.3	24	18.0	5.5	24	19.5	5.9	23	19.9	7.0	24
d 35 -> 42	15.5 n	5.6	24	12.0	7.0	24	13.7	7.0	23	16.0	6.7	24
d 42 -> 49	11.2 n	5.4	24	9.9	6.6	24	12.4	6.2	23	12.8	7.2	24

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Ascentos™ 1.3

Study

90R0066/05R034_F1

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

	Test Group 10/F			Test Group 11/F			Test Group 12/F			Test Group 13/F		
			0 mg/kg bw/d			20 mg/kg bw/d			60 mg/kg bw/d			180 mg/kg bw/d
d 49 -> 56	Mean		14.5 n			17.8			15.2			18.3
	S.d.		6.9			4.9			7.3			4.7
	N		24			24			23			24
d 56 -> 63	Mean		6.7 n			7.0			8.3			2.6
	S.d.		7.0			5.5			6.8			7.3
	N		24			24			23			24
d 63 -> 70	Mean		6.8 n			3.1			4.6			5.1
	S.d.		6.2			7.0			6.9			8.0
	N		24			24			23			24
d 0 -> 70	Mean		192.2 n			189.4			205.6			210.8 *
	S.d.		26.5			19.2			19.8			23.1
	N		24			24			23			24

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

4-DEC-18

05R034M1

TABLE : IA-

136

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - F1 MALES
MEAN PARENTAL BODY WEIGHT CHANGE -- GRAMS

MALES

		TEST GROUP 10			TEST GROUP 11			TEST GROUP 12			TEST GROUP 13		
		0 MG/KG BW/D			20 MG/KG BW/D			60 MG/KG BW/D			180 MG/KG BW/D		
WEEK	0 TO	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
1	0 TO 1	17.2 D	7.92	24	16.6	7.57	24	13.5	9.20	24	12.6	8.22	24
2	1 TO 2	10.5 D	5.87	24	8.7	6.06	24	10.9	6.69	24	12.7	10.46	24
3	2 TO 3	8.5 D	4.78	24	9.1	6.60	24	6.9	6.95	24	7.4	6.50	24
4	3 TO 4	13.0 D	6.43	24	13.8	5.26	24	17.5*	6.03	24	16.6	6.03	24
5	4 TO 5	12.2 D	4.60	24	12.7	4.64	24	13.3	10.70	24	12.6	6.15	24
5	0 TO 5	61.3 D	16.42	24	61.0	15.80	24	62.1	21.26	24	61.9	12.90	24

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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05R034L2

TABLE : IA- 137

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

DAYS	0 TO 7	TEST GROUP 10			TEST GROUP 11			TEST GROUP 12			TEST GROUP 13		
		0 MG/KG BW/D			20 MG/KG BW/D			60 MG/KG BW/D			180 MG/KG BW/D		
		MEAN	36.0 D		34.3			31.9			32.1		
		S.D.	6.28		7.04			7.19			12.42		
		N	24		24			21			23		
		MEAN	33.2 D		30.2			32.2			32.2		
		S.D.	4.90		6.80			9.44			7.58		
		N	24		24			21			23		
		MEAN	80.1 D		77.2			80.1			60.0**		
		S.D.	11.71		12.78			17.75			25.03		
		N	24		24			21			23		
		MEAN	149.2 D		141.7			144.2			124.4**		
		S.D.	14.76		21.48			26.29			30.19		
		N	24		24			21			23		

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034L2

TABLE : 1A-

138

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
MEAN MATERNAL BODY WEIGHT CHANGE DURING LACTATION -- GRAMS

DAYS	0 TO 1	TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
	MEAN	-4.8 D	-11.2	-9.3	-12.9
	S.D.	12.81	12.59	14.09	12.25
	N	24	24	21	21
DAYS	1 TO 4	MEAN	16.9 D	16.9	17.8
	S.D.	8.37	9.72	8.30	11.71
	N	24	24	21	21
DAYS	4 TO 7	MEAN	11.2 D	8.3	8.7
	S.D.	7.25	9.74	13.52	12.27
	N	24	24	21	21
DAYS	7 TO 10	MEAN	5.4 D	11.9	12.0
	S.D.	11.38	7.4	14.81	15.65
	N	24	24	21	21
DAYS	10 TO 14	MEAN	-9.0 D	0.4	-0.6
	S.D.	18.95	17.29	10.71	16.01
	N	24	24	21	21
DAYS	14 TO 17	MEAN	8.6 D	-3.7*	-7.0**
	S.D.	20.85	16.62	15.44	12.10
	N	24	24	21	21
DAYS	17 TO 19	MEAN	-8.3 D	-5.5	0.6
	S.D.	18.09	11.44	14.97	11.16
	N	24	24	21	21
DAYS	19 TO 21	MEAN	-8.3 D	-6.0	-6.9
	S.D.	14.24	12.61	14.60	13.76
	N	24	24	21	21
DAYS	0 TO 21	MEAN	11.7 D	12.8	11.7
	S.D.	17.38	19.03	13.20	14.84
	N	24	24	21	21

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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05R034DO
TABLE : 1A-
139

PROJ. NO. 90R0066/05R034: MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - DCO (COHORT 1B)

SUMMARY OF MALE CLINICAL OBSERVATIONS

MALES

	GROUP#	WEEK OF STUDY																	
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	TOTAL
# OF ANIMALS EXAMINED	10	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	11	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	12	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	13	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24

NORMAL

NOTHING ABNORMAL DETECTED	10	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	11	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	12	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	13	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24

4-DEC-18	05R034DO	TABLE : 1A-	140																		
PROJ. NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - DCO (COHORT 1B)																					
FEMALES																					
SUMMARY OF FEMALE CLINICAL OBSERVATIONS																					
# OF ANIMALS EXAMINED	GROUP#	WEEK OF STUDY																			
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	TOTAL
NORMAL	10	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	11	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	12	24	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23
	13	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
DEAD	10	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	11	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
	12	24	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	24
	13	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	23	24	24	24
ACCIDENTAL DEATH	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MISCELLANEOUS	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1

4-DEC-18

05R034F1

TABLE : IA- 141

PROJ.NO. 90R0066/05R034:MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOXICITY STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - F1 FEMALES
SUMMARY OF MEAN ESTROUS CYCLE DURATION

	TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
MEAN# OF DAYS FROM ESTRUS TO ESTRUS	3.9 D	4.0	4.0	4.5
S.D.	0.29	0.16	0.13	1.51
N	24	24	23	24

Statistics: D=Dunnett-test (two-sided)
* : $p \leq 0.05$ ** : $p \leq 0.01$

4-DEC-18

05R034L2

TABLE : 1A- 142

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)

SUMMARY OF COHABITATION DATA

	TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
Males placed with females	N 24	24	23	24
mated (A)	N 24 F	24	23	24
male mating index (B)	100	100	100	100
did not mate	N 0 F	0	0	0
	% 0.0	0.0	0.0	0.0
with females pregnant (C)	N 24 F	24	22	23
male fertility index (D)	100	100	96	96
without females pregnant	N 0 F	0	1	1
	% 0.0	0.0	4.3	4.2

Statistics: F=Fisher's exact test (two-sided)

* : p<=0.05 ** : p<=0.01

(A) DEFINED BY A FEMALE WITH VAGINAL SPERM, OR THAT GAVE BIRTH TO A LITTER, OR WITH PUPS/IMPLANTATIONS IN UTERO

(B) MALE MATING INDEX = NUMBER OF MALES WITH CONFIRMED MATINGS

NUMBER OF MALES PLACED WITH FEMALES X 100

(C) DEFINED BY A FEMALE GIVING BIRTH TO A LITTER, OR WITH PUPS/IMPLANTATIONS IN UTERO

(D) MALE FERTILITY INDEX = NUMBER OF MALES PROVING THEIR FERTILITY X 100

NUMBER OF MALES PLACED WITH FEMALES

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05R034L2

TABLE : IA- 143

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY OF FEMALE REPRODUCTION AND DELIVERY DATA

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
Females on Study	N	24	24	23	24
Females Mated	N	24F1	24	23	24
Female Mating Index	%	100	100	100	100
Mating days until day 0 pc	MEAN	3.0 D	2.4	2.5	3.0
	S.D.	1.16	1.18	1.22	1.99
	N	24	24	22	24
days 1 to 4	N	23	24	22	22
	%	96	100	100	92
days 5 to 8	N	1	0	0	1
	%	4.2	0.0	0.0	4.2
days 9 to 14	N	0	0	0	1
	%	0.0	0.0	0.0	4.2
days 15 to 21	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Females Pregnant	N	24F1	24	22	23
Female Fertility Index	%	100	100	96	96
Duration of Gestation (Days)	MEAN	22.0 D	21.9	22.0	22.0
	S.D.	0.00	0.28	0.32	0.55
Implantation sites	TOTAL	364	350	338	316
	MEAN	15.2 D	14.6	15.4	13.7
	S.D.	2.55	2.12	3.65	3.83
	N	24	24	22	23
Postimplantation Loss	TOTAL	22	18	25	76
	MEAN	0.9 D	0.8	1.1	3.3**
	S.D.	0.97	0.79	1.28	3.94
	N	24	24	22	23
% Postimplantation Loss	MEAN	6.4 D	5.3	11.1	24.6**
	S.D.	6.43	5.71	21.25	30.10
	N	24	24	22	23

Statistics: D=Dunnett-test (two-sided) F1=Fisher's exact test (one-sided)

* : p<=0.05 ** : p<=0.01

THE INDICES ARE DEFINED IN THE TEXT

4-DEC-18

05R034L2

TABLE : IA- 144

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY OF FEMALE REPRODUCTION AND DELIVERY DATA

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
Females with Liveborn Gestation Index	N %	24Fi 100	24 100	21 95	21 91
with Stillborn Pups	N %	5Fi 21	2 8.3	2 9.5	6 29
with all Stillborn	N %	0Fi 0.0	0 0.0	0 0.0	0 0.0
Pups Delivered	MEAN	14.3 D	13.8	14.9	11.4**
	S.D.	2.82	2.35	1.73	4.49
	TOTAL	342	332	313	240
Liveborn	N	336Fi	330	311	234
Live Birth Index	%	98	99	99	98
Stillborn	N	6Fi	2	2	6
	%	1.8	0.6	0.6	2.5

Statistics: D=Dunnett-test (two-sided) Fi =Fisher's exact test (one-sided)

* : p<=0.05 ** : p<=0.01

THE INDICES ARE DEFINED IN THE TEXT

4-DEC-18

05R034L2

TABLE : IA- 145

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY OF LITTER DATA

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
(Total Number of) Litters	N	24	24	21	21
Litters with Liveborn Pups	N	24Fi	24	21	21
	%	100	100	100	100
Litters with Stillborn Pups	N	5Fi	2	2	6
	%	21	8.3	9.5	29
Litters with all Stillborn Pups	N	0Fi	0	0	0
	%	0.0	0.0	0.0	0.0
Pups Delivered	TOTAL	342	332	313	240
	MEAN	14.3 D	13.8	14.9	11.4**
	S.D.	2.82	2.35	1.73	4.49
Pups Liveborn	N	336Fi	330	311	234
	%	98	99	99	98
Pups Stillborn	N	6Fi	2	2	6
	%	1.8	0.6	0.6	2.5
Pups Died	N	2Fi	0	4	2
	%	0.6	0.0	1.3	0.8
Pups Sacrificed Moribund	N	0Fi	0	0	0
	%	0.0	0.0	0.0	0.0
Pups Cannibalized	N	5Fi	2	4	1
	%	1.5	0.6	1.3	0.4
Pups Accidental Death	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Pups Sacrificed, Maternal Death	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Pups Culled day 4	N	93	93	94	50
	%	27	28	30	21

Statistics: D=Dunnett-test (two-sided) Fi =Fisher's exact test (one-sided)

* : p<=0.05 ** : p<=0.01

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05R034L2

TABLE : IA- 146

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY OF LITTER DATA

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
Pups dead day 0	N %	0 0.0	0 0.0	1 0.3	0 0.0
days 1 to 4	N %	7 2.1	1 0.3	6 1.9	2 0.9
days 5 to 7	N %	0 0.0	0 0.0	1 0.3	1 0.4
days 8 to 14	N %	0 0.0	1 0.3	0 0.0	0 0.0
days 15 to 21	N %	0 0.0	0 0.0	0 0.0	0 0.0
Pups Surviving days 0 to 4 Viability Index	N %	329Fi 98	329 100	304 98	232 99
Pups Surviving days 4 to 21 Lactation Index	N %	236Fi 100	235 100	209 100	181 99

Statistics: Fi =Fisher's exact test (one-sided)

* : p<=0.05 ** : p<=0.01

THE INDICES ARE DEFINED IN THE TEXT. Pups Dead = Pups Died + Sacrificed Moribund + Cannibalized

4-DEC-18
05R034L2
TABLE : IA-
147

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)

SUMMARY OF LITTER DATA

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
Live Pups/Litter					
day 1	MEAN	13.8	13.8	14.6	11.0
	S.D.	2.73	2.47	1.88	4.33
	TOTAL	332	330	307	232
day 4 (preculling)	MEAN	13.7	13.7	14.5	11.0
	S.D.	2.71	2.44	2.09	4.33
	TOTAL	329	329	304	232
day 4 (postculling)	MEAN	9.8	9.8	10.0	8.7
	S.D.	0.82	0.56	0.00	2.31
	TOTAL	236	236	210	182
day 7	MEAN	9.8	9.8	10.0	8.6
	S.D.	0.82	0.56	0.22	2.29
	TOTAL	236	236	209	181
day 14	MEAN	9.8	9.8	10.0	8.6
	S.D.	0.82	0.59	0.22	2.29
	TOTAL	236	235	209	181
day 21	MEAN	9.8	9.8	10.0	8.6
	S.D.	0.82	0.59	0.22	2.29
	TOTAL	236	235	209	181
Sex Ratio					
day 0	- live Males	52.7	52.1	47.3	48.7
	- live Females	47.3	47.9	52.7	51.3
day 21	- live Males	51.7	49.4	47.8	47.0
	- live Females	48.3	50.6	52.2	53.0

4-DEC-18

05R034L2

TABLE : IA- 148

PROJ.NO. 90R0066/05R034:MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY - PRESENCE OF AREOLAS/NIPPLES

	TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
AREOLAS/NIPPLES				
Litters tested	24	24	21	21
Pups tested	122	116	100	85
Pups reaching criteria	96	88	77	56
%	79	76	77	66
Pups reaching criteria/litter	79.5W1	75.7	76.3	59.8
MEAN%				
S.D.	20.88	27.05	22.85	40.06

Statistics: Wt =Wilcoxon-test (one-sided)

* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034L2

TABLE : IA- 149

PROJ.NO. 90R0066/05R034:MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY - PRESENCE OF AREOLAS/NIPPLES

	TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
AREOLAS/NIPPLES - SECOND OBS				
Litters tested	24	24	21	21
Pups tested	122	116	100	85
Pups reaching criteria	0	0	0	0
%	0.0	0.0	0.0	0.0
Pups reaching criteria/litter	0.071	0.0	0.0	0.0
MEAN%	0.00	0.00	0.00	0.00
S.D.				

Statistics: Wt =Wilcoxon-test (one-sided)

* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034L2

TABLE : IA-

150

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY OF PUP BODY WEIGHTS -- GRAMS

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
day 1 males	MEAN S.D. N	7.5 D 0.48 24	7.5 0.66 24	7.4 0.65 21	8.0 1.10 21
day 1 females	MEAN S.D. N	7.2 D 0.48 24	7.0 0.57 24	7.0 0.59 21	7.7* 0.97 20
day 1 males+females	MEAN S.D. N	7.4 D 0.48 24	7.2 0.59 24	7.2 0.60 21	7.9 1.03 21
day 4 males preculling	MEAN S.D. N	11.3 D 1.04 24	11.0 1.27 24	11.0 1.11 21	12.2 2.11 21
day 4 females preculling	MEAN S.D. N	10.9 D 1.06 24	10.4 1.22 24	10.3 1.00 21	11.7 2.01 20
day 4 males+females preculling	MEAN S.D. N	11.1 D 1.03 24	10.7 1.20 24	10.6 1.02 21	12.0 2.04 21
day 4 males postculling	MEAN S.D. N	11.3 D 1.05 24	11.0 1.26 24	11.0 1.12 21	12.3 2.04 21
day 4 females postculling	MEAN S.D. N	10.9 D 1.00 24	10.5 1.20 24	10.5 1.13 21	11.8 1.96 20
day 4 males+females postculling	MEAN S.D. N	11.1 D 1.02 24	10.7 1.19 24	10.8 1.10 21	12.1 1.97 21

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034L2

TABLE : IA-

151

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY OF PUP BODY WEIGHTS -- GRAMS

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
day 7 males	MEAN S.D. N	18.5 D 1.50 24	17.9 1.78 24	18.1 1.38 21	19.3 2.62 21
day 7 females	MEAN S.D. N	17.9 D 1.31 24	17.0 1.61 24	17.4 1.58 21	18.6 2.56 20
day 7 males+females	MEAN S.D. N	18.2 D 1.40 24	17.5 1.66 24	17.7 1.46 21	19.0 2.56 21
day 14 males	MEAN S.D. N	35.9 D 3.01 24	35.4 3.23 24	35.3 2.21 21	37.4 4.58 21
day 14 females	MEAN S.D. N	34.9 D 2.80 24	34.2 2.95 24	34.4 2.40 21	36.2 4.55 20
day 14 males+females	MEAN S.D. N	35.4 D 2.93 24	34.8 3.06 24	34.9 2.28 21	36.9 4.55 21
day 21 males	MEAN S.D. N	59.1 D 4.61 24	58.9 4.84 24	58.6 3.68 21	61.1 7.26 21
day 21 females	MEAN S.D. N	56.9 D 4.00 24	56.2 4.25 24	56.5 3.96 21	58.3 6.50 20
day 21 males+females	MEAN S.D. N	58.1 D 4.35 24	57.5 4.48 24	57.5 3.83 21	60.0 6.93 21

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18
05R034L2
TABLE : IA-
152

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY OF PUP BODY WEIGHT CHANGES -- GRAMS

DAYS 1 TO 4		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
males	MEAN	3.7 D	3.5	3.5	4.2
	S.D.	0.68	0.72	0.71	1.10
	N	24	24	21	21
females	MEAN	3.7 D	3.4	3.4	4.1
	S.D.	0.71	0.76	0.66	1.14
	N	24	24	21	20
males+females	MEAN	3.7 D	3.5	3.5	4.1
	S.D.	0.69	0.71	0.67	1.10
	N	24	24	21	21
DAYS 4 TO 7					
males	MEAN	7.2 D	6.9	7.0	7.0
	S.D.	0.79	0.98	0.63	0.92
	N	24	24	21	21
females	MEAN	6.9 D	6.6	6.8	6.8
	S.D.	0.77	0.88	0.64	0.93
	N	24	24	21	20
males+females	MEAN	7.1 D	6.7	6.9	6.9
	S.D.	0.77	0.93	0.62	0.91
	N	24	24	21	21
DAYS 7 TO 14					
males	MEAN	17.4 D	17.5	17.3	18.1
	S.D.	1.88	1.96	1.17	2.29
	N	24	24	21	21
females	MEAN	17.0 D	17.1	17.1	17.7
	S.D.	1.85	1.75	1.23	2.35
	N	24	24	21	20
males+females	MEAN	17.2 D	17.3	17.2	18.0
	S.D.	1.88	1.83	1.17	2.32
	N	24	24	21	21

Statistics: D=Punnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18
05R034L2
TABLE : 1A-
153

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)

SUMMARY OF PUP BODY WEIGHT CHANGES -- GRAMS

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
DAYS 14 TO 21					
males	MEAN	23.3 D	23.4	23.3	23.7
	S.D.	2.18	1.99	1.92	3.10
	N	24	24	21	21
females	MEAN	22.0 D	22.1	22.0	22.1
	S.D.	1.70	1.76	1.98	2.37
	N	24	24	21	20
males+females	MEAN	22.7 D	22.8	22.6	23.0
	S.D.	1.94	1.79	1.94	2.80
	N	24	24	21	21
DAYS 4 TO 21					
males	MEAN	47.9 D	47.9	47.7	48.9
	S.D.	4.12	4.30	3.01	5.54
	N	24	24	21	21
females	MEAN	46.0 D	45.8	46.1	46.6
	S.D.	3.57	3.64	3.27	4.80
	N	24	24	21	20
males+females	MEAN	47.0 D	46.9	46.9	47.9
	S.D.	3.88	3.91	3.15	5.23
	N	24	24	21	21

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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05R034L2

TABLE : IA- 154

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)

SUMMARY OF PUP ANOGENITAL DISTANCE

AG DIST DAY 1 of Male Pups	UNITS: MM	TEST GROUP 10 0 MG/KG BW/D			TEST GROUP 11 20 MG/KG BW/D			TEST GROUP 12 60 MG/KG BW/D			TEST GROUP 13 180 MG/KG BW/D		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
		3.44	0.203	24	3.49	0.248	24	3.42	0.198	21	3.56	0.283	21

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

4-DEC-18
05R034L2
TABLE : IA-
155

PROJ.NO. 90R0066/05R034:MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)

SUMMARY OF PUP ANOGENITAL DISTANCE

AG DIST DAY 1	UNITS: MM	TEST GROUP 10			TEST GROUP 11			TEST GROUP 12			TEST GROUP 13		
		0 MG/KG BW/D			20 MG/KG BW/D			60 MG/KG BW/D			180 MG/KG BW/D		
of Female Pups	MEAN	1.67 D			1.67			1.65			1.71		
	S.D.	0.094			0.092			0.057			0.104		
	N	24			24			21			20		

Statistics: D=Dunnett-test (two-sided)
* : $p \leq 0.05$ ** : $p \leq 0.01$

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05R034L2

TABLE : IA- 156

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY OF POP ANOGENITAL INDEX (FORMULA WITH CUBIC ROOT)

AG DIST DAY 1 of Male Pups	TEST GROUP 10 0 MG/KG BW/D		TEST GROUP 11 20 MG/KG BW/D		TEST GROUP 12 60 MG/KG BW/D		TEST GROUP 13 180 MG/KG BW/D	
	MEAN	N	MEAN	N	MEAN	N	MEAN	N
	1.75 D	24	1.79	24	1.75	21	1.78	21
	0.098		0.104		0.088		0.089	

Statistics: D=Dunnett-test (two-sided)
* : p<=0.05 ** : p<=0.01

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05R034L2

TABLE : IA- 157

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)
SUMMARY OF POP ANOGENITAL INDEX (FORMULA WITH CUBIC ROOT)

AG DIST DAY 1 of Female Pups	TEST GROUP 10 0 MG/KG BW/D		TEST GROUP 11 20 MG/KG BW/D		TEST GROUP 12 60 MG/KG BW/D		TEST GROUP 13 180 MG/KG BW/D	
	MEAN	N	MEAN	N	MEAN	N	MEAN	N
	0.87 D	24	0.88	24	0.86	21	0.87	20
	0.044		0.042		0.034		0.036	

Statistics: D=Dunnett-test (two-sided)
* : $p \leq 0.05$ ** : $p \leq 0.01$

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05R034L2

TABLE : IA- 158

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)

SUMMARY OF PUP DATA

PUP ORGAN WEIGHTS IN GRAMS		TEST GROUP 10	TEST GROUP 11	TEST GROUP 12	TEST GROUP 13
		0 MG/KG BW/D	20 MG/KG BW/D	60 MG/KG BW/D	180 MG/KG BW/D
BRAIN Males+Females	MEAN	1.502KW	1.496	1.488	1.514
	S.D.	0.0713	0.0585	0.0704	0.0568
	N	24	24	21	21
of Male Pups	MEAN	1.518KW	1.521	1.507	1.521
	S.D.	0.0784	0.0890	0.0947	0.0724
	N	24	24	21	21
of Female Pups	MEAN	1.486KW	1.471	1.469	1.507
	S.D.	0.0765	0.0645	0.0624	0.0605
	N	24	24	21	20
THYMUS Males+Females	MEAN	0.246KW	0.229	0.219	0.228
	S.D.	0.0511	0.0386	0.0495	0.0487
	N	24	24	21	21
of Male Pups	MEAN	0.236KW	0.228	0.220	0.221
	S.D.	0.0525	0.0405	0.0635	0.0606
	N	24	24	21	21
of Female Pups	MEAN	0.256KW	0.229	0.219	0.238
	S.D.	0.0599	0.0481	0.0486	0.0494
	N	24	24	21	20
SPLEEN Males+Females	MEAN	0.201KW	0.223	0.196	0.222
	S.D.	0.0524	0.0334	0.0460	0.0632
	N	24	24	21	21
of Male Pups	MEAN	0.196KW	0.232	0.190	0.234
	S.D.	0.0607	0.0503	0.0501	0.0786
	N	24	24	21	21
of Female Pups	MEAN	0.205KW	0.213	0.202	0.210
	S.D.	0.0509	0.0423	0.0527	0.0627
	N	24	24	21	20

Statistics: KW=Kruskal-Wallis + Wilcoxon-test (two-sided)

* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034L2

TABLE : IA- 159

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)

SUMMARY OF PUP DATA
PUP ORGAN WEIGHT TO BODY WEIGHT RATIO

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
BRAIN Males+Females	MEAN S.D. N	2.569KW 0.1959 24	2.578 0.2106 24	2.605 0.1617 21	2.534 0.2675 21
of Male Pups	MEAN S.D. N	2.566KW 0.2099 24	2.549 0.2765 24	2.612 0.1796 21	2.475 0.2553 21
of Female Pups	MEAN S.D. N	2.573KW 0.2119 24	2.607 0.1791 24	2.598 0.1971 21	2.617 0.2832 20
THYMUS Males+Females	MEAN S.D. N	0.418KW 0.0724 24	0.393 0.0670 24	0.382 0.0797 21	0.380 0.0774 21
of Male Pups	MEAN S.D. N	0.396KW 0.0700 24	0.382 0.0731 24	0.377 0.1032 21	0.355 0.0935 21
of Female Pups	MEAN S.D. N	0.440KW 0.0929 24	0.404 0.0823 24	0.387 0.0782 21	0.411 0.0824 20
SPLEEN Males+Females	MEAN S.D. N	0.338KW 0.0730 24	0.381 0.0518 24	0.342 0.0721 21	0.362 0.0830 21
of Male Pups	MEAN S.D. N	0.326KW 0.0825 24	0.385 0.0736 24	0.328 0.0845 21	0.370 0.1029 21
of Female Pups	MEAN S.D. N	0.351KW 0.0751 24	0.377 0.0726 24	0.355 0.0867 21	0.357 0.0878 20

Statistics: KW=Kruskal-Wallis + Wilcoxon-test (two-sided)

* : p<=0.05 ** : p<=0.01

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05R034L2

TABLE : IA-

160

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)

SUMMARY OF PUP NECROPSY OBSERVATIONS

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
Litters Evaluated	N	24	24	21	21
Pups Evaluated	N	336	330	309	239
Live	N	330	328	307	233
Stillborn	N	6	2	2	6
POST MORTEM AUTOLYSIS					
Pup Incidence	N	3	1	1	0
	%	0.9	0.3	0.3	0.0
Litter Incidence	N	3Fi	1	1	0
	%	13	4.2	4.8	0.0
Affected Pups/Litter	MEAN%	0.9Wi	0.5	0.4	0.0
	S.D.	2.57	2.27	1.68	0.00
EMPTY STOMACH					
Pup Incidence	N	0	0	1	1
	%	0.0	0.0	0.3	0.4
Litter Incidence	N	0Fi	0	1	1
	%	0.0	0.0	4.8	4.8
Affected Pups/Litter	MEAN%	0.0Wi	0.0	0.3	0.3
	S.D.	0.00	0.00	1.56	1.28
DILATED RENAL PELVIS					
Pup Incidence	N	5	2	2	2
	%	1.5	0.6	0.6	0.8
Litter Incidence	N	5Fi	2	2	2
	%	21	8.3	9.5	9.5
Affected Pups/Litter	MEAN%	1.5Wi	0.7	0.6	0.8
	S.D.	3.05	2.59	1.88	2.76

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)

* : p<=0.05 ** : p<=0.01

4-DEC-18

05R034L2

TABLE : IA- 161

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) F1 FEMALES (L2 LITTER)

SUMMARY OF PUP NECROPSY OBSERVATIONS

		TEST GROUP 10 0 MG/KG BW/D	TEST GROUP 11 20 MG/KG BW/D	TEST GROUP 12 60 MG/KG BW/D	TEST GROUP 13 180 MG/KG BW/D
Litters Evaluated	N	24	24	21	21
Pups Evaluated	N	336	330	309	239
Live	N	330	328	307	233
Stillborn	N	6	2	2	6
SMALL TESTIS Pup Incidence	N	1	0	0	0
	%	0.3	0.0	0.0	0.0
Litter Incidence	N	1Fi	0	0	0
	%	4.2	0.0	0.0	0.0
Affected Pups/Litter	MEAN%	0.3Wi	0.0	0.0	0.0
	S.D.	1.46	0.00	0.00	0.00
TOTAL PUP NECROPSY OBSERVATIONS	N	9	3	4	3
Pup Incidence	%	2.7	0.9	1.3	1.3
Litter Incidence	N	7Fi	2	4	3
	%	29	8.3	19	14
Affected Pups/Litter	MEAN%	2.7Wi	1.2	1.3	1.1
	S.D.	5.01	4.68	2.76	2.97

Statistics: Fi =Fisher's exact test (one-sided) Wi =Wilcoxon-test (one-sided)

* : p<=0.05 ** : p<=0.01

IA- 162
12-Dec-2018 09:48
Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
Animals examined	N	10	10	10
Animals with signs	N	0	0	0
head	N	0	0	0
salivation	N	0	0	0
dead	N	10	10	10
sacrificed scheduled	N	10	10	10
normal	N	10	10	10
NAD	N	10	10	10

day 0 [00:00 - 24:00] -> day 50 [00:00 - 24:00]

IA- 163
12-Dec-2018 09:49
Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary - Clinical Observation

Sex: **Female** - Phase: **In-life**

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
Animals examined	N 10	10	10	10
Animals with signs	N 0	0	0	1
head	N 0	0	0	1
salivation	N 0	0	0	1
dead	N 10	10	10	10
sacrificed scheduled	N 10	10	10	10
normal	N 10	10	10	10
NAD	N 10	10	10	10

day 0 [00:00 - 24:00] -> day 50 [00:00 - 24:00]

IA- 164
12-Dec-2018 09:52
Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
Animals examined	N 10	10	10	10
Animals with signs	N 0	0	0	0
head	N 0	0	0	0
salivation	N 0	0	0	0
normal	N 10	10	10	10
NAD				

day 0 -> 49
[-03:00-00:00]

IA- 165
12-Dec-2018 09:52
Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
Animals examined	N 10	10	10	10
Animals with signs	N 0	0	0	3
head	N 0	0	0	3
salivation	N 0	0	0	3
normal	N 10	10	10	10
NAD	N 10	10	10	10

day 0 -> 49
[00:00-02:00]

IA- 166
12-Dec-2018 09:52
Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
Animals examined	N 10	10	10	10
Animals with signs	N 0	0	0	0
head	N 0	0	0	0
salivation	N 0	0	0	0
normal	N 10	10	10	10
NAD	N 10	10	10	10

day 0 -> 49
[02:00-05:00]

IA- 167

12-Dec-2018 09:53

Ascentos™ 1.3

Study 90R0066/05R034_2A

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: Female - Phase: In-life

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
	N	10	10	10
Animals examined	N	0	0	0
Animals with signs	N	0	0	0
head	N	0	0	0
salivation	N	0	0	0
normal	N	10	10	10
NAD	N	10	10	10

day 0 -> 49
[-03:00-00:00]

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12-Dec-2018 09:53

Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: Female - Phase: In-life

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
Animals examined	N	10	10	10
Animals with signs	N	0	0	1
head	N	0	0	1
salivation	N	0	0	1
normal	N	10	10	10
NAD	N	10	10	10

day 0 -> 49
[00:00-02:00]

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12-Dec-2018 09:53

Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: Female - Phase: In-life

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
Animals examined	N	10	10	10
Animals with signs	N	0	0	0
head	N	0	0	0
salivation	N	0	0	0
normal	N	10	10	10
NAD	N	10	10	10

day 0 -> 49
[02:00-05:00]

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12-Dec-2018 09:56

Ascentos™ 1.3

Study 90R0066/05R034_2A

Summary Water Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 0 -> 4	Mean [g]	20.9 n	21.0	23.3	21.9
	S.d.	1.0	1.4	2.7	2.5
	N	5	5	5	5
	Deviation Vs Control [%]		0.3	11.2	4.5
d 7 -> 11	Mean [g]	27.7 n	27.5	28.3	29.2
	S.d.	1.5	1.1	2.0	3.5
	N	5	5	5	5
	Deviation Vs Control [%]		-0.8	2.1	5.2
d 14 -> 18	Mean [g]	30.2 n	30.1	32.0	33.3
	S.d.	1.7	1.9	2.7	3.4
	N	5	5	5	5
	Deviation Vs Control [%]		-0.5	5.9	10.1
d 21 -> 25	Mean [g]	33.6 n	33.4	33.6	36.1
	S.d.	3.6	2.4	3.0	4.1
	N	5	5	5	5
	Deviation Vs Control [%]		-0.6	0.2	7.5
d 28 -> 32	Mean [g]	36.1 n	36.3	37.5	39.0
	S.d.	5.3	2.3	3.1	2.3
	N	5	5	5	5
	Deviation Vs Control [%]		0.5	3.7	7.8

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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12-Dec-2018 09:56

Ascentos™ 1.3

Study 90R0066/05R034_2A

Summary Water Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 35 -> 39					
	Mean [g]	38.1 n	38.1	39.0	40.6
	S.d.	6.2	1.7	2.7	3.1
	N	5	5	5	5
	Deviation Vs Control [%]		-0.2	2.3	6.3
d 42 -> 46					
	Mean [g]	36.3 n	36.2	37.4	38.4
	S.d.	6.2	2.2	4.0	2.4
	N	5	5	5	5
	Deviation Vs Control [%]		-0.3	2.9	5.8

Statistic Profile = Dunnett test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
n=DUNNETT; d = day

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12-Dec-2018 09:58

Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Water Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 0 -> 4	Mean [g]	18.5 n	17.7	19.7	20.3
	S.d.	1.4	1.6	1.6	3.4
	N	5	5	5	5
	Deviation Vs Control [%]		-4.2	6.8	9.9
d 7 -> 11	Mean [g]	21.7 n	21.1	22.7	23.3
	S.d.	2.7	2.0	2.4	3.6
	N	5	5	5	5
	Deviation Vs Control [%]		-2.9	4.6	7.4
d 14 -> 18	Mean [g]	21.9 n	21.3	22.2	23.1
	S.d.	3.5	2.2	2.2	2.1
	N	5	5	5	5
	Deviation Vs Control [%]		-2.6	1.6	5.5
d 21 -> 25	Mean [g]	22.5 n	21.2	22.6	23.5
	S.d.	3.9	3.1	2.7	3.0
	N	5	5	5	5
	Deviation Vs Control [%]		-6.0	0.3	4.3
d 28 -> 32	Mean [g]	25.3 n	25.3	25.7	28.3
	S.d.	3.6	3.3	3.6	2.5
	N	5	5	5	5
	Deviation Vs Control [%]		0.0	1.2	11.5

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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12-Dec-2018 09:58

Ascentos™ 1.3

Study 90R0066/05R034_2A

Summary Water Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 35 -> 39	Mean [g]	27.5 n	26.5	27.2	28.9
	S.d.	4.6	4.2	4.3	2.2
	N	5	5	5	5
	Deviation Vs Control [%]		-3.6	-0.9	5.0
d 42 -> 46	Mean [g]	27.8 n	25.7	27.3	27.6
	S.d.	5.3	3.6	3.7	2.2
	N	5	5	5	5
	Deviation Vs Control [%]		-7.5	-1.8	-0.8

Statistic Profile = Dunnett test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
n=DUNNETT; d = day

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12-Dec-2018 10:00

Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Food Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 0 -> 7	Mean [g]	17.5 n	16.8	17.4	17.4
	S.d.	0.6	1.4	1.2	1.3
	N	5	5	5	5
	Deviation Vs Control [%]		-3.9	-0.4	-0.5
d 7 -> 14	Mean [g]	23.5 n	22.4	23.6	24.1
	S.d.	0.7	1.4	0.8	2.3
	N	5	5	5	5
	Deviation Vs Control [%]		-4.7	0.3	2.3
d 14 -> 21	Mean [g]	26.7 n	24.9	26.8	27.4
	S.d.	1.0	2.0	0.6	2.1
	N	5	5	5	5
	Deviation Vs Control [%]		-6.6	0.5	2.7
d 21 -> 28	Mean [g]	31.2 n	28.5	30.0	31.5
	S.d.	1.7	2.3	0.9	2.0
	N	5	5	5	5
	Deviation Vs Control [%]		-8.5	-3.9	1.1
d 28 -> 35	Mean [g]	30.9 n	29.8	30.7	32.0
	S.d.	1.9	2.5	1.2	1.5
	N	5	5	5	5
	Deviation Vs Control [%]		-3.6	-0.6	3.4

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Food Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 35 -> 42	Mean [g]	28.8 n	29.5	28.8	31.2
	S.d.	1.8	3.5	0.8	2.4
	N	5	5	5	5
	Deviation Vs Control [%]		2.3	-0.1	8.0
d 0 -> 42	Mean [g]	26.4 n	25.3	26.2	27.3
	S.d.	0.8	2.1	0.4	1.3
	N	5	5	5	5
	Deviation Vs Control [%]		-4.2	-0.8	3.1

Statistic Profile = Dunnett test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
n=DUNNETT; d = day

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12-Dec-2018 10:02
Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Food Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 0 -> 7	Mean [g]	13.9 n	13.6	14.8	15.0
	S.d.	1.1	0.8	0.5	1.7
	N	5	5	5	5
	Deviation Vs Control [%]		-2.1	6.0	7.7
d 7 -> 14	Mean [g]	16.5 n	15.9	17.2	19.4
	S.d.	1.0	0.7	0.8	4.8
	N	5	5	5	5
	Deviation Vs Control [%]		-3.5	4.5	17.6
d 14 -> 21	Mean [g]	16.9 n	16.8	17.2	18.2
	S.d.	0.9	1.0	1.6	1.9
	N	5	5	5	5
	Deviation Vs Control [%]		-0.3	2.1	7.9
d 21 -> 28	Mean [g]	18.6 n	18.4	19.2	19.6
	S.d.	0.7	1.9	2.0	2.1
	N	5	5	5	5
	Deviation Vs Control [%]		-1.0	3.2	5.5
d 28 -> 35	Mean [g]	19.8 n	19.4	20.6	20.7
	S.d.	1.0	2.0	2.8	1.9
	N	5	5	5	5
	Deviation Vs Control [%]		-1.9	3.9	4.6

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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Ascentos™ 1.3

Study 90R0066/05R034_2A

Summary Food Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 35 -> 42	Mean [g]	19.7 n	19.6	20.0	21.2
	S.d.	0.8	1.7	3.1	2.0
	N	5	5	5	5
	Deviation Vs Control [%]		-0.3	1.4	7.7
d 0 -> 42	Mean [g]	17.6 n	17.3	18.2	19.0
	S.d.	0.6	1.2	1.6	1.9
	N	5	5	5	5
	Deviation Vs Control [%]		-1.5	3.4	8.3

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT; d = day

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Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
day 0	Mean	102.5n	101.9	104.2	101.0
	S.d.	9.5	8.8	7.5	6.3
	N	10	10	10	10
	Deviation Vs Control [%]		-0.6	1.6	-1.5
day 7	Mean	159.6n	158.0	164.9	160.4
	S.d.	15.9	11.2	11.4	9.3
	N	10	10	10	10
	Deviation Vs Control [%]		-1.0	3.3	0.5
day 14	Mean	223.2n	220.1	230.8	226.5
	S.d.	20.0	13.9	13.0	14.7
	N	10	10	10	10
	Deviation Vs Control [%]		-1.4	3.4	1.5
day 21	Mean	288.0n	281.6	297.4	294.1
	S.d.	23.1	18.9	12.5	19.2
	N	10	10	10	10
	Deviation Vs Control [%]		-2.2	3.3	2.1
day 28	Mean	340.6n	333.6	351.1	348.6
	S.d.	24.6	20.0	13.4	20.2
	N	10	10	10	10
	Deviation Vs Control [%]		-2.1	3.1	2.4

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

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Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Body Weights - BW / Body Weights [g]

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
day 35	Mean	374.3n	370.1	386.1	384.2
	S.d.	30.3	21.7	20.5	20.2
	N	10	10	10	10
	Deviation Vs Control [%]		-1.1	3.2	2.6
day 42	Mean	402.5n	399.6	413.3	408.2
	S.d.	35.9	27.3	22.2	17.1
	N	10	10	10	10
	Deviation Vs Control [%]		-0.7	2.7	1.4

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

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12-Dec-2018 11:15

Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
day 0	Mean	89.0 n	87.3	93.4	95.3
	S.d.	7.5	5.6	7.3	15.1
	N	10	10	10	10
	Deviation Vs Control [%]		-1.8	4.9	7.1
day 7	Mean	129.2 n	126.8	137.3	139.0
	S.d.	11.2	7.9	7.8	18.7
	N	10	10	10	10
	Deviation Vs Control [%]		-1.9	6.2	7.5
day 14	Mean	161.5 n	160.9	171.5	171.6
	S.d.	14.9	10.8	10.1	22.4
	N	10	10	10	10
	Deviation Vs Control [%]		-0.4	6.2	6.3
day 21	Mean	187.3 n	185.3	193.6	199.1
	S.d.	17.5	14.5	12.1	25.2
	N	10	10	10	10
	Deviation Vs Control [%]		-1.1	3.4	6.3
day 28	Mean	208.3 n	206.5	211.1	220.6
	S.d.	20.0	17.9	9.0	27.4
	N	10	10	10	10
	Deviation Vs Control [%]		-0.9	1.3	5.9

Statistic Profile = Dunnett test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
n=DUNNETT

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12-Dec-2018 11:15

Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
day 35	Mean	226.8 n	222.2	229.1	236.7
	S.d.	19.8	22.6	11.3	25.0
	N	10	10	10	10
	Deviation Vs Control [%]		-2.0	1.0	4.4
day 42	Mean	235.8 n	235.2	237.8	253.0
	S.d.	14.8	23.4	11.0	28.1
	N	10	10	10	10
	Deviation Vs Control [%]		-0.3	0.8	7.3

Statistic Profile = Dunnett test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
n=DUNNETT

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12-Dec-2018 11:25
Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Changes Body Weights - BW / Body Weights [g]

Sex: **Male** - Phase: **In-life**

	Test Group 10/M			Test Group 11/M			Test Group 12/M			Test Group 13/M		
	0 mg/kg bw/d			20 mg/kg bw/d			60 mg/kg bw/d			180 mg/kg bw/d		
d 0 -> 7	Mean	57.1 n		56.1			60.7			59.4		
	S.d.	7.0		4.3			4.8			5.9		
	N	10		10			10			10		
d 7 -> 14	Mean	63.6 n		62.1			66.0			66.2		
	S.d.	6.4		5.8			4.2			7.9		
	N	10		10			10			10		
d 14 -> 21	Mean	64.7 n		61.5			66.6			67.5		
	S.d.	6.5		6.0			4.9			6.9		
	N	10		10			10			10		
d 21 -> 28	Mean	52.7 n		52.0			53.7			54.6		
	S.d.	6.3		4.1			6.4			5.2		
	N	10		10			10			10		
d 28 -> 35	Mean	33.6 n		36.5			35.0			35.5		
	S.d.	11.1		6.3			11.3			7.5		
	N	10		10			10			10		
d 35 -> 42	Mean	28.2 n		29.6			27.2			24.0		
	S.d.	7.2		6.7			4.9			6.5		
	N	10		10			10			10		
d 0 -> 42	Mean	300.0 n		297.7			309.2			307.1		
	S.d.	32.3		23.3			22.1			16.5		
	N	10		10			10			10		

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

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12-Dec-2018 11:26

Ascentos™ 1.3

Study

90R0066/05R034_2A

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 0 -> 7	Mean	40.3 n	39.5	43.9	43.6
	S.d.	5.4	3.6	4.0	5.3
	N	10	10	10	10
d 7 -> 14	Mean	32.3 n	34.1	34.2	32.7
	S.d.	6.3	5.8	4.8	6.4
	N	10	10	10	10
d 14 -> 21	Mean	25.8 n	24.4	22.2	27.4
	S.d.	5.7	4.8	8.2	6.3
	N	10	10	10	10
d 21 -> 28	Mean	21.0 n	21.2	17.5	21.5
	S.d.	6.2	5.3	5.3	7.1
	N	10	10	10	10
d 28 -> 35	Mean	18.5 n	15.7	18.0	16.1
	S.d.	3.0	7.9	5.0	5.5
	N	10	10	10	10
d 35 -> 42	Mean	9.0 n	13.0	8.7	16.3
	S.d.	9.1	5.4	7.0	8.4
	N	10	10	10	10
d 0 -> 42	Mean	146.8 n	147.9	144.4	157.7
	S.d.	11.7	19.5	12.1	15.9
	N	10	10	10	10

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

12-DEC-18
05R034D2
TABLE : 1A-
184

PROJ. NO. 90R0066/05R034: MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - DCO (COHORT 2A)

MALES

SUMMARY OF MALE CLINICAL OBSERVATIONS

	GROUP#	WEEK OF STUDY						6 TOTAL
		0	1	2	3	4	5	
# OF ANIMALS EXAMINED	10	10	10	10	10	10	10	10
	11	10	10	10	10	10	10	10
	12	10	10	10	10	10	10	10
	13	10	10	10	10	10	10	10

NORMAL

NOTHING ABNORMAL DETECTED	10	10	10	10	10	10	10	10
	11	10	10	10	10	10	10	10
	12	10	10	10	10	10	10	10
	13	10	10	10	10	10	10	10

12-DEC-18
05R034D2
TABLE : 1A-
185

PROJ. NO. 90R0066/05R034: MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - DCO (COHORT 2A)
FEMALES
SUMMARY OF FEMALE CLINICAL OBSERVATIONS

	GROUP#	WEEK OF STUDY						6 TOTAL
		0	1	2	3	4	5	
# OF ANIMALS EXAMINED	10	10	10	10	10	10	10	10
	11	10	10	10	10	10	10	10
	12	10	10	10	10	10	10	10
	13	10	10	10	10	10	10	10

NORMAL

NOTHING ABNORMAL DETECTED	10	10	10	10	10	10	10	10
	11	10	10	10	10	10	10	10
	12	10	10	10	10	10	10	10
	13	10	10	10	10	10	10	10

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STARTLE RESPONSE PND 24

	Block 1					Block 2					Block 3					Block 4					Block 5					Block 1-5 Mean	
	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.				
TEST GROUP 10 0 MG/KG BW/D																											
M	316.1	268.5	247.5	245.1	252.2	265.9	76.4	10																			
SD	95.2	60.0	67.9	96.5	95.1	10																					
N	10	10	10	10	10	10																					
TEST GROUP 11 20 MG/KG BW/D																											
M	252.2	184.2	**	185.7	157.7	*	162.4	*	188.4	*																	
SD	57.1	47.1		64.9	56.8		50.2		46.9																		
N	10	10		10	10		10		10																		
TEST GROUP 12 60 MG/KG BW/D																											
M	300.6	233.1		206.5	204.1		204.5		229.8																		
SD	75.2	53.2		55.1	56.9		41.0		47.7																		
N	10	10		10	10		10		10																		
TEST GROUP 13 180 MG/KG BW/D																											
M	326.5	287.9		247.8	257.2		241.2		272.1																		
SD	58.3	87.0		90.0	76.5		65.4		65.0																		
N	10	10		10	10		10		10																		

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Ar)																											

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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STARTLE RESPONSE PND 24

M A L E S		Block 1		Block 2		Block 3		Block 4		Block 5		Block 1-5	
		Latency msec		Latency msec		Latency msec		Latency msec		Latency msec		Mean Latency msec	
TEST GROUP 10													
0 MG/KG BW/D													
M	20.2	18.7		18.7		18.7		19.6		19.7		19.4	
SD	2.3	1.2		1.2		1.9		1.9		3.5		1.1	
N	10	10		10		10		10		10		10	
TEST GROUP 11													
20 MG/KG BW/D													
M	20.2	19.9		19.6		19.6		20.9		20.9		20.3	
SD	2.7	2.6		3.5		3.5		3.6		3.0		2.0	
N	10	10		10		10		10		10		10	
TEST GROUP 12													
60 MG/KG BW/D													
M	21.3	20.2		18.9		18.9		18.5		18.8		19.6	
SD	1.9	3.5		1.0		1.0		0.9		1.1		0.9	
N	10	10		10		10		10		10		10	
TEST GROUP 13													
180 MG/KG BW/D													
M	20.4	19.1		18.7		18.7		20.7		19.3		19.6	
SD	2.2	1.5		2.2		2.2		6.6		2.1		1.7	
N	10	10		10		10		10		10		10	

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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GROUP MEANS

STARTLE RESPONSE PND 24

F E M A L E S

	Block 1	Block 2	Block 3	Block 4	Block 5	Block 1-5 Mean
Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.	Max. Ampl.

TEST GROUP 10

0 MG/KG BW/D

M	285.6	212.4	202.0	185.7	204.3	218.0
SD	83.6	79.4	71.5	61.0	55.2	59.0
N	10	10	10	10	10	10

TEST GROUP 11

20 MG/KG BW/D

M	256.8	229.9	210.8	188.4	185.1	214.2
SD	77.2	64.0	56.1	58.5	65.6	54.4
N	10	10	10	10	10	10

TEST GROUP 12

60 MG/KG BW/D

M	254.2	242.7	203.8	194.2	212.8	221.6
SD	76.7	81.2	70.6	84.7	99.9	75.1
N	10	10	10	10	10	10

TEST GROUP 13

180 MG/KG BW/D

M	286.1	222.2	207.8	197.7	213.1	225.4
SD	64.8	67.3	58.7	40.0	41.5	45.3
N	10	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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PRINT DATE 23MAR18

BASF
Project Number 90R0066/05R034

GROUP MEANS STARTLE RESPONSE PND 24

F E M A L E S

	Block 1	Block 2	Block 3	Block 4	Block 5	Block 1-5
	Latency msec	Latency msec	Latency msec	Latency msec	Latency msec	Mean Latency msec

TEST GROUP 10
0 MG/KG BW/D

M	22.0	19.2	19.7	20.6	22.3	20.7
SD	4.5	2.0	2.6	2.5	6.7	2.9
N	10	10	10	10	10	10

TEST GROUP 11
20 MG/KG BW/D

M	21.4	18.5	18.8	20.1	20.2	19.8
SD	3.2	1.7	2.1	2.4	3.1	1.5
N	10	10	10	10	10	10

TEST GROUP 12
60 MG/KG BW/D

M	22.0	19.5	21.9	20.8	21.2	21.1
SD	4.3	2.3	3.6	4.1	4.1	2.8
N	10	10	10	10	10	10

TEST GROUP 13
180 MG/KG BW/D

M	19.2	19.9	19.4	18.4	19.1	19.2
SD	1.4	2.3	2.4	1.8	3.3	1.6
N	10	10	10	10	10	10

-----Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

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12-Dec-2018

FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

male animals

Summary values day 75

HOME CAGE OBSERVATION	Rank	Test group 10 0 mg/kg bw/d N=10				Test group 11 60 mg/kg bw/d N=10				Test group 12 180 mg/kg bw/d N=10			
		0	1	2	3	0	1	2	3	0	1	2	3
posture													
- animal is sitting or laying		0	0	0	0	0	0	0	0	2	2	2	2
- animal is standing or moving		1	10	0	0	10	0	8	0	8	8	8	8
- squatting posture		2	0	0	0	0	0	0	0	0	0	0	0
- abdominal position		3	0	0	0	0	0	0	0	0	0	0	0
- abdominal position with splayed limbs		4	0	0	0	0	0	0	0	0	0	0	0
- lateral position		5	0	0	0	0	0	0	0	0	0	0	0
- oblique head posture		6	0	0	0	0	0	0	0	0	0	0	0
- opisthotonus		7	0	0	0	0	0	0	0	0	0	0	0
tremors													
- no tremors		0	10	0	0	10	0	10	0	10	10	10	10
- slight tremors		1	0	0	0	0	0	0	0	0	0	0	0
- moderate tremors		2	0	0	0	0	0	0	0	0	0	0	0
- severe tremors		3	0	0	0	0	0	0	0	0	0	0	0
convulsions													
- no convulsions		0	10	0	0	10	0	10	0	10	10	10	10
- slight convulsions		1	0	0	0	0	0	0	0	0	0	0	0
- moderate convulsions		2	0	0	0	0	0	0	0	0	0	0	0
- severe convulsions		3	0	0	0	0	0	0	0	0	0	0	0
abnormal movements													
- no abnormalities		0	10	0	0	10	0	10	0	10	10	10	10
- manege movements		1	0	0	0	0	0	0	0	0	0	0	0
- head shaking		2	0	0	0	0	0	0	0	0	0	0	0
- excessive cleaning		3	0	0	0	0	0	0	0	0	0	0	0
- frequent chewing		4	0	0	0	0	0	0	0	0	0	0	0
gait													
- animal is not walking during observation		0	0	0	0	0	0	2	0	2	2	2	2
- no impairment of gait		1	10	0	0	10	0	8	0	8	8	8	8
- stiff gait		2	0	0	0	0	0	0	0	0	0	0	0
- slight impairment of coordination, unsteady gait		3	0	0	0	0	0	0	0	0	0	0	0
- moderate impairment of coordination, shuffling gait		4	0	0	0	0	0	0	0	0	0	0	0
- severe impairment of coordination, dragging of the hindlimbs		5	0	0	0	0	0	0	0	0	0	0	0
- severe impairment of coordination, with splayed limbs		6	0	0	0	0	0	0	0	0	0	0	0
- animal is unable to walk (abdominal or lateral position)		7	0	0	0	0	0	0	0	0	0	0	0
other findings		0	10	0	0	10	0	10	0	10	10	10	10

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12-Dec-2018

FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

male animals

Summary values day 75

Test group 10 0 mg/kg bw/d N=10
Test group 11 20 mg/kg bw/d N=10
Test group 12 60 mg/kg bw/d N=10
Test group 13 180 mg/kg bw/d N=10

OPEN FIELD OBSERVATIONS

behavior on removal from the cage

- animal is tense, but it shows no resistance against handling
- animal shows a slight resistance against the handling
- animal shows no resistance against the handling but appears indifferent
- animal is difficult to handle, it shows aggressiveness
- animal is very difficult to handle, it shows severe aggressiveness

fur

- nothing abnormal detected
- discolored fur
- urine staining of anogenital region
- piloerection
- alopecia
- reduced care on fur

skin

- nothing abnormal detected
- discolored skin
- reddening
- paleness
- dehydration (exsiccosis)
- hypothermia (skin is cold during handling)
- lesion(s)
- crust(s)

salivation

- no salivation
- slight salivation (area around the mouth is moist)
- moderate salivation (wet mouth)
- severe salivation (mouth very wet, wet paws)

nasal discharge

- no discharge, dry nose
- clear discharge
- reddish discharge

Rank

0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0

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12-Dec-2018

FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

male animals

Summary values day 75

Test group 10 0 mg/kg bw/d N=10
Test group 11 20 mg/kg bw/d N=10
Test group 12 60 mg/kg bw/d N=10
Test group 13 180 mg/kg bw/d N=10

OPEN FIELD OBSERVATIONS

lacrimation

- no lacrimation
- slight lacrimation
- moderate lacrimation
- severe lacrimation

eyes/pupil size

- nothing abnormal detected, pupils contracted at room light
- chromodacryorrhea
- exophthalmos
- pupils dilated
- abnormal shape of pupils
- oblique eye posture
- opacity
- cataract

posture

- animal is sitting or laying
- animal is standing or moving
- squatting posture
- abdominal position
- abdominal position with splayed limbs
- lateral position
- oblique head posture
- opisthotonus

palpebral closure

- nothing abnormal detected
- eyelid(s) slight closure
- eyelid(s) half closure
- eyelid(s) permanent closure

Rank

0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	0	0
0	0	0	0	0	1
1	10	10	10	10	9
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0

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12-Dec-2018

FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

male animals

Summary values day 75

OPEN FIELD OBSERVATIONS	Rank	Test group 10 0 mg/kg bw/d N=10				Test group 11 20 mg/kg bw/d N=10				Test group 12 60 mg/kg bw/d N=10				Test group 13 180 mg/kg bw/d N=10			
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0
respiration																	
- nothing abnormal detected		10	0	0	0	0	10	0	0	0	0	10	0	0	0	0	10
- respiration labored		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- gasping/respiratory sounds		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- respiration accelerated		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- respiration irregular		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
tremors																	
- no tremors		10	0	0	0	0	10	0	0	0	0	10	0	0	0	0	10
- slight tremors		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- moderate tremors		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- severe tremors		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
convulsions																	
- no convulsions		10	0	0	0	0	10	0	0	0	0	10	0	0	0	0	10
- slight convulsions		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- moderate convulsions		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- severe convulsions		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
abnormal movements/stereotypics																	
- no abnormalities		10	0	0	0	0	10	0	0	0	0	10	0	0	0	0	10
- manege movements		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- head shaking		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- excessive cleaning		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- frequent chewing		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
gait																	
- animal is not walking during observation		1	9	0	0	0	1	9	0	0	0	0	0	1	9	0	0
- no impairment of gait		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- stiff gait		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- slight impairment of coordination, unsteady gait		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- moderate impairment of coordination, shuffling gait		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- severe impairment of coordination, dragging of the hindlimbs		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- severe impairment of coordination, with splayed limbs		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- animal is unable to walk (abdominal or lateral position)		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

male animals

Summary values day 75

	Rank	Test group 10	Test group 11	Test group 12	Test group 13
		0 mg/kg bw/d N=10	20 mg/kg bw/d N=10	60 mg/kg bw/d N=10	180 mg/kg bw/d N=10
OPEN FIELD OBSERVATIONS					
activity/arousal level					
- normal exploration of the area	0	9	10	10	9
- reduced exploration of the area	1	1	0	0	1
- severe reduced exploration of the area, animal apathetic	2	0	0	0	0
- increased exploration of the area, sudden or jerky movements	3	0	0	0	0
- hyperactivity	4	0	0	0	0
feces					
- no defecation during observation period	0	10	10	10	9
- feces without abnormalities	1	0	0	0	1
- discolored feces	2	0	0	0	0
- crumbly feces	3	0	0	0	0
- soft feces	4	0	0	0	0
- muicid feces	5	0	0	0	0
- diarrhea	6	0	0	0	0
urine					
- no urination during observation period	0	10	10	8	8
- urine without abnormalities (some wet areas on the filter paper)	1	0	0	2	2
- discoloration of urine	2	0	0	0	0
- polyuria (great wet areas on the filter paper)	3	0	0	0	0
other findings					
	0	10	10	10	10

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12-Dec-2018

FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

male animals

Summary values day 75

Test group 10 0 mg/kg bw/d N=10
Test group 11 20 mg/kg bw/d N=10
Test group 12 60 mg/kg bw/d N=10
Test group 13 180 mg/kg bw/d N=10

SENSORIMOTOR TESTS/REFLEXES

approach response

- no reaction
- approaching to object
- escape reaction
- aggressive reaction and attacking of object

touch response

- no reaction
- orientation to the stimulus
- escape after touch
- aggressive reaction and attacking of object
- reaction to the stimulus but no ability to localize (e.g. turning to wrong side)

vision

- nothing abnormal detected (grasping with forelimbs)
- no grasping

pupillary reflex

- nothing abnormal detected, physiological adaptation of the pupil to light
- retarded adaptation of the pupil to light
- no adaptation of the pupil to light, pupils permanently contracted
- no adaptation of the pupil to light, pupils permanently dilated

pinna reflex

- immediate response to the stimulus
- no response to the stimulus

audition

- nothing abnormal detected, immediate normal response to the stimulus
- no response
- increased response
- hyperreaction

coordination of movements

- nothing abnormal detected, immediate righting response
- retarded righting response
- fails to turn into upright position, animal stays in lateral position
- no righting response, animal stays in dorsal position

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FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

male animals

Summary values day 75

	Rank	Test group 10 0 mg/kg bw/d N=10	Test group 11 20 mg/kg bw/d N=10	Test group 12 60 mg/kg bw/d N=10	Test group 13 180 mg/kg bw/d N=10
SENSORIMOTOR TESTS/REFLEXES					
behavior during handling					
- normal behavior, easy to handle, animal is tense, but it shows no resistance against handling	0	10	10	10	10
- very easy to handle, animal is limply hanging in the hand	1	0	0	0	0
- slightly difficult to handle, animal shows a slight resistance against handling	2	0	0	0	0
- difficult to handle, animal shows a severe resistance against handling	3	0	0	0	0
vocalization					
- no or only sporadic vocalizations when touched	0	10	10	10	10
- very frequent vocalizations when touched	1	0	0	0	0
- vocalizations always when touched	2	0	0	0	0
- vocalization without touching	3	0	0	0	0
pain perception					
- nothing abnormal detected, immediate response to the stimulus	0	10	10	10	10
- weak or retarded reaction to the stimulus	1	0	0	0	0
- no response to the stimulus	2	0	0	0	0
- hyperreaction to the stimulus	3	0	0	0	0
other findings					
	0	10	10	10	10

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12-Dec-2018

FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

female animals

Summary values day 75

Test group 10 0 mg/kg bw/d N=10
Test group 11 20 mg/kg bw/d N=10
Test group 12 60 mg/kg bw/d N=10
Test group 13 180 mg/kg bw/d N=10

HOME CAGE OBSERVATION

posture

- animal is sitting or laying
- animal is standing or moving
- squatting posture
- abdominal position
- abdominal position with splayed limbs
- lateral position
- oblique head posture
- opisthotonus

tremors

- no tremors
- slight tremors
- moderate tremors
- severe tremors

convulsions

- no convulsions
- slight convulsions
- moderate convulsions
- severe convulsions

abnormal movements

- no abnormalities
- manege movements
- head shaking
- excessive cleaning
- frequent chewing

gait

- animal is not walking during observation
- no impairment of gait
- stiff gait
- slight impairment of coordination, unsteady gait
- moderate impairment of coordination, shuffling gait
- severe impairment of coordination, dragging of the hindlimbs
- severe impairment of coordination, with splayed limbs
- animal is unable to walk (abdominal or lateral position)

other findings

Rank

0	1	0	3	0
1	9	10	7	10
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0
0	10	10	10	10
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
0	10	10	10	10
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
0	10	10	10	10
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
0	1	0	3	0
1	9	10	7	10
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0
0	10	10	10	10

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12-Dec-2018

FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

female animals

Summary values day 75

Test group 10 0 mg/kg bw/d N=10
Test group 11 20 mg/kg bw/d N=10
Test group 12 60 mg/kg bw/d N=10
Test group 13 180 mg/kg bw/d N=10

OPEN FIELD OBSERVATIONS

behavior on removal from the cage

- animal is tense, but it shows no resistance against handling
- animal shows a slight resistance against the handling
- animal shows no resistance against the handling but appears indifferent
- animal is difficult to handle, it shows aggressiveness
- animal is very difficult to handle, it shows severe aggressiveness

fur

- nothing abnormal detected
- discolored fur
- urine staining of anogenital region
- piloerection
- alopecia
- reduced care on fur

skin

- nothing abnormal detected
- discolored skin
- reddening
- paleness
- dehydration (exsiccosis)
- hypothermia (skin is cold during handling)
- lesion(s)
- crust(s)

salivation

- no salivation
- slight salivation (area around the mouth is moist)
- moderate salivation (wet mouth)
- severe salivation (mouth very wet, wet paws)

nasal discharge

- no discharge, dry nose
- clear discharge
- reddish discharge

Rank

0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0

Table IA - 199
12-Dec-2018

FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

female animals

Summary values day 75

Test group 10 0 mg/kg bw/d N=10
Test group 11 20 mg/kg bw/d N=10
Test group 12 60 mg/kg bw/d N=10
Test group 13 180 mg/kg bw/d N=10

OPEN FIELD OBSERVATIONS

lacrimation

- no lacrimation
- slight lacrimation
- moderate lacrimation
- severe lacrimation

eyes/pupil size

- nothing abnormal detected, pupils contracted at room light
- chromodacryorrhea
- exophthalmos
- pupils dilated
- abnormal shape of pupils
- oblique eye posture
- opacity
- cataract

posture

- animal is sitting or laying
- animal is standing or moving
- squatting posture
- abdominal position
- abdominal position with splayed limbs
- lateral position
- oblique head posture
- opisthotonus

palpebral closure

- nothing abnormal detected
- eyelid(s) slight closure
- eyelid(s) half closure
- eyelid(s) permanent closure

Rank

0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	0	0
0	0	0	0	0	0
1	10	10	10	10	10
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	0	0
0	10	10	10	10	10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0

Table IA - 200
12-Dec-2018

FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

female animals

Summary values

day 75

Test group 10
0 mg/kg bw/d

Test group 11
20 mg/kg bw/d

Test group 12
60 mg/kg bw/d

Test group 13
180 mg/kg bw/d

OPEN FIELD OBSERVATIONS

respiration

- nothing abnormal detected
- respiration labored
- gasping/respiratory sounds
- respiration accelerated
- respiration irregular

tremors

- no tremors
- slight tremors
- moderate tremors
- severe tremors

convulsions

- no convulsions
- slight convulsions
- moderate convulsions
- severe convulsions

abnormal movements/stereotypics

- no abnormalities
- manege movements
- head shaking
- excessive cleaning
- frequent chewing

gait

- animal is not walking during observation
- no impairment of gait
- stiff gait
- slight impairment of coordination, unsteady gait
- moderate impairment of coordination, shuffling gait
- severe impairment of coordination, dragging of the hindlimbs
- severe impairment of coordination, with splayed limbs
- animal is unable to walk (abdominal or lateral position)

Rank

0

1

2

3

4

0

1

2

3

0

1

2

3

0

1

2

3

0

1

2

3

0

1

2

3

0

1

2

3

0

1

2

3

0

1

2

3

0

1

2

Table IA - 201
12-Dec-2018

FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

female animals

Summary values day 75

Test group 10 0 mg/kg bw/d N=10
Test group 11 20 mg/kg bw/d N=10
Test group 12 60 mg/kg bw/d N=10
Test group 13 180 mg/kg bw/d N=10

OPEN FIELD OBSERVATIONS

activity/arousal level

- normal exploration of the area
- reduced exploration of the area
- severe reduced exploration of the area, animal apathetic
- increased exploration of the area, sudden or jerky movements
- hyperactivity

feces

- no defecation during observation period
- feces without abnormalities
- discolored feces
- crumbly feces
- soft feces
- muicid feces
- diarrhea

urine

- no urination during observation period
- urine without abnormalities (some wet areas on the filter paper)
- discoloration of urine
- polyuria (great wet areas on the filter paper)

other findings

Rank	Test group 10 0 mg/kg bw/d N=10	Test group 11 20 mg/kg bw/d N=10	Test group 12 60 mg/kg bw/d N=10	Test group 13 180 mg/kg bw/d N=10
0	10	10	10	10
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
0	10	10	10	10
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
6	0	0	0	0
0	10	10	10	10
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
0	10	10	10	10

Table IA - 202
12-Dec-2018

FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

female animals

Summary values day 75

Test group 10
0 mg/kg bw/d
N=10

Test group 11
20 mg/kg bw/d
N=10

Test group 12
60 mg/kg bw/d
N=10

Test group 13
180 mg/kg bw/d
N=10

SENSORIMOTOR TESTS/REFLEXES

	Rank	Test group 10 0 mg/kg bw/d N=10	Test group 11 20 mg/kg bw/d N=10	Test group 12 60 mg/kg bw/d N=10	Test group 13 180 mg/kg bw/d N=10
approach response					
- no reaction	0	9	9	8	10
- approaching to object	1	1	1	2	0
- escape reaction	2	0	0	0	0
- aggressive reaction and attacking of object	3	0	0	0	0
touch response					
- no reaction	0	10	10	10	10
- orientation to the stimulus	1	0	0	0	0
- escape after touch	2	0	0	0	0
- aggressive reaction and attacking of object	3	0	0	0	0
- reaction to the stimulus but no ability to localize (e.g. turning to wrong side)	4	0	0	0	0
vision					
- nothing abnormal detected (grasping with forelimbs)	0	10	10	10	10
- no grasping	1	0	0	0	0
pupillary reflex					
- nothing abnormal detected, physiological adaptation of the pupil to light	0	10	10	10	10
- retarded adaptation of the pupil to light	1	0	0	0	0
- no adaptation of the pupil to light, pupils permanently contracted	2	0	0	0	0
- no adaptation of the pupil to light, pupils permanently dilated	3	0	0	0	0
pinna reflex					
- immediate response to the stimulus	0	10	10	10	10
- no response to the stimulus	1	0	0	0	0
audition					
- nothing abnormal detected, immediate normal response to the stimulus	0	10	10	10	10
- no response	1	0	0	0	0
- increased response	2	0	0	0	0
- hyperreaction	3	0	0	0	0
coordination of movements					
- nothing abnormal detected, immediate righting response	0	10	10	10	10
- retarded righting response	1	0	0	0	0
- fails to turn into upright position, animal stays in lateral position	2	0	0	0	0
- no righting response, animal stays in dorsal position	3	0	0	0	0

Table IA - 203
12-Dec-2018

FUNCTIONAL OBSERVATIONAL BATTERY

Project No.: 90R0066/05R034 (Cohort 2A)

female animals

Summary values day 75

Test group 10 0 mg/kg bw/d N=10
Test group 11 20 mg/kg bw/d N=10
Test group 12 60 mg/kg bw/d N=10
Test group 13 180 mg/kg bw/d N=10

SENSORIMOTOR TESTS/REFLEXES

behavior during handling

- normal behavior, easy to handle, animal is tense, but it shows no resistance against handling
- very easy to handle, animal is limply hanging in the hand
- slightly difficult to handle, animal shows a slight resistance against handling
- difficult to handle, animal shows a severe resistance against handling

vocalization

- no or only sporadic vocalizations when touched
- very frequent vocalizations when touched
- vocalizations always when touched
- vocalization without touching

pain perception

- nothing abnormal detected, immediate response to the stimulus
- weak or retarded reaction to the stimulus
- no response to the stimulus
- hyperreaction to the stimulus

other findings

Rank	Test group 10 0 mg/kg bw/d N=10	Test group 11 20 mg/kg bw/d N=10	Test group 12 60 mg/kg bw/d N=10	Test group 13 180 mg/kg bw/d N=10
0	10	10	10	10
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
0	10	10	10	10
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
0	10	10	10	10
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
0	10	10	10	10
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
0	10	10	10	10

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12-Dec-2018 11:48

Ascentos™ 1.3

Study 90R0066/05R034_FOB

Summary Functional Observational Battery

Sex: **Male** - Phase: **In-life**

			Test Group 10/M		Test Group 11/M		Test Group 12/M		Test Group 13/M	
			0 mg/kg bw/d		20 mg/kg bw/d		60 mg/kg bw/d		180 mg/kg bw/d	
Rearing [N] day 75	Mean		8k		8		6		6	
	S.d.		3		3		2		3	
	N		10		10		10		10	
GS F [Newton] day 75	Mean		9.7 k		10.2		10.5		10.3	
	S.d.		0.8		1.5		1.1		1.5	
	N		10		10		10		10	
GS H [Newton] day 75	Mean		5.7 k		5.4		6.1		6.3	
	S.d.		0.8		1.3		1.0		1.2	
	N		10		10		10		10	
FST [cm] day 75	Mean		12.6 k		11.6		12.8		12.0	
	S.d.		1.4		2.0		1.0		1.7	
	N		10		10		10		10	

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

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Ascentos™ 1.3

Study 90R0066/05R034_FOB

Summary Functional Observational Battery

Sex: Female - Phase: In-life

			Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
Rearing [N] day 75	Mean		12 k	13	12	13
	S.d.		3	4	5	3
	N		10	10	10	10
GS F [Newton] day 75	Mean		7.8 k	8.0	7.4	8.6
	S.d.		1.2	1.4	1.1	0.9
	N		10	10	10	10
GS H [Newton] day 75	Mean		4.4 k	4.3	4.6	4.7
	S.d.		0.7	1.0	0.7	0.7
	N		10	10	10	10
FST [cm] day 75	Mean		10.1 k	11.4	10.4	11.1
	S.d.		1.8	1.6	1.5	2.0
	N		10	10	10	10

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

BASF		IA-206	
Project Number 90R0066/05R034		PRINT DATE 04MAY18	
GROUP MEANS		MOTOR ACTIVITY DAY 75	
M A L E S			
TEST GROUP 10 0 MG/KG BW/D	Interv. 1		Interv. 8
	Beam		Beam
	Interr.		Interr.
M	1072.1	266.1	84.9
SD	173.8	72.9	96.8
N	10	10	10
TEST GROUP 11 20 MG/KG BW/D	Interv. 2		Interv. 7
	Beam		Beam
	Interr.		Interr.
M	970.5	328.3	133.4
SD	211.4	116.3	138.0
N	10	10	10
TEST GROUP 12 60 MG/KG BW/D	Interv. 3		Interv. 6
	Beam		Beam
	Interr.		Interr.
M	953.7	425.7	84.6
SD	196.1	140.8	151.2
N	10	10	10
TEST GROUP 13 180 MG/KG BW/D	Interv. 4		Interv. 5
	Beam		Beam
	Interr.		Interr.
M	909.6	351.6	89.6
SD	225.5	145.9	133.5
N	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

IA-207
PRINT DATE 04MAY18

BASF
Project Number 90R0066/05R034

GROUP MEANS MOTOR ACTIVITY DAY 75

M A L E S

	Interv. 9	Interv. 10	Interv. 11	Interv. 12	Interv. 1-12
	Beam	Beam	Beam	Beam	Sum
	Interr.	Interr.	Interr.	Interr.	Interr.

TEST GROUP 10
0 MG/KG BW/D

M	16.2	13.7	6.2	16.0	2811.8
SD	25.9	17.9	16.9	16.9	729.9
N	10	10	10	10	10

TEST GROUP 11
20 MG/KG BW/D

M	77.1	48.2	53.6 *	26.4	2951.3
SD	126.3	61.0	77.7	19.6	875.2
N	10	10	10	10	10

TEST GROUP 12
60 MG/KG BW/D

M	15.1	12.0	24.8 *	29.1	2495.9
SD	21.1	18.6	31.4	28.1	562.1
N	10	10	10	10	10

TEST GROUP 13
180 MG/KG BW/D

M	27.4	20.1	23.9 *	16.6	2487.7
SD	31.9	21.0	38.3	24.3	1045.2
N	10	10	10	10	10

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

BASF Project Number 90R0066/05R034		REARING										IA-208
GROUP MEANS		DAY 75										PRINT DATE 04MAY18
M A L E S												
		Interv. 1	Interv. 2	Interv. 3	Interv. 4	Interv. 5	Interv. 6	Interv. 7	Interv. 8			
		Beam	Beam	Beam	Beam	Beam	Beam	Beam	Beam	Beam	Beam	
		Interr.	Interr.	Interr.	Interr.	Interr.	Interr.	Interr.	Interr.	Interr.	Interr.	
TEST GROUP 10												
0 MG/KG BW/D												
M	234.2	121.6	87.3	52.7	21.6		7.8	1.9	0.3			
SD	45.3	37.0	55.1	45.9	34.7		12.0	6.0	0.9			
N	10	10	10	10	10		10	10	10			
TEST GROUP 11												
20 MG/KG BW/D												
M	236.8	149.1	53.0	60.5	31.1		11.2	9.5	10.5			
SD	64.0	37.1	43.8	55.5	35.9		20.9	21.1	23.2			
N	10	10	10	10	10		10	10	10			
TEST GROUP 12												
60 MG/KG BW/D												
M	218.6	137.0	72.9	26.1	13.3		9.2	0.0	0.0			
SD	44.7	57.0	40.3	28.0	24.5		29.1	0.0	0.0			
N	10	10	10	10	10		10	10	10			
TEST GROUP 13												
180 MG/KG BW/D												
M	230.3	116.2	61.1	34.9	24.7		11.3	2.9	0.4			
SD	61.4	33.0	31.7	40.6	36.1		24.7	9.2	1.3			
N	10	10	10	10	10		10	10	10			

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

BASF Project Number 90R0066/05R034		REARING		DAY 75		IA-209		PRINT DATE 04MAY18	
GROUP MEANS									
M A L E S									
TEST GROUP 10 0 MG/KG BW/D		Interv. 9 Beam Interr.	Interv. 10 Beam Interr.	Interv. 11 Beam Interr.	Interv. 12 Beam Interr.	Interv. 1-12 Sum Interr.			
M	1.0	0.0	0.0	0.0	0.0	528.4			
SD	3.2	0.0	0.0	0.0	0.0	182.5			
N	10	10	10	10	10	10			
TEST GROUP 11 20 MG/KG BW/D		7.2 SD 17.6 N 10	2.5 6.6 10	1.6 5.1 10	0.6 1.6 10	573.6 228.6 10			
TEST GROUP 12 60 MG/KG BW/D		0.1 SD 0.3 N 10	0.0 0.0 10	0.0 0.0 10	0.1 0.3 10	477.3 147.2 10			
TEST GROUP 13 180 MG/KG BW/D		0.0 SD 0.0 N 10	0.0 0.0 10	0.0 0.0 10	0.4 1.3 10	482.2 180.3 10			

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)									

BASF Project Number 90R0066/05R034		IA-210		PRINT DATE 04MAY18	
GROUP MEANS		MOTOR ACTIVITY DAY 75			
F E M A L E S					
TEST GROUP 10 0 MG/KG BW/D		Interv. 1	Interv. 2	Interv. 3	Interv. 4
		Beam	Beam	Beam	Beam
		Interr.	Interr.	Interr.	Interr.
TEST GROUP 11 20 MG/KG BW/D		Interv. 5	Interv. 6	Interv. 7	Interv. 8
		Beam	Beam	Beam	Beam
		Interr.	Interr.	Interr.	Interr.
TEST GROUP 12 60 MG/KG BW/D		Interv. 1	Interv. 2	Interv. 3	Interv. 4
		Beam	Beam	Beam	Beam
		Interr.	Interr.	Interr.	Interr.
TEST GROUP 13 180 MG/KG BW/D		Interv. 5	Interv. 6	Interv. 7	Interv. 8
		Beam	Beam	Beam	Beam
		Interr.	Interr.	Interr.	Interr.

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

IA-211
PRINT DATE 04MAY18

BASF
Project Number 90R0066/05R034

GROUP MEANS MOTOR ACTIVITY DAY 75

F E M A L E S

		Interv. 9		Interv. 10		Interv. 11		Interv. 12		Interv. 1-12	
		Beam	Interr.	Beam	Interr.	Beam	Interr.	Beam	Interr.	Sum	Interr.
TEST GROUP 10 0 MG/KG BW/D	M	34.4		43.5		29.8		51.4		3731.3	
	SD	39.7		63.3		28.6		66.0		1344.3	
	N	10		10		10		10		10	
TEST GROUP 11 20 MG/KG BW/D	M	12.7		19.0		24.4		30.0		3685.1	
	SD	9.5		16.1		33.2		41.9		1491.0	
	N	10		10		10		10		10	
TEST GROUP 12 60 MG/KG BW/D	M	36.3		37.9		52.0		123.6		3389.9	
	SD	66.9		25.9		120.2		185.8		995.2	
	N	10		10		10		10		10	
TEST GROUP 13 180 MG/KG BW/D	M	37.8		7.4		18.5		26.4		3227.5	
	SD	44.9		7.0		19.8		36.4		1061.7	
	N	10		10		10		10		10	

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

BASF Project Number 90R0066/05R034		REARING		DAY 75		IA-212			
GROUP MEANS						PRINT DATE 04MAY18			
F E M A L E S									
		Interv. 1	Interv. 2	Interv. 3	Interv. 4	Interv. 5	Interv. 6	Interv. 7	Interv. 8
		Beam	Beam	Beam	Beam	Beam	Beam	Beam	Beam
		Interr.	Interr.	Interr.	Interr.	Interr.	Interr.	Interr.	Interr.
TEST GROUP 10									
0 MG/KG BW/D									
M	258.9	148.0	73.5	62.7	32.7	18.7	7.3	2.1	
SD	51.5	35.5	62.1	45.6	28.1	26.5	11.6	6.6	
N	10	10	10	10	10	10	10	10	
TEST GROUP 11									
20 MG/KG BW/D									
M	254.8	153.2	78.0	41.3	33.9	11.3	7.6	1.4	
SD	69.9	95.3	40.2	23.2	26.9	21.6	15.1	4.4	
N	10	10	10	10	10	10	10	10	
TEST GROUP 12									
60 MG/KG BW/D									
M	227.5	126.1	65.8	56.3	24.2	6.7	0.0	8.4	
SD	59.2	50.9	28.8	59.6	39.9	11.5	0.0	17.1	
N	10	10	10	10	10	10	10	10	
TEST GROUP 13									
180 MG/KG BW/D									
M	221.2	128.4	42.9	38.7	8.2	9.0	10.8	0.8	
SD	25.6	25.9	35.6	37.2	15.9	19.0	22.8	1.4	
N	10	10	10	10	10	10	10	10	

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

Kruskal-Wallis + Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)

BASF Project Number 90R0066/05R034		REARING		DAY 75		IA-213		PRINT DATE 04MAY18	
GROUP MEANS									
F E M A L E S									
TEST GROUP 10 0 MG/KG BW/D		Interv. 9 Beam Interr.	Interv. 10 Beam Interr.	Interv. 11 Beam Interr.	Interv. 12 Beam Interr.	Interv. 1-12 Sum Interr.			
M	0.0	3.3	0.0	2.3	609.5				
SD	0.0	7.3	0.0	7.3	163.5				
N	10	10	10	10	10				
TEST GROUP 11 20 MG/KG BW/D		M	0.0	2.4	0.7	584.6			
SD	0.0	0.0	7.2	1.6	217.3				
N	10	10	10	10	10				
TEST GROUP 12 60 MG/KG BW/D		M	3.5	0.4	4.3	12.1	535.3		
SD	11.1	1.3	13.6	20.9	197.2				
N	10	10	10	10	10				
TEST GROUP 13 180 MG/KG BW/D		M	1.1	0.0	0.0	0.1	461.2		
SD	2.8	0.0	0.0	0.0	0.3	137.3			
N	10	10	10	10	10				
-----Wilcoxon-tests (two-sided): * p<=0.05; ** p<=0.01 (Statistical unit = Animal)									

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Learning

IA-214
SAS9.4 06MAY19

Endpoint=Mean Cumul. Distance (cm) sex=M

			Day			
			1	2	3	4
Test group	Dose					
10	0 mg/kg bw/d	Mean	109939.4	44195.3	26804.5	23282.4
		Median	89632.6	40700.7	25947.3	21339.0
		Min	55552.3	22005.7	11961.0	12338.3
		25% quantile	68864.3	31385.4	21124.4	15979.3
		75% quantile	146020.5	51366.5	33612.9	32332.3
		Max	200115.4	75043.0	42837.3	36495.6
		N	10	10	10	10
		p-value				
		SIG				
11	20 mg/kg bw/d	Mean	120616.2	36789.1	23618.1	30615.9
		Median	103907.0	39492.7	19159.9	39506.8
		Min	73152.1	18321.9	5783.5	5191.1
		25% quantile	91437.4	26111.1	15134.9	11866.6
		75% quantile	170938.1	47270.7	30522.4	43781.0
		Max	197028.0	58025.6	61820.1	48608.1
		N	10	10	10	10
		p-value	0.1965	0.7356	0.9048	0.1399
		SIG				

(Continued)

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Learning

IA-215
SAS9.4 06MAY19

Endpoint=Mean Cumul. Distance (cm) sex=M

			Day			
			1	2	3	4
Test group	Dose					
12	60 mg/kg bw/d	Mean	113809.1	44854.6	16086.4	30908.4
		Median	111009.9	29000.4	14689.5	20412.5
		Min	48487.8	14984.1	10710.5	7144.3
		25% quantile	99672.0	23858.2	13971.4	7467.7
		75% quantile	145590.3	45061.1	16266.9	30252.2
		Max	163307.1	162290.8	26777.3	134796.9
		N	10	10	10	10
		p-value	0.2894	0.9173	0.9974	0.6579
		SIG				
13	180 mg/kg bw/d	Mean	119463.9	46090.5	24773.5	41351.6
		Median	106236.1	36431.4	23593.4	27015.9
		Min	62233.3	15847.7	11144.3	7076.0
		25% quantile	91072.3	30293.0	14174.0	14063.5
		75% quantile	159619.3	57742.6	34670.4	69905.1
		Max	188214.5	114605.5	48589.3	117231.5
		N	10	10	10	10
		p-value	0.2406	0.6579	0.7356	0.3697
		SIG				

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Learning

IA-216
SAS9.4 06MAY19

Endpoint=Mean Cumul. Distance (cm) sex=F

			Day			
			1	2	3	4
Test group	Dose					
10	0 mg/kg bw/d	Mean	93981.0	48406.2	36996.6	47550.5
		Median	94866.6	33520.4	30468.7	30381.5
		Min	66454.0	18837.8	12802.0	10157.9
		25% quantile	73449.8	29518.8	27306.5	21188.3
		75% quantile	113305.1	75238.8	53861.8	70887.4
		Max	125420.2	94656.2	80601.0	116397.3
		N	10	10	10	10
		p-value				
		SIG				
11	20 mg/kg bw/d	Mean	140207.3	43069.4	55256.4	32484.5
		Median	116378.2	34470.0	39973.6	30175.3
		Min	76781.7	24200.2	21211.7	8675.2
		25% quantile	102924.4	25083.9	26914.6	10588.8
		75% quantile	160273.5	50540.6	46859.7	54382.5
		Max	284205.6	100899.6	191651.2	63211.2
		N	10	10	10	10
		p-value	0.0216	0.5147	0.2406	0.8425
		SIG	*			

(Continued)

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Learning

IA-217
SAS9.4 06MAY19

Endpoint=Mean Cumul. Distance (cm) sex=F

			Day			
			1	2	3	4
Test group	Dose					
12	60 mg/kg bw/d	Mean	123301.7	36504.2	35006.3	26717.0
		Median	110696.3	36397.4	31014.5	27809.0
		Min	53624.3	10194.0	7738.7	6263.7
		25% quantile	74420.9	20214.7	17224.7	17149.1
		75% quantile	161275.8	46440.2	51877.4	33913.2
		Max	255522.9	69657.3	77990.9	49984.3
		N	10	10	10	10
		p-value	0.2179	0.7594	0.7106	0.8763
		SIG				
13	180 mg/kg bw/d	Mean	154551.5	41593.1	34114.6	31356.4
		Median	147635.8	34822.9	33153.4	32870.9
		Min	63576.0	13120.2	14458.0	10774.7
		25% quantile	99631.6	18344.7	25664.6	21086.5
		75% quantile	179341.4	53914.6	42641.5	41603.9
		Max	262017.7	92850.3	54715.7	50268.4
		N	10	10	10	10
		p-value	0.0116	0.7594	0.4853	0.6847
		SIG	*			

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Learning

IA-218
SAS9.4 06MAY19

Endpoint=Median latency time (ms) sex=M

			Day			
			1	2	3	4
Test group	Dose					
10	0 mg/kg bw/d	Median	41232.0	11431.0	12551.3	9971.5
		Min	15661.0	7721.5	3902.5	4625.0
		25% quantile	26763.0	10282.0	9626.5	7544.0
		75% quantile	62404.0	14537.5	19042.5	12442.5
		Max	NR	31401.0	20323.0	16563.0
		N	10	10	10	10
		p-value				
		SIG				
11	20 mg/kg bw/d	Median	37162.8	11992.3	10222.3	9832.0
		Min	21437.5	4921.5	4002.0	3505.5
		25% quantile	26145.5	8062.5	7181.5	7023.0
		75% quantile	45303.0	19882.5	13102.0	13583.5
		Max	NR	25163.5	27726.0	20602.5
		N	10	10	10	10
		p-value	0.7056	0.5733	0.8035	0.5733
		SIG				

(Continued)

Wilcoxon test (one-sided+): * p <= 0.05 ** p<= 0.01
NR= Not reached

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Learning

IA-219
SAS9.4 06MAY19

Endpoint=Median latency time (ms) sex=M

			Day			
			1	2	3	4
Test group	Dose					
12	60 mg/kg bw/d	Median	36791.3	10572.0	7784.3	8992.3
		Min	13424.0	7264.0	4001.5	4539.5
		25% quantile	21943.5	9642.5	5798.0	5804.5
		75% quantile	44604.5	15539.5	8545.0	16703.5
		Max	66502.5	NR	14847.0	76140.0
		N	10	10	10	10
		p-value	0.8558	0.7106	0.9823	0.5441
		SIG				
13	180 mg/kg bw/d	Median	45872.0	12863.8	8281.0	8651.3
		Min	20163.0	5941.5	5941.5	4543.0
		25% quantile	31322.5	10564.0	6120.5	5962.0
		75% quantile	NR	16962.5	13322.5	17103.5
		Max	NR	50382.5	21205.0	57315.0
		N	10	10	10	10
		p-value	0.3407	0.4267	0.8035	0.5147
		SIG				

Wilcoxon test (one-sided+): * p <= 0.05 ** p<= 0.01
NR= Not reached

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Learning

IA-220
SAS9.4 06MAY19

Endpoint=Median latency time (ms) sex=F

			Day			
			1	2	3	4
Test group	Dose					
10	0 mg/kg bw/d	Median	33985.3	19182.0	10582.8	16452.5
		Min	14806.5	8419.5	4722.0	6522.0
		25% quantile	23702.0	13499.5	6942.0	13423.0
		75% quantile	42323.5	29923.0	13843.0	31302.0
		Max	52425.5	38398.0	33884.0	43921.0
		N	10	10	10	10
		p-value				
		SIG				
11	20 mg/kg bw/d	Median	42142.3	17311.3	11709.8	8160.8
		Min	18345.5	4419.5	5981.0	4865.0
		25% quantile	38818.0	9800.5	8902.0	6140.5
		75% quantile	NR	18840.5	16363.5	15701.0
		Max	NR	41928.5	NR	29304.0
		N	10	10	10	10
		p-value	0.0374	0.6847	0.2406	0.9784
		SIG	*			

(Continued)

Wilcoxon test (one-sided+): * p <= 0.05 ** p<= 0.01
NR= Not reached

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Learning

IA-221
SAS9.4 06MAY19

Endpoint=Median latency time (ms) sex=F

			Day			
			1	2	3	4
Test group	Dose					
12	60 mg/kg bw/d	Median	39123.8	15481.8	11652.0	10001.5
		Min	14643.0	3622.0	4241.5	3299.5
		25% quantile	19863.5	9203.0	7202.5	8282.0
		75% quantile	77623.5	17722.0	29483.0	11262.5
		Max	NR	20981.0	36882.5	20123.5
		N	10	10	10	10
		p-value	0.2644	0.9048	0.8153	0.9823
		SIG				
13	180 mg/kg bw/d	Median	69668.3	15442.8	13758.3	14222.0
		Min	29922.5	5702.5	6082.5	4960.5
		25% quantile	38102.0	7882.0	7861.0	7222.0
		75% quantile	NR	25682.5	18425.5	18540.5
		Max	NR	30643.0	28342.5	25682.5
		N	10	10	10	10
		p-value	0.0042	0.8601	0.1965	0.8601
		SIG	**			

Wilcoxon test (one-sided+): * p <= 0.05 ** p<= 0.01
NR= Not reached

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Memory
Probe trial 1, quadrant 2

IA-222
SAS9.4 06MAY19

Sex=M

			Cumul. Distance (cm)
Test group	Dose		
10	0 mg/kg bw/d	Mean	58656.0
		Median	59416.4
		Min	41767.0
		25% quantile	51032.5
		75% quantile	66850.5
		Max	73685.2
		N	10
		SIG	
11	20 mg/kg bw/d	Mean	56388.3
		Median	59718.2
		Min	37072.3
		25% quantile	52671.6
		75% quantile	62856.4
		Max	67165.2
		N	10
		SIG	

(Continued)

Wilcoxon test (one-sided+): * p <= 0.05 ** p<= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Memory
Probe trial 1, quadrant 2

IA-223
SAS9.4 06MAY19

Sex=M

			Cumul. Distance (cm)
Test group	Dose		
12	60 mg/kg bw/d	Mean	55747.1
		Median	55208.3
		Min	42790.8
		25% quantile	54251.6
		75% quantile	59665.1
		Max	68697.4
		N	10
		SIG	
13	180 mg/kg bw/d	Mean	54259.7
		Median	49222.1
		Min	44844.8
		25% quantile	45424.3
		75% quantile	64921.0
		Max	69137.3
		N	10
		SIG	

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Memory
Probe trial 1, quadrant 2

IA-224
SAS9.4 06MAY19

Sex=F

			Cumul. Distance (cm)
Test group	Dose		
10	0 mg/kg bw/d	Mean	60733.0
		Median	58819.8
		Min	39951.9
		25% quantile	56886.4
		75% quantile	66596.2
		Max	74860.9
		N	10
		SIG	
11	20 mg/kg bw/d	Mean	60243.4
		Median	61117.5
		Min	51904.6
		25% quantile	55059.9
		75% quantile	62529.0
		Max	68934.7
		N	10
		SIG	

(Continued)

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Memory
Probe trial 1, quadrant 2

IA-225
SAS9.4 06MAY19

Sex=F

			Cumul. Distance (cm)
Test group	Dose		
12	60 mg/kg bw/d	Mean	59975.4
		Median	59637.0
		Min	49684.7
		25% quantile	55914.5
		75% quantile	63416.3
		Max	74406.4
		N	10
		SIG	
13	180 mg/kg bw/d	Mean	57643.8
		Median	57149.0
		Min	42040.4
		25% quantile	52968.7
		75% quantile	62688.6
		Max	72771.0
		N	10
		SIG	

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Memory
Probe trial 1, quadrant 2

IA-226
SAS9.4 06MAY19

Sex=M

			% Time in target quadrant
Test group	Dose		
10	0 mg/kg bw/d	Mean	24.7
		Median	21.7
		Min	0.0
		25% quantile	14.4
		75% quantile	39.5
		Max	50.1
		N	10
		SIG	
11	20 mg/kg bw/d	Mean	21.9
		Median	19.2
		Min	5.6
		25% quantile	8.5
		75% quantile	26.5
		Max	53.6
		N	10
		SIG	

(Continued)

Wilcoxon test (one-sided-): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Memory
Probe trial 1, quadrant 2

IA-227
SAS9.4 06MAY19

Sex=M

			% Time in target quadrant
Test group	Dose		
12	60 mg/kg bw/d	Mean	23.9
		Median	20.1
		Min	10.7
		25% quantile	14.8
		75% quantile	36.1
		Max	42.1
		N	10
		SIG	
13	180 mg/kg bw/d	Mean	26.4
		Median	29.3
		Min	6.9
		25% quantile	14.8
		75% quantile	36.5
		Max	43.9
		N	10
		SIG	

Wilcoxon test (one-sided-): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Memory
Probe trial 1, quadrant 2

IA-228
SAS9.4 06MAY19

Sex=F

			% Time in target quadrant
Test group	Dose		
10	0 mg/kg bw/d	Mean	23.1
		Median	20.9
		Min	6.0
		25% quantile	12.5
		75% quantile	29.6
		Max	51.9
		N	10
		SIG	
11	20 mg/kg bw/d	Mean	21.9
		Median	22.2
		Min	6.9
		25% quantile	14.0
		75% quantile	31.1
		Max	36.6
		N	10
		SIG	

(Continued)

Wilcoxon test (one-sided-): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 60 +/-2
Memory
Probe trial 1, quadrant 2

IA-229
SAS9.4 06MAY19

Sex=F

			% Time in target quadrant
Test group	Dose		
12	60 mg/kg bw/d	Mean	22.2
		Median	21.9
		Min	9.7
		25% quantile	19.1
		75% quantile	25.6
		Max	33.0
		N	10
		SIG	
13	180 mg/kg bw/d	Mean	26.8
		Median	27.1
		Min	13.1
		25% quantile	17.6
		75% quantile	32.7
		Max	46.1
		N	10
		SIG	

Wilcoxon test (one-sided-): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Relearning

IA-230
SAS9.4 06MAY19

Endpoint=Mean Cumul. Distance (cm) sex=M

			Day			
			6	7	8	9
Test group	Dose					
10	0 mg/kg bw/d	Mean	39305.3	25605.5	18368.6	17520.7
		Median	30025.7	17646.1	12532.2	10449.2
		Min	12326.0	5372.1	7407.1	6008.9
		25% quantile	19927.2	8018.0	8866.9	7976.9
		75% quantile	57457.0	29398.6	26130.8	32420.9
		Max	91040.9	84604.4	53605.3	41345.4
		N	10	10	10	10
		p-value				
		SIG				
11	20 mg/kg bw/d	Mean	67564.2	26582.4	22044.8	24455.7
		Median	31185.2	16534.8	14097.8	15690.5
		Min	8580.1	8282.2	7146.5	8574.8
		25% quantile	14383.1	13305.2	12092.6	13190.8
		75% quantile	136460.3	38700.6	32220.8	30585.5
		Max	156652.3	59295.8	53800.7	84509.4
		N	10	10	10	10
		p-value	0.3421	0.2179	0.1763	0.1763
		SIG				

(Continued)

Wilcoxon test (one-sided+): * p <= 0.05 ** p<= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Relearning

IA-231
SAS9.4 06MAY19

Endpoint=Mean Cumul. Distance (cm) sex=M

			Day			
			6	7	8	9
Test group	Dose					
12	60 mg/kg bw/d	Mean	33109.5	35749.7	23446.0	16109.0
		Median	24360.3	33077.2	17105.0	11930.9
		Min	8200.8	10048.0	5625.7	4472.4
		25% quantile	16808.6	10914.9	9398.2	6288.8
		75% quantile	47239.6	55155.1	31685.9	28637.1
		Max	68938.7	72021.9	57575.9	34934.5
		N	10	10	10	10
		p-value	0.7106	0.1088	0.2894	0.7106
		SIG				
13	180 mg/kg bw/d	Mean	42331.4	31374.5	19910.2	25269.0
		Median	41184.7	26456.1	14576.4	16008.5
		Min	11191.1	9218.2	5477.6	7234.4
		25% quantile	29151.3	15841.4	9513.8	9611.8
		75% quantile	45877.9	39110.8	28465.8	28451.9
		Max	81729.4	69780.2	53295.2	91981.8
		N	10	10	10	10
		p-value	0.2894	0.1763	0.4559	0.2644
		SIG				

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Relearning

IA-232
SAS9.4 06MAY19

Endpoint=Mean Cumul. Distance (cm) sex=F

			Day			
			6	7	8	9
Test group	Dose					
10	0 mg/kg bw/d	Mean	41815.2	24911.5	33169.2	26111.0
		Median	25904.4	26028.3	29059.9	22928.5
		Min	20576.1	13238.1	6393.6	8243.2
		25% quantile	21218.5	17872.6	22562.7	18601.1
		75% quantile	43823.9	31710.2	36919.9	33057.8
		Max	119623.3	36134.0	75740.0	63655.8
		N	10	10	10	10
		p-value				
		SIG				
11	20 mg/kg bw/d	Mean	41719.3	20785.0	28938.8	23675.0
		Median	29749.0	15318.2	26308.0	21739.4
		Min	14506.4	8577.5	3679.2	6428.9
		25% quantile	23971.9	9795.0	8884.0	6917.0
		75% quantile	76882.8	25884.7	38215.6	26939.1
		Max	88234.0	61085.3	87444.5	70817.6
		N	10	10	10	10
		p-value	0.4853	0.9554	0.7106	0.7356
		SIG				

(Continued)

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Relearning

IA-233
SAS9.4 06MAY19

Endpoint=Mean Cumul. Distance (cm) sex=F

			Day			
			6	7	8	9
Test group	Dose					
12	60 mg/kg bw/d	Mean	43567.1	26228.4	21488.0	17311.8
		Median	37433.2	21618.3	16342.5	13618.0
		Min	15465.3	4863.9	8477.5	6797.3
		25% quantile	19492.9	12092.2	14619.8	10854.3
		75% quantile	68824.1	29223.6	24051.7	22712.2
		Max	85995.3	67379.5	53172.4	38665.3
		N	10	10	10	10
		p-value	0.6303	0.8237	0.9385	0.9173
		SIG				
13	180 mg/kg bw/d	Mean	33506.2	29318.7	32905.8	28368.1
		Median	36297.4	24681.5	24343.0	24588.3
		Min	16895.6	12497.8	8911.8	9425.1
		25% quantile	18633.8	18101.7	12425.5	16181.6
		75% quantile	41326.0	39755.0	57834.2	30541.0
		Max	52572.0	58743.7	73558.3	69223.6
		N	10	10	10	10
		p-value	0.6020	0.4267	0.6847	0.3697
		SIG				

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Relearning

IA-234
SAS9.4 06MAY19

Endpoint=Median latency time (ms) sex=M

			Day			
			6	7	8	9
Test group	Dose					
10	0 mg/kg bw/d	Median	13411.3	8241.8	7662.0	6172.3
		Min	6462.0	3262.0	4422.0	3022.0
		25% quantile	7982.0	5061.5	5481.5	4682.5
		75% quantile	20602.0	11922.0	8662.0	11081.5
		Max	30318.5	35202.0	12962.0	22622.0
		N	10	10	10	10
		p-value				
		SIG				
11	20 mg/kg bw/d	Median	14649.0	9132.8	6384.3	10982.5
		Min	4842.0	4662.0	3682.0	2520.5
		25% quantile	7801.5	6862.0	4621.0	5952.5
		75% quantile	84942.0	22002.5	16440.5	16603.5
		Max	NR	27522.0	25242.5	41703.0
		N	10	10	10	10
		p-value	0.3421	0.2406	0.5147	0.1965
		SIG				

(Continued)

Wilcoxon test (one-sided+): * p <= 0.05 ** p<= 0.01
NR= Not reached

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Relearning

IA-235
SAS9.4 06MAY19

Endpoint=Median latency time (ms) sex=M

			Day			
			6	7	8	9
Test group	Dose					
12	60 mg/kg bw/d	Median	10961.8	12343.0	6271.5	7150.8
		Min	5563.5	3342.5	3442.0	2643.5
		25% quantile	9662.5	7222.0	5739.0	4442.0
		75% quantile	24141.5	18759.5	10300.0	13403.0
		Max	36622.5	22402.5	25236.5	17703.0
		N	10	10	10	10
		p-value	0.4559	0.1575	0.6303	0.6847
		SIG				
13	180 mg/kg bw/d	Median	12582.8	8802.0	8811.5	5191.0
		Min	6202.5	5380.5	3322.0	3143.0
		25% quantile	7822.5	6125.5	4479.5	3620.5
		75% quantile	17442.5	17482.5	10223.0	5703.0
		Max	30423.0	35062.0	26383.0	15381.5
		N	10	10	10	10
		p-value	0.6579	0.2406	0.4853	0.8912
		SIG				

Wilcoxon test (one-sided+): * p <= 0.05 ** p<= 0.01
NR= Not reached

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Relearning

IA-236
SAS9.4 06MAY19

Endpoint=Median latency time (ms) sex=F

			Day			
			6	7	8	9
Test group	Dose					
10	0 mg/kg bw/d	Median	11321.8	11372.8	12952.0	11011.3
		Min	3222.5	4643.0	2801.5	4503.5
		25% quantile	7258.0	7002.5	7820.0	5982.5
		75% quantile	18024.5	14563.0	15182.0	16322.5
		Max	48423.5	17542.0	30101.5	21142.5
		N	10	10	10	10
		p-value				
		SIG				
11	20 mg/kg bw/d	Median	10982.5	8384.0	12582.8	7872.5
		Min	6982.0	3844.0	2381.0	3761.0
		25% quantile	7782.5	6262.5	4960.0	5541.5
		75% quantile	16303.5	14503.0	17025.0	12243.0
		Max	35183.0	24643.0	42522.0	30119.0
		N	10	10	10	10
		p-value	0.5147	0.6921	0.5147	0.8237
		SIG				

(Continued)

Wilcoxon test (one-sided+): * p <= 0.05 ** p<= 0.01
NR= Not reached

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Relearning

IA-237
SAS9.4 06MAY19

Endpoint=Median latency time (ms) sex=F

			Day			
			6	7	8	9
Test group	Dose					
12	60 mg/kg bw/d	Median	14851.8	9132.8	10461.8	6854.3
		Min	7443.0	3262.0	2524.0	4063.0
		25% quantile	12061.5	5239.5	6861.5	5541.5
		75% quantile	24802.0	14242.0	12802.5	14602.5
		Max	36603.0	18501.5	17382.5	18963.5
		N	10	10	10	10
		p-value	0.1399	0.6847	0.8237	0.7106
		SIG				
13	180 mg/kg bw/d	Median	12472.5	9992.8	11802.5	10361.3
		Min	3822.0	5022.0	5421.0	5160.5
		25% quantile	8700.5	7261.5	6825.0	8022.5
		75% quantile	18980.0	15782.5	22060.5	16542.0
		Max	24942.0	24161.0	35180.0	38838.5
		N	10	10	10	10
		p-value	0.4853	0.4559	0.5147	0.3153
		SIG				

Wilcoxon test (one-sided+): * p <= 0.05 ** p<= 0.01
NR= Not reached

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Memory
Probe trial 2, quadrant 4

IA-238
SAS9.4 06MAY19

Sex=M

			Cumul. Distance (cm)
Test group	Dose		
10	0 mg/kg bw/d	Mean	45657.0
		Median	45989.6
		Min	29658.2
		25% quantile	35251.8
		75% quantile	55141.5
		Max	63751.4
		N	10
		SIG	
11	20 mg/kg bw/d	Mean	50628.4
		Median	54380.2
		Min	35636.5
		25% quantile	41699.0
		75% quantile	56322.4
		Max	63913.3
		N	10
		SIG	

(Continued)

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Memory
Probe trial 2, quadrant 4

IA-239
SAS9.4 06MAY19

Sex=M

			Cumul. Distance (cm)
Test group	Dose		
12	60 mg/kg bw/d	Mean	52250.8
		Median	53636.8
		Min	35427.9
		25% quantile	44979.8
		75% quantile	59108.1
		Max	67344.5
		N	10
		SIG	
13	180 mg/kg bw/d	Mean	51347.9
		Median	53608.0
		Min	39293.3
		25% quantile	46204.7
		75% quantile	57076.3
		Max	59394.5
		N	10
		SIG	

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Memory
Probe trial 2, quadrant 4

IA-240
SAS9.4 06MAY19

Sex=F

			Cumul. Distance (cm)
Test group	Dose		
10	0 mg/kg bw/d	Mean	57808.8
		Median	60169.3
		Min	41552.5
		25% quantile	56222.6
		75% quantile	64536.0
		Max	65992.5
		N	10
		SIG	
11	20 mg/kg bw/d	Mean	56307.3
		Median	55607.2
		Min	46041.6
		25% quantile	51523.9
		75% quantile	60591.7
		Max	68923.5
		N	10
		SIG	

(Continued)

Wilcoxon test (one-sided+): * p <= 0.05 ** p<= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Memory
Probe trial 2, quadrant 4

IA-241
SAS9.4 06MAY19

Sex=F

			Cumul. Distance (cm)
Test group	Dose		
12	60 mg/kg bw/d	Mean	55738.7
		Median	57165.8
		Min	36513.4
		25% quantile	45803.1
		75% quantile	63635.0
		Max	72326.0
		N	10
		SIG	
13	180 mg/kg bw/d	Mean	57934.6
		Median	55867.8
		Min	46013.0
		25% quantile	50330.8
		75% quantile	65241.1
		Max	76518.8
		N	10
		SIG	

Wilcoxon test (one-sided+): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Memory
Probe trial 2, quadrant 4

IA-242
SAS9.4 06MAY19

Sex=M

			% Time in target quadrant
Test group	Dose		
10	0 mg/kg bw/d	Mean	37.9
		Median	36.1
		Min	14.8
		25% quantile	21.5
		75% quantile	55.3
		Max	64.7
		N	10
		SIG	
11	20 mg/kg bw/d	Mean	28.8
		Median	25.3
		Min	9.2
		25% quantile	21.5
		75% quantile	42.0
		Max	48.8
		N	10
		SIG	

(Continued)

Wilcoxon test (one-sided-): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Memory
Probe trial 2, quadrant 4

IA-243
SAS9.4 06MAY19

Sex=M

			% Time in target quadrant
Test group	Dose		
12	60 mg/kg bw/d	Mean	29.8
		Median	23.9
		Min	8.8
		25% quantile	16.0
		75% quantile	40.0
		Max	61.3
		N	10
		SIG	
13	180 mg/kg bw/d	Mean	30.3
		Median	27.1
		Min	18.0
		25% quantile	22.7
		75% quantile	42.1
		Max	49.2
		N	10
		SIG	

Wilcoxon test (one-sided-): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Memory
Probe trial 2, quadrant 4

IA-244
SAS9.4 06MAY19

Sex=F

			% Time in target quadrant
Test group	Dose		
10	0 mg/kg bw/d	Mean	28.0
		Median	28.2
		Min	15.3
		25% quantile	18.5
		75% quantile	31.5
		Max	47.6
		N	10
		SIG	
11	20 mg/kg bw/d	Mean	25.1
		Median	24.0
		Min	14.3
		25% quantile	16.0
		75% quantile	30.8
		Max	40.4
		N	10
		SIG	

(Continued)

Wilcoxon test (one-sided-): * p <= 0.05 ** p <= 0.01

Project No. 90R0066/05R034
Morris water maze on PND 67 +/-2
Memory
Probe trial 2, quadrant 4

IA-245
SAS9.4 06MAY19

Sex=F

			% Time in target quadrant
Test group	Dose		
12	60 mg/kg bw/d	Mean	25.9
		Median	24.6
		Min	9.5
		25% quantile	13.9
		75% quantile	35.1
		Max	50.9
		N	10
		SIG	
13	180 mg/kg bw/d	Mean	22.9
		Median	25.4
		Min	1.9
		25% quantile	15.7
		75% quantile	28.4
		Max	40.7
		N	10
		SIG	

Wilcoxon test (one-sided-): * p <= 0.05 ** p <= 0.01

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15-Apr-2019 12:37
Ascentos™ 1.3

Study 90R0066/05R034_3

Summary - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M		Test Group 11/M		Test Group 12/M		Test Group 13/M	
	0 mg/kg bw/d	10 mg/kg bw/d	20 mg/kg bw/d	60 mg/kg bw/d	180 mg/kg bw/d	180 mg/kg bw/d	180 mg/kg bw/d	180 mg/kg bw/d
Animals examined	N	10	10	10	10	10	10	10
dead	N	10	10	10	10	10	10	10
sacrificed	N	10	10	10	10	10	10	10
normal	N	10	10	10	10	10	10	10
NAD	N	10	10	10	10	10	10	10

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15-Apr-2019 12:39
Ascentos™ 1.3

Study 90R0066/05R034_3

Summary - Clinical Observation

Sex: **Female** - Phase: **In-life**

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
Animals examined	N 10	10	10	10
dead	N 10	10	10	10
found dead	N 0	1	0	0
sacrificed scheduled	N 10	9	10	10
normal	N 10	10	10	10
NAD				

day 0 [00:00 - 24:00] -> day 36 [00:00 - 24:00]

IA- 248
15-Apr-2019 12:46
Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
day 0 -> 35	N	10	10	10
Animals examined				
normal				
NAD				
[-03:00-00:00]				

IA- 249

15-Apr-2019 12:46

Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
day 0 -> 35	N	10	10	10
[00:00-02:00]	Animals examined			
	normal			
	NAD			

IA- 250
15-Apr-2019 12:46
Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Male** - Phase: **In-life**

	Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
day 0 -> 35	N	10	10	10
[02:00-05:00]	Animals examined			
	normal			
	NAD			

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15-Apr-2019 12:48
Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: Female - Phase: In-life

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
day 0 -> 35	N	10	10	10
[-03:00-00:00]	Animals examined			
	normal			
	NAD			

IA- 252
15-Apr-2019 12:48
Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: Female - Phase: In-life

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
day 0 -> 35	N	10	10	10
[00:00-02:00]	N	10	10	10
Animals examined	N	10	10	10
normal				
NAD				

IA- 253

15-Apr-2019 12:48

Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Signs Pre- and/or Post-Dosing - Clinical Observation

Sex: **Female** - Phase: **In-life**

	Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
day 0 -> 35	N	10	10	10
[02:00-05:00]	N	10	10	10
Animals examined	N	10	10	10
normal				
NAD				

IA- 254
15-Apr-2019 12:51
Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Water Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 0 -> 4	Mean [g]	20.6 n	21.6	22.1	20.7
	S.d.	1.2	1.6	1.3	2.1
	N	5	5	5	5
	Deviation Vs Control [%]		4.9	7.3	0.4
d 7 -> 11	Mean [g]	25.9 n	26.6	26.8	27.0
	S.d.	2.7	1.2	1.3	2.8
	N	5	5	5	5
	Deviation Vs Control [%]		2.5	3.2	3.9
d 14 -> 18	Mean [g]	28.7 n	29.8	29.8	31.3
	S.d.	2.0	2.2	0.7	3.1
	N	5	5	5	5
	Deviation Vs Control [%]		3.9	3.6	9.1
d 21 -> 25	Mean [g]	31.5 n	33.5	31.4	34.1
	S.d.	2.1	2.7	1.3	3.9
	N	5	5	5	5
	Deviation Vs Control [%]		6.4	-0.3	8.3

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

IA- 255

15-Apr-2019 12:53

Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Water Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 0 -> 4	Mean [g]	17.8 n	19.5	17.9	19.4
	S.d.	0.8	2.2	2.5	2.4
	N	5	5	5	5
	Deviation Vs Control [%]		9.5	0.6	8.8
d 7 -> 11	Mean [g]	19.8 n	22.1	20.9	21.9
	S.d.	1.6	2.6	2.9	2.8
	N	4	5	5	5
	Deviation Vs Control [%]		11.1	5.2	10.6
d 14 -> 18	Mean [g]	19.7 n	21.9	20.8	22.1
	S.d.	1.6	3.1	3.5	2.5
	N	5	5	5	5
	Deviation Vs Control [%]		11.4	5.9	12.7
d 21 -> 25	Mean [g]	20.3 n	24.8	21.3	23.2
	S.d.	2.4	4.0	3.0	1.6
	N	5	5	5	5
	Deviation Vs Control [%]		22.0	5.0	14.6

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

IA- 256
15-Apr-2019 12:56
Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Food Consumption Per Animal And Day

Sex: **Male** - Phase: **In-life**

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
d 0 -> 7	Mean [g]	16.4 n	16.8	17.6	16.6
	S.d.	1.1	0.7	0.9	1.4
	N	5	5	5	5
	Deviation Vs Control [%]		2.7	7.8	1.7
d 7 -> 14	Mean [g]	21.5 n	22.1	22.8	23.3
	S.d.	2.3	0.6	0.9	2.0
	N	5	5	5	5
	Deviation Vs Control [%]		3.1	6.3	8.6
d 14 -> 21	Mean [g]	25.0 n	25.8	26.3	27.0
	S.d.	2.2	0.9	1.2	1.9
	N	5	5	5	5
	Deviation Vs Control [%]		3.1	5.2	7.9
d 21 -> 28	Mean [g]	28.4 n	29.1	29.5	30.9
	S.d.	2.1	1.5	2.9	2.5
	N	5	5	5	5
	Deviation Vs Control [%]		2.5	3.9	8.9
d 0 -> 28	Mean [g]	22.8 n	23.5	24.1	24.5
	S.d.	1.9	0.8	1.4	1.8
	N	5	5	5	5
	Deviation Vs Control [%]		2.8	5.5	7.3

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

IA- 257

15-Apr-2019 12:58

Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Food Consumption Per Animal And Day

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 0 -> 7	Mean [g]	13.7 n	13.9	15.6	15.1
	S.d.	0.6	1.0	4.2	1.0
	N	5	5	5	5
	Deviation Vs Control [%]		2.1	14.3	10.7
d 7 -> 14	Mean [g]	15.6 n	16.1	16.3	17.8
	S.d.	0.9	0.9	2.5	2.0
	N	5	5	5	5
	Deviation Vs Control [%]		3.5	4.4	14.1
d 14 -> 21	Mean [g]	16.2 n	16.7	16.7	17.5
	S.d.	1.5	1.6	2.2	1.0
	N	5	5	5	5
	Deviation Vs Control [%]		3.2	3.5	8.5
d 21 -> 28	Mean [g]	18.0 n	18.5	18.7	19.5
	S.d.	2.3	0.6	2.2	1.3
	N	5	5	5	5
	Deviation Vs Control [%]		3.0	3.8	8.3
d 0 -> 28	Mean [g]	15.9 n	16.2	16.8	17.5
	S.d.	1.3	0.7	2.5	1.2
	N	5	5	5	5
	Deviation Vs Control [%]		2.5	6.1	10.3

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

IA- 258

15-Apr-2019 13:02

Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

		Test Group 10/M 0 mg/kg bw/d	Test Group 11/M 20 mg/kg bw/d	Test Group 12/M 60 mg/kg bw/d	Test Group 13/M 180 mg/kg bw/d
day 0	Mean	100.2n	100.6	105.9	98.7
	S.d.	10.2	10.4	6.3	11.1
	N	10	10	10	10
	Deviation Vs Control [%]		0.5	5.7	-1.4
day 7	Mean	155.3n	156.5	164.2	155.2
	S.d.	17.2	14.7	8.0	15.8
	N	10	10	10	10
	Deviation Vs Control [%]		0.8	5.7	-0.1
day 14	Mean	214.5n	219.2	228.4	219.3
	S.d.	24.1	18.6	10.7	20.4
	N	10	10	10	10
	Deviation Vs Control [%]		2.1	6.4	2.2
day 21	Mean	274.5n	283.2	291.9	286.4
	S.d.	29.4	24.0	14.4	26.1
	N	10	10	10	10
	Deviation Vs Control [%]		3.2	6.3	4.4
day 28	Mean	328.8n	339.9	344.1	344.6
	S.d.	29.4	30.2	18.3	28.0
	N	10	10	10	10
	Deviation Vs Control [%]		3.4	4.6	4.8

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

IA- 259

15-Apr-2019 13:04

Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
day 0	Mean	91.2 n	93.1	88.8	92.9
	S.d.	6.6	8.5	10.6	7.0
	N	10	10	10	10
	Deviation Vs Control [%]		2.1	-2.6	1.9
day 7	Mean	130.5 n	131.3	129.6	136.4
	S.d.	10.1	11.5	16.4	9.7
	N	10	10	10	10
	Deviation Vs Control [%]		0.6	-0.7	4.5
day 14	Mean	160.8 n	160.8	161.1	173.2
	S.d.	15.7	12.9	21.5	14.2
	N	10	10	10	10
	Deviation Vs Control [%]		0.0	0.1	7.7
day 21	Mean	180.7 n	183.8	182.0	195.5
	S.d.	18.6	13.7	21.0	14.8
	N	10	9	10	10
	Deviation Vs Control [%]		1.7	0.7	8.2
day 28	Mean	203.7 n	204.8	202.4	217.4
	S.d.	23.3	13.7	25.1	15.3
	N	10	9	10	10
	Deviation Vs Control [%]		0.5	-0.7	6.7

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
n=DUNNETT

IA- 260
15-Apr-2019 13:07
Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

	Test Group 10/M			Test Group 11/M			Test Group 12/M			Test Group 13/M		
	0 mg/kg bw/d			20 mg/kg bw/d			60 mg/kg bw/d			180 mg/kg bw/d		
d 0 -> 7	Mean	55.2 n		55.9			58.3			56.4		
	S.d.	7.8		4.7			2.6			6.6		
	N	10		10			10			10		
d 7 -> 14	Mean	59.2 n		62.6			64.1			64.2		
	S.d.	9.7		5.4			5.8			6.4		
	N	10		10			10			10		
d 14 -> 21	Mean	59.9 n		64.0			63.5			67.1		
	S.d.	7.0		7.7			4.6			7.5		
	N	10		10			10			10		
d 21 -> 28	Mean	54.3 n		56.8			52.2			58.1		
	S.d.	5.8		8.1			8.5			5.0		
	N	10		10			10			10		
d 0 -> 28	Mean	228.6 n		239.3			238.2			245.8		
	S.d.	21.4		22.2			16.1			20.2		
	N	10		10			10			10		

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

IA- 261
15-Apr-2019 13:08
Ascentos™ 1.3

Study 90R0066/05R034_3

Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

		Test Group 10/F 0 mg/kg bw/d	Test Group 11/F 20 mg/kg bw/d	Test Group 12/F 60 mg/kg bw/d	Test Group 13/F 180 mg/kg bw/d
d 0 -> 7	Mean	39.4 n	38.3	40.8	43.6
	S.d.	5.6	6.6	7.1	6.1
	N	10	10	10	10
d 7 -> 14	Mean	30.3 n	29.5	31.4	36.8
	S.d.	8.5	4.8	8.2	5.9
	N	10	10	10	10
d 14 -> 21	Mean	19.8 n	23.0	20.9	22.3
	S.d.	4.5	4.2	5.3	4.9
	N	10	9	10	10
d 21 -> 28	Mean	23.0 n	21.0	20.4	21.9
	S.d.	7.5	5.3	7.4	7.0
	N	10	9	10	10
d 0 -> 28	Mean	112.5 n	111.8	113.6	124.5
	S.d.	21.1	11.7	17.8	14.2
	N	10	9	10	10

Statistic Profile = Dunnett test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
d = day; n=DUNNETT

15-APR-19
05R034D3
TABLE : 1A-
262

PROJ. NO. 90R0066/05R034: MOD. EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - DCO (COHORT 3)
SUMMARY OF MALE CLINICAL OBSERVATIONS

	GROUP#	WEEK OF STUDY					TOTAL
		0	1	2	3	4	
# OF ANIMALS EXAMINED	10	10	10	10	10	10	10
	11	10	10	10	10	10	10
	12	10	10	10	10	10	10
	13	10	10	10	10	10	10

NORMAL

NOTHING ABNORMAL DETECTED	10	10	10	10	10	10	10
	11	10	10	10	10	10	10
	12	10	10	10	10	10	10
	13	10	10	10	10	10	10

15-APR-19
05R034D3
TABLE : 1A-
263

PROJ.NO. 90R0066/05R034:MOD.EXTENDED ONE-GENERATION REPRODUCTION
TOX. STUDY IN SPRAGUE DAWLEY RATS (GAVAGE) - DCO (COHORT 3)
SUMMARY OF FEMALE CLINICAL OBSERVATIONS

	GROUP#	WEEK OF STUDY				TOTAL
		0	1	2	3	
# OF ANIMALS EXAMINED	10	10	10	10	10	10
	11	10	10	10	9	9
	12	10	10	10	10	10
	13	10	10	10	10	10
NORMAL						
NOTHING ABNORMAL DETECTED	10	10	10	10	10	10
	11	10	10	9	9	10
	12	10	10	10	10	10
	13	10	10	10	10	10
DEAD						
FOUND DEAD	10	0	0	0	0	0
	11	0	0	1	0	1
	12	0	0	0	0	0
	13	0	0	0	0	0

Study

90R0066/05R034_K

IB 1

31-Jul-2018 09:49

Ascentos™ 1.3

Red blood cell + coagulation parameters

Sex: **Male** - Phase: **In-life**

		G 00 / M 0 mg/kg bw/d	G 01 / M 20 mg/kg bw/d	G 02 / M 60 mg/kg bw/d	G 03 / M 180 mg/kg bw/d
RBC [tera/L] week 15	Mean	8.44 k	8.48	8.38	8.10
	S.d.	0.60	0.27	0.42	0.60
	N	10	10	10	10
	Median	8.30	8.52	8.44	8.22
	Deviation Vs Control [%]		0.49	-0.72	-3.96
HGB [mmol/L] week 15	Mean	9.0 k	9.0	9.1	9.0
	S.d.	0.3	0.3	0.4	0.6
	N	10	10	10	10
	Median	9.0	9.0	9.1	9.2
	Deviation Vs Control [%]		-0.2	1.4	0.0
HCT [L/L] week 15	Mean	0.419 k	0.415	0.420	0.413
	S.d.	0.016	0.014	0.020	0.027
	N	10	10	10	10
	Median	0.416	0.416	0.424	0.418
	Deviation Vs Control [%]		-0.884	0.382	-1.314
MCV [fL] week 15	Mean	49.8 v	48.9	50.2	51.0
	S.d.	2.0	1.3	1.2	1.1
	N	10	10	10	10
	Median	50.2	49.2	50.7	51.1
	Deviation Vs Control [%]		-1.6	0.9	2.6
MCH [fmol] week 15	Mean	1.07 v	1.06	1.09	1.11 *
	S.d.	0.05	0.04	0.04	0.04
	N	10	10	10	10
	Median	1.08	1.08	1.11	1.12
	Deviation Vs Control [%]		-1.31	1.96	3.65
MCHC [mmol/L] week 15	Mean	21.46 k	21.57	21.71	21.72
	S.d.	0.23	0.23	0.46	0.33
	N	10	10	10	10
	Median	21.49	21.58	21.67	21.66
	Deviation Vs Control [%]		0.52	1.16	1.23
RETA [giga/L] week 15	Mean	143.7 k	152.0	143.6	160.6
	S.d.	30.4	30.4	23.0	65.2
	N	10	10	10	10
	Median	141.4	148.2	149.3	138.1
	Deviation Vs Control [%]		5.7	-0.1	11.7
PLT [giga/L] week 15	Mean	787 k	873	891	766
	S.d.	127	112	183	137
	N	10	10	10	10
	Median	768	850	824	790
	Deviation Vs Control [%]		11	13	-3
HQT [sec] week 15	Mean	36.6 k	35.8	36.0	38.2
	S.d.	2.9	3.3	2.4	3.4
	N	10	10	10	10
	Median	36.0	34.8	36.3	38.7
	Deviation Vs Control [%]		-2.2	-1.5	4.4

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS; v=KRUSKALL-WALLIS-WILCOX

Study

90R0066/05R034_K

IB 2

31-Jul-2018 10:56

Ascentos™ 1.3

Red blood cell + coagulation parameters

Sex: **Female** - Phase: **In-life**

		G 00 / F 0 mg/kg bw/d	G 01 / F 20 mg/kg bw/d	G 02 / F 60 mg/kg bw/d	G 03 / F 180mg/kg bw/d
RBC [tera/L] day 122	Mean	8.22 k	8.22	8.39	8.14
	S.d.	0.30	0.38	0.24	0.22
	N	10	10	10	10
	Median	8.20	8.15	8.43	8.13
	Deviation Vs Control [%]		-0.06	2.09	-0.96
HGB [mmol/L] day 122	Mean	9.7 k	9.7	9.8	9.7
	S.d.	0.4	0.3	0.2	0.2
	N	10	10	10	10
	Median	9.8	9.7	9.8	9.9
	Deviation Vs Control [%]		-0.5	1.0	-0.1
HCT [L/L] day 122	Mean	0.445 k	0.444	0.450	0.448
	S.d.	0.017	0.018	0.008	0.013
	N	10	10	10	10
	Median	0.446	0.444	0.450	0.448
	Deviation Vs Control [%]		-0.225	0.943	0.539
MCV [fL] day 122	Mean	54.2 k	54.1	53.6	55.0
	S.d.	1.6	1.3	1.3	1.1
	N	10	10	10	10
	Median	54.2	54.5	53.2	55.3
	Deviation Vs Control [%]		-0.2	-1.1	1.5
MCH [fmol] day 122	Mean	1.18 k	1.18	1.17	1.19
	S.d.	0.04	0.04	0.03	0.03
	N	10	10	10	10
	Median	1.18	1.18	1.16	1.19
	Deviation Vs Control [%]		-0.34	-0.85	1.19
MCHC [mmol/L] day 122	Mean	21.81 k	21.77	21.84	21.70
	S.d.	0.25	0.39	0.15	0.25
	N	10	10	10	10
	Median	21.85	21.80	21.87	21.75
	Deviation Vs Control [%]		-0.18	0.13	-0.52
RETA [giga/L] day 122	Mean	20.3 k	26.2	22.2	22.5
	S.d.	11.6	16.5	8.5	12.0
	N	10	10	10	10
	Median	19.7	20.9	21.2	22.3
	Deviation Vs Control [%]		29.0	9.7	10.9
PLT [giga/L] day 122	Mean	678 k	810	691	779
	S.d.	82	133	193	114
	N	10	10	10	10
	Median	684	826	690	768
	Deviation Vs Control [%]		20	2	15
HQT [sec] day 122	Mean	36.9 k	35.6	35.1	36.2
	S.d.	1.9	1.8	1.2	1.9
	N	10	10	10	10
	Median	37.8	35.2	35.0	36.0
	Deviation Vs Control [%]		-3.4	-4.9	-1.9

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKAL-WALLIS

Study 90R0066/05R034_K

IB 3
31-Jul-2018 10:58
Ascentos™ 1.3

Total white and differential blood cell count

Sex: **Male** - Phase: **In-life**

		G 00 / M 0 mg/kg bw/d	G 01 / M 20 mg/kg bw/d	G 02 / M 60 mg/kg bw/d	G 03 / M 180 mg/kg bw/d
WBC [giga/L] week 15	Mean	8.65 k	8.04	8.45	8.32
	S.d.	1.17	1.33	1.86	1.33
	N	10	10	10	10
	Median	8.64	7.99	7.95	7.92
	Deviation Vs Control [%]		-7.06	-2.30	-3.86
NEUTA [giga/L] week 15	Mean	1.01 k	1.08	1.18	1.22
	S.d.	0.23	0.26	0.33	0.46
	N	10	10	10	10
	Median	1.06	1.10	1.12	1.09
	Deviation Vs Control [%]		6.21	16.67	19.82
LYMPHA [giga/L] week 15	Mean	7.23 k	6.61	6.83	6.69
	S.d.	1.10	1.16	1.45	0.99
	N	10	10	10	10
	Median	7.22	6.54	6.49	6.64
	Deviation Vs Control [%]		-8.59	-5.53	-7.45
MONOA [giga/L] week 15	Mean	0.21 k	0.19	0.20	0.20
	S.d.	0.10	0.05	0.06	0.10
	N	10	10	10	10
	Median	0.18	0.18	0.19	0.20
	Deviation Vs Control [%]		-10.10	-3.37	-1.92
EOSA [giga/L] week 15	Mean	0.12 k	0.11	0.16	0.14
	S.d.	0.03	0.04	0.08	0.04
	N	10	10	10	10
	Median	0.12	0.12	0.14	0.14
	Deviation Vs Control [%]		-9.68	30.65	12.90
BASOA [giga/L] week 15	Mean	0.03 k	0.02	0.04	0.03
	S.d.	0.01	0.01	0.01	0.01
	N	10	10	10	10
	Median	0.03	0.02	0.04	0.03
	Deviation Vs Control [%]		-23.33	20.00	-3.33
LUCA [giga/L] week 15	Mean	0.04 k	0.04	0.04	0.03
	S.d.	0.01	0.02	0.02	0.01
	N	10	10	10	10
	Median	0.04	0.03	0.03	0.04
	Deviation Vs Control [%]		-20.00	-6.67	-24.44

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

Study

90R0066/05R034_K

IB 4

31-Jul-2018 10:58

Ascentos™ 1.3

Total white and differential blood cell count

Sex: **Male** - Phase: **In-life**

		G 00 / M 0 mg/kg bw/d	G 01 / M 20 mg/kg bw/d	G 02 / M 60 mg/kg bw/d	G 03 / M 180 mg/kg bw/d
NEUT [%] week 15	Mean	11.8 k	13.5	13.9	14.4
	S.d.	2.9	3.0	2.0	3.7
	N	10	10	10	10
	Median	11.3	13.7	13.8	14.1
	Deviation Vs Control [%]		14.3	17.7	22.2
LYMPH [%] week 15	Mean	83.4 k	82.1	81.0	80.7
	S.d.	3.4	3.4	2.5	4.6
	N	10	10	10	10
	Median	84.4	81.8	81.0	81.6
	Deviation Vs Control [%]		-1.6	-2.9	-3.3
MONO [%] week 15	Mean	2.4 k	2.4	2.4	2.4
	S.d.	1.3	0.6	0.3	0.9
	N	10	10	10	10
	Median	2.0	2.4	2.3	2.6
	Deviation Vs Control [%]		-3.3	-2.9	-1.6
EOS [%] week 15	Mean	1.4 k	1.4	1.8	1.7
	S.d.	0.4	0.5	0.7	0.7
	N	10	10	10	10
	Median	1.4	1.2	1.8	1.6
	Deviation Vs Control [%]		-4.1	26.9	19.3
BASO [%] week 15	Mean	0.4 v	0.3 *	0.4	0.4
	S.d.	0.1	0.1	0.1	0.2
	N	10	10	10	10
	Median	0.4	0.2	0.4	0.3
	Deviation Vs Control [%]		27.8	16.7	0.0
LUC [%] week 15	Mean	0.5 k	0.4	0.5	0.4
	S.d.	0.2	0.2	0.2	0.1
	N	10	10	10	10
	Median	0.4	0.4	0.4	0.4
	Deviation Vs Control [%]		-19.6	-2.0	-19.6

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS; v=KRUSKALL-WALLIS-WILCOX

Study 90R0066/05R034_K

IB 5
31-Jul-2018 10:57
Ascentos™ 1.3

Total white and differential blood cell count

Sex: **Female** - Phase: **In-life**

		G 00 / F 0 mg/kg bw/d	G 01 / F 20 mg/kg bw/d	G 02 / F 60 mg/kg bw/d	G 03 / F 180mg/kg bw/d
WBC [giga/L] day 122	Mean	6.61 k	6.84	6.14	6.36
	S.d.	1.48	1.97	2.11	2.20
	N	10	10	10	10
	Median	6.42	7.39	5.90	5.96
	Deviation Vs Control [%]		3.50	-6.99	-3.66
NEUTA [giga/L] day 122	Mean	0.84 k	0.77	0.63	0.76
	S.d.	0.33	0.29	0.21	0.38
	N	10	10	10	10
	Median	0.88	0.78	0.63	0.58
	Deviation Vs Control [%]		-8.40	-25.44	-10.65
LYMPHA [giga/L] day 122	Mean	5.30 k	5.61	5.11	5.19
	S.d.	1.22	1.76	1.92	1.91
	N	10	10	10	10
	Median	5.49	5.64	4.74	5.00
	Deviation Vs Control [%]		5.95	-3.51	-2.08
MONOA [giga/L] day 122	Mean	0.19 k	0.16	0.16	0.16
	S.d.	0.04	0.06	0.05	0.04
	N	10	10	10	10
	Median	0.18	0.14	0.16	0.15
	Deviation Vs Control [%]		-12.83	-15.51	-12.83
EOSA [giga/L] day 122	Mean	0.21 k	0.21	0.18	0.20
	S.d.	0.08	0.08	0.08	0.08
	N	10	10	10	10
	Median	0.18	0.21	0.18	0.16
	Deviation Vs Control [%]		0.00	-11.06	-5.77
BASOA [giga/L] day 122	Mean	0.04 k	0.04	0.04	0.03
	S.d.	0.01	0.02	0.01	0.01
	N	10	10	10	10
	Median	0.04	0.04	0.04	0.03
	Deviation Vs Control [%]		-6.67	-22.22	-31.11
LUCA [giga/L] day 122	Mean	0.02 k	0.03	0.02	0.03
	S.d.	0.01	0.02	0.01	0.02
	N	10	10	10	10
	Median	0.02	0.03	0.02	0.03
	Deviation Vs Control [%]		33.33	4.17	33.33

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

Study 90R0066/05R034_K

IB 6

31-Jul-2018 10:57

Ascentos™ 1.3

Total white and differential blood cell count

Sex: **Female** - Phase: **In-life**

		G 00 / F 0 mg/kg bw/d	G 01 / F 20 mg/kg bw/d	G 02 / F 60 mg/kg bw/d	G 03 / F 180mg/kg bw/d
NEUT [%] day 122	Mean	12.8 k	11.6	10.8	12.0
	S.d.	4.1	3.7	3.7	4.7
	N	10	10	10	10
	Median	13.4	11.4	9.2	11.1
	Deviation Vs Control [%]		-9.1	-15.9	-5.9
LYMPH [%] day 122	Mean	80.1 k	81.7	82.3	80.9
	S.d.	4.8	4.7	4.7	6.4
	N	10	10	10	10
	Median	79.8	82.6	83.4	81.2
	Deviation Vs Control [%]		2.0	2.8	1.0
MONO [%] day 122	Mean	2.9 k	2.5	2.8	2.7
	S.d.	0.7	0.7	1.3	0.6
	N	10	10	10	10
	Median	2.6	2.6	2.3	2.6
	Deviation Vs Control [%]		-15.5	-5.2	-8.6
EOS [%] day 122	Mean	3.2 k	3.1	3.1	3.4
	S.d.	0.9	1.0	0.9	1.8
	N	10	10	10	10
	Median	2.6	2.8	3.2	2.8
	Deviation Vs Control [%]		-2.2	-1.9	7.6
BASO [%] day 122	Mean	0.7 k	0.7	0.6	0.5
	S.d.	0.2	0.2	0.2	0.1
	N	10	10	10	10
	Median	0.6	0.7	0.6	0.5
	Deviation Vs Control [%]		-2.9	-11.8	-23.5
LUC [%] day 122	Mean	0.4 k	0.4	0.4	0.5
	S.d.	0.1	0.2	0.2	0.2
	N	10	10	10	10
	Median	0.4	0.4	0.4	0.4
	Deviation Vs Control [%]		18.9	16.2	27.0

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKAL-WALLIS

Study 90R0066/05R034_K

IB 7

31-Jul-2018 10:59

Ascentos™ 1.3

Enzymes

Sex: **Male** - Phase: **In-life**

		G 00 / M 0 mg/kg bw/d	G 01 / M 20 mg/kg bw/d	G 02 / M 60 mg/kg bw/d	G 03 / M 180 mg/kg bw/d
ALT [μkat/L] week 15	Mean	0.72 k	0.73	0.74	2.60
	S.d.	0.13	0.12	0.13	5.68
	N	10	10	10	10
	Median	0.72	0.74	0.70	0.80
	Deviation Vs Control [%]		1.68	3.50	263.64
AST [μkat/L] week 15	Mean	1.99 k	2.12	1.97	12.29
	S.d.	0.45	0.50	0.63	32.80
	N	10	10	10	10
	Median	2.09	2.06	1.81	1.96
	Deviation Vs Control [%]		6.55	-0.81	519.03
ALP [μkat/L] week 15	Mean	1.32 k	1.36	1.24	1.45
	S.d.	0.25	0.20	0.18	0.21
	N	10	10	10	10
	Median	1.38	1.33	1.24	1.39
	Deviation Vs Control [%]		2.96	-6.22	10.09
GGT_C [nkat/L] week 15	Mean	25 NA	25	25	25
	S.d.	0	0	0	0
	N	10	10	10	10
	Median	25	25	25	25
	Deviation Vs Control [%]		0	0	0

Statistic Profile = Wilcoxon test (one-sided+), Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics

k=KRUSKALL-WALLIS; NA=No Test Applicable

Study 90R0066/05R034_K

IB 8

31-Jul-2018 11:00

Ascentos™ 1.3

Enzymes

Sex: **Female** - Phase: **In-life**

		G 00 / F 0 mg/kg bw/d	G 01 / F 20 mg/kg bw/d	G 02 / F 60 mg/kg bw/d	G 03 / F 180mg/kg bw/d
ALT [µkat/L] day 122	Mean	0.77 k	0.70	0.72	0.81
	S.d.	0.08	0.12	0.10	0.09
	N	10	10	10	10
	Median	0.78	0.70	0.70	0.80
	Deviation Vs Control [%]		-8.87	-6.26	5.74
AST [µkat/L] day 122	Mean	1.78 k	1.70	1.91	1.93
	S.d.	0.26	0.39	0.92	0.48
	N	10	10	10	10
	Median	1.67	1.52	1.62	1.82
	Deviation Vs Control [%]		-4.54	7.12	8.30
ALP [µkat/L] day 122	Mean	1.21 k	1.21	1.10	1.48
	S.d.	0.30	0.28	0.29	0.51
	N	10	10	10	10
	Median	1.12	1.15	1.13	1.33
	Deviation Vs Control [%]		0.00	-9.08	22.36
GGT_C [nkat/L] day 122	Mean	25 NA	25	25	25
	S.d.	0	0	0	0
	N	10	10	10	10
	Median	25	25	25	25
	Deviation Vs Control [%]		0	0	0

Statistic Profile = Wilcoxon test (one-sided+), Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics

k=KRUSKALL-WALLIS; NA=No Test Applicable

Study 90R0066/05R034_K

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31-Jul-2018 13:32

Ascentos™ 1.3

Substrates

Sex: Male - Phase: In-life

		G 00 / M 0 mg/kg bw/d	G 01 / M 20 mg/kg bw/d	G 02 / M 60 mg/kg bw/d	G 03 / M 180 mg/kg bw/d
UREA [mmol/L] week 15	Mean	5.04 k	5.21	5.09	5.39
	S.d.	0.32	0.97	0.78	1.29
	N	10	10	10	10
	Median	4.90	4.77	4.84	5.14
	Deviation Vs Control [%]		3.37	0.89	6.82
CREA [mmol/L] week 15	Mean	20.4 k	20.9	19.0	20.4
	S.d.	2.7	3.0	2.8	2.6
	N	10	10	10	10
	Median	19.5	20.7	19.1	20.8
	Deviation Vs Control [%]		2.6	-6.5	0.1
GLUC [mmol/L] week 15	Mean	5.86 k	6.03	6.00	6.06
	S.d.	0.61	0.57	0.49	0.77
	N	10	10	10	10
	Median	5.69	5.96	5.98	5.85
	Deviation Vs Control [%]		3.01	2.54	3.59
TBIL_C [μmol/L] week 15	Mean	2.15 k	1.85	1.78	1.95
	S.d.	0.52	0.44	0.33	0.77
	N	10	10	10	10
	Median	1.90	1.80	1.78	1.84
	Deviation Vs Control [%]		-13.61	-16.81	-9.35
TPROT [g/L] week 15	Mean	64.45 k	64.38	65.16	63.27
	S.d.	1.96	1.79	2.82	2.50
	N	10	10	10	10
	Median	64.24	64.08	64.18	63.11
	Deviation Vs Control [%]		-0.11	1.09	-1.84
ALB [g/L] week 15	Mean	38.30 k	38.55	38.44	37.76
	S.d.	1.49	0.81	1.50	1.25
	N	10	10	10	10
	Median	37.93	38.68	38.20	38.12
	Deviation Vs Control [%]		0.66	0.38	-1.39
GLOB [g/L] week 15	Mean	26.15 k	25.83	26.71	25.50
	S.d.	0.99	1.81	1.57	1.45
	N	10	10	10	10
	Median	26.31	25.76	26.28	25.28
	Deviation Vs Control [%]		-1.25	2.13	-2.48
CHOL [mmol/L] week 15	Mean	1.70 k	1.93	1.90	1.46
	S.d.	0.37	0.34	0.55	0.31
	N	10	10	10	10
	Median	1.58	1.85	1.90	1.60
	Deviation Vs Control [%]		13.45	11.63	-14.10
TRIG [mmol/L] week 15	Mean	0.59 k	0.90	0.63	0.81
	S.d.	0.17	0.52	0.21	0.21
	N	10	10	10	10
	Median	0.58	0.76	0.60	0.81
	Deviation Vs Control [%]		50.93	5.90	36.42

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKAL-WALLIS

Study 90R0066/05R034_K

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Substrates

Sex: **Female** - Phase: **In-life**

		G 00 / F 0 mg/kg bw/d	G 01 / F 20 mg/kg bw/d	G 02 / F 60 mg/kg bw/d	G 03 / F 180mg/kg bw/d
UREA [mmol/L] day 122	Mean	6.61 k	6.41	5.53	6.40
	S.d.	1.15	1.61	0.62	0.85
	N	10	10	10	10
	Median	6.39	5.82	5.60	6.30
	Deviation Vs Control [%]		-3.01	-16.27	-3.13
CREA [mmol/L] day 122	Mean	29.4 k	28.6	28.3	30.4
	S.d.	2.5	1.9	3.3	2.4
	N	10	10	10	10
	Median	29.3	28.5	28.6	29.3
	Deviation Vs Control [%]		-2.9	-3.7	3.3
GLUC [mmol/L] day 122	Mean	5.89 k	5.57	5.73	5.91
	S.d.	0.62	0.74	0.65	0.59
	N	10	10	10	10
	Median	5.88	5.38	5.54	6.12
	Deviation Vs Control [%]		-5.33	-2.62	0.46
TBIL_C [μmol/L] day 122	Mean	1.90 k	1.94	1.87	1.63
	S.d.	0.29	0.37	0.47	0.34
	N	10	10	10	10
	Median	1.93	1.81	1.99	1.70
	Deviation Vs Control [%]		2.19	1.56	-14.35
TPROT [g/L] day 122	Mean	65.19 k	64.77	66.45	68.38
	S.d.	2.15	3.07	3.75	3.99
	N	10	10	10	10
	Median	65.02	64.54	65.70	69.20
	Deviation Vs Control [%]		-0.64	1.93	4.89
ALB [g/L] day 122	Mean	38.98 k	38.56	39.31	40.40
	S.d.	1.60	1.53	2.11	1.46
	N	10	10	10	10
	Median	38.94	38.51	40.05	40.48
	Deviation Vs Control [%]		-1.06	0.86	3.65
GLOB [g/L] day 122	Mean	26.21 k	26.21	27.13	27.98
	S.d.	1.36	2.02	2.20	3.09
	N	10	10	10	10
	Median	26.16	25.65	27.20	28.66
	Deviation Vs Control [%]		-0.02	3.51	6.73
CHOL [mmol/L] day 122	Mean	1.75 v	1.87	2.07 **	1.67
	S.d.	0.25	0.21	0.22	0.44
	N	10	10	10	10
	Median	1.77	1.84	2.09	1.60
	Deviation Vs Control [%]		6.73	18.25	-4.96
TRIG [mmol/L] day 122	Mean	1.46 k	1.15	1.27	1.27
	S.d.	0.41	0.40	0.65	0.58
	N	10	10	10	10
	Median	1.45	1.12	1.02	1.17
	Deviation Vs Control [%]		-21.77	-13.17	-13.45

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS; v=KRUSKALL-WALLIS-WILCOX

Study

90R0066/05R034_K

IB 11

25-Sep-2018 09:18

Ascentos™ 1.3

Electrolytes + minerals

Sex: **Male** - Phase: **In-life**

		G 00 / M 0 mg/kg bw/d	G 01 / M 20 mg/kg bw/d	G 02 / M 60 mg/kg bw/d	G 03 / M 180 mg/kg bw/d
NA [mmol/L] week 15	Mean	142.3 k	142.8	143.3	142.8
	S.d.	2.5	1.7	1.4	3.1
	N	10	10	10	10
	Median	143.0	143.3	143.6	143.8
	Deviation Vs Control [%]		0.4	0.7	0.3
K [mmol/L] week 15	Mean	5.10 k	5.17	5.37	5.11
	S.d.	0.42	0.42	0.51	0.33
	N	10	10	10	10
	Median	5.19	5.25	5.38	5.09
	Deviation Vs Control [%]		1.41	5.33	0.08
CL [mmol/L] week 15	Mean	98.1 k	98.5	98.2	98.2
	S.d.	2.1	1.7	1.7	2.5
	N	10	10	10	10
	Median	98.4	98.5	98.8	99.0
	Deviation Vs Control [%]		0.4	0.1	0.1
INP [mmol/L] week 15	Mean	1.97 k	2.03	2.02	1.98
	S.d.	0.19	0.14	0.10	0.15
	N	10	10	10	10
	Median	1.94	1.98	2.00	1.98
	Deviation Vs Control [%]		3.30	2.49	0.51
CA [mmol/L] week 15	Mean	2.65 k	2.64	2.66	2.67
	S.d.	0.07	0.05	0.06	0.05
	N	10	10	10	10
	Median	2.65	2.65	2.66	2.65
	Deviation Vs Control [%]		-0.23	0.49	0.76

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

Study 90R0066/05R034_K

IB 12

31-Jul-2018 13:34

Ascentos™ 1.3

Electrolytes + minerals

Sex: **Female** - Phase: **In-life**

		G 00 / F 0 mg/kg bw/d	G 01 / F 20 mg/kg bw/d	G 02 / F 60 mg/kg bw/d	G 03 / F 180mg/kg bw/d
NA [mmol/L] day 122	Mean	138.9 k	138.5	139.7	139.0
	S.d.	0.9	1.9	1.0	0.9
	N	10	10	10	10
	Median	138.6	138.8	139.6	138.9
	Deviation Vs Control [%]		-0.3	0.6	0.1
K [mmol/L] day 122	Mean	4.74 k	4.85	5.06	5.03
	S.d.	0.35	0.45	0.37	0.31
	N	10	10	10	10
	Median	4.82	4.92	5.04	5.06
	Deviation Vs Control [%]		2.45	6.76	6.31
CL [mmol/L] day 122	Mean	97.2 k	96.9	97.6	97.0
	S.d.	1.7	1.8	1.1	1.3
	N	10	10	10	10
	Median	97.5	97.6	97.7	97.1
	Deviation Vs Control [%]		-0.3	0.4	-0.2
INP [mmol/L] day 122	Mean	1.61 k	1.60	1.58	1.57
	S.d.	0.16	0.18	0.21	0.24
	N	10	10	10	10
	Median	1.60	1.56	1.64	1.56
	Deviation Vs Control [%]		-0.56	1.81	-2.05
CA [mmol/L] day 122	Mean	2.62 k	2.56	2.65	2.65
	S.d.	0.06	0.09	0.06	0.08
	N	10	10	10	10
	Median	2.62	2.54	2.66	2.64
	Deviation Vs Control [%]		-2.36	1.07	0.92

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKAL-WALLIS

Study 90R0066/05R034_K

IB 13

25-Sep-2018 09:34

Ascentos™ 1.3

Thyroid hormones

Sex: **Male** - Phase: **In-life**

		G 00 / M 0 mg/kg bw/d	G 01 / M 20 mg/kg bw/d	G 02 / M 60 mg/kg bw/d	G 03 / M 180 mg/kg bw/d
T4 [nmol/L] week 15 [00:00-24:00]	Mean	56.15 k	51.97	54.31	53.04
	S.d.	3.44	5.68	11.25	9.54
	N	10	10	10	10
	Median	56.05	50.58	52.55	50.52
	Deviation Vs Control [%]		-7.45	-3.27	-5.54
TSH [µg/L] week 15 [00:00-24:00]	Mean	8.47 k	9.40	9.05	8.65
	S.d.	3.29	6.13	2.57	2.51
	N	10	10	10	10
	Median	8.17	7.90	9.35	9.08
	Deviation Vs Control [%]		10.99	6.83	2.15

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

Study 90R0066/05R034_K

IB 14

25-Sep-2018 09:36

Ascentos™ 1.3

Thyroid hormones

Sex: **Female** - Phase: **In-life**

		G 00 / F 0 mg/kg bw/d	G 01 / F 20 mg/kg bw/d	G 02 / F 60 mg/kg bw/d	G 03 / F 180mg/kg bw/d
T4 [nmol/L] day 122	Mean	35.24 k	37.40	36.21	33.43
	S.d.	5.59	5.68	4.54	8.95
	N	10	10	10	10
	Median	35.14	37.29	35.54	30.30
	Deviation Vs Control [%]		6.14	2.76	-5.12
TSH [µg/L] day 122	Mean	5.50 k	5.21	5.54	4.52
	S.d.	2.20	1.65	1.05	0.93
	N	10	10	10	10
	Median	4.88	4.85	5.47	4.46
	Deviation Vs Control [%]		-5.20	0.69	-17.81

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

Study

90R0066/05R034_K

IB 15

25-Sep-2018 09:44

Ascentos™ 1.3

Urinalysis

Sex: **Male** - Phase: **In-life**

		G 00 / M 0 mg/kg bw/d	G 01 / M 20 mg/kg bw/d	G 02 / M 60 mg/kg bw/d	G 03 / M 180 mg/kg bw/d
PH_C [---] day 101	Mean	6.75 v	6.85	6.80	6.35 *
	S.d.	0.26	0.24	0.35	0.34
	N	10	10	10	10
	Median	6.75	7.00	7.00	6.50
PRO_C [---] day 101	Mean	1.10 x+	1.00	1.00	1.00
	S.d.	0.32	0.00	0.00	0.00
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
GLU_C [---] day 101	Mean	0.00 NA	0.00	0.00	0.00
	S.d.	0.00	0.00	0.00	0.00
	N	10	10	10	10
	Median	0.00	0.00	0.00	0.00
KET_C [---] day 101	Mean	1.00 x+	1.00	1.00	1.10
	S.d.	0.00	0.00	0.00	0.32
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
UBG_C [---] day 101	Mean	1.00 NA	1.00	1.00	1.00
	S.d.	0.00	0.00	0.00	0.00
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
BIL_C [---] day 101	Mean	1.00 NA	1.00	1.00	1.00
	S.d.	0.00	0.00	0.00	0.00
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
BLOOD_C [---] day 101	Mean	1.00 x+	1.00	1.30	1.20
	S.d.	0.00	0.00	0.67	0.42
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
VOL [ml] day 101	Mean	7.01 k	7.63	7.48	7.52
	S.d.	2.29	3.10	1.40	1.34
	N	10	10	10	10
	Median	8.00	7.00	7.55	7.75
SP.GR._C [g/L] day 101	Mean	1,047.3 k	1,038.8	1,040.1	1,040.0
	S.d.	21.0	10.3	6.8	5.6
	N	10	10	10	10
	Median	1,038.5	1,037.5	1,038.5	1,041.5

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), Wilcoxon test (one-sided+), * p<=0.05, ** p <=0.01, X = Group excluded from statistics

v=KRUSKALL-WALLIS-WILCOX; x=WILCOX; NA=No Test Applicable; k=KRUSKALL-WALLIS

Study

90R0066/05R034_K

IB 16

25-Sep-2018 09:44

Ascentos™ 1.3

Urinalysis

Sex: **Male** - Phase: **In-life**

		G 00 / M 0 mg/kg bw/d	G 01 / M 20 mg/kg bw/d	G 02 / M 60 mg/kg bw/d	G 03 / M 180 mg/kg bw/d
CRYST_C [---] day 101	Mean	3.00 x+	2.90	2.90	3.00
	S.d.	0.00	0.32	0.32	0.00
	N	10	10	10	10
	Median	3.00	3.00	3.00	3.00
RENAL EC_C [---] day 101	Mean	1.00 NA	1.00	1.00	1.00
	S.d.	0.00	0.00	0.00	0.00
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
TRANS EC_C [---] day 101	Mean	1.00 NA	1.00	1.00	1.00
	S.d.	0.00	0.00	0.00	0.00
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
SQUAM EC_C [---] day 101	Mean	1.00 NA	1.00	1.00	1.00
	S.d.	0.00	0.00	0.00	0.00
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
CASTS_C [---] day 101	Mean	0.00 NA	0.00	0.00	0.00
	S.d.	0.00	0.00	0.00	0.00
	N	10	10	10	10
	Median	0.00	0.00	0.00	0.00
ERY_C [---] day 101	Mean	1.00 x+	1.00	1.20	1.00
	S.d.	0.00	0.00	0.63	0.00
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
LEUCO_C [---] day 101	Mean	1.00 NA	1.00	1.00	1.00
	S.d.	0.00	0.00	0.00	0.00
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00

Statistic Profile = Wilcoxon test (one-sided+), Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
x=WILCOX; NA=No Test Applicable

Study

90R0066/05R034_K

IB 17

25-Sep-2018 09:45

Ascentos™ 1.3

Urinalysis

Sex: **Female** - Phase: **In-life**

		G 00 / F 0 mg/kg bw/d	G 01 / F 20 mg/kg bw/d	G 02 / F 60 mg/kg bw/d	G 03 / F 180mg/kg bw/d
PH_C	Mean	6.65 k	6.65	6.55	6.30
[--]	S.d.	0.34	0.34	0.28	0.75
day 120	N	10	10	10	10
	Median	6.50	6.50	6.50	6.50
PRO_C	Mean	1.00 NA	1.00	1.00	1.00
[--]	S.d.	0.00	0.00	0.00	0.00
day 120	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
GLU_C	Mean	0.00 NA	0.00	0.00	0.00
[--]	S.d.	0.00	0.00	0.00	0.00
day 120	N	10	10	10	10
	Median	0.00	0.00	0.00	0.00
KET_C	Mean	1.00 NA	1.00	1.00	1.00
[--]	S.d.	0.00	0.00	0.00	0.00
day 120	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
UBG_C	Mean	1.00 NA	1.00	1.00	1.00
[--]	S.d.	0.00	0.00	0.00	0.00
day 120	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
BIL_C	Mean	1.00 NA	1.00	1.00	1.00
[--]	S.d.	0.00	0.00	0.00	0.00
day 120	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
BLOOD_C	Mean	1.00 NA	1.00	1.00	1.00
[--]	S.d.	0.00	0.00	0.00	0.00
day 120	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
VOL	Mean	5.81 k	7.47	6.85	7.77
[ml]	S.d.	1.23	2.89	2.49	3.66
day 120	N	10	10	10	10
	Median	5.45	6.35	6.25	7.10
SP.GR._C	Mean	1,039.6 k	1,037.3	1,035.5	1,048.4
[g/L]	S.d.	6.7	6.6	5.2	21.2
day 120	N	10	10	10	10
	Median	1,040.0	1,037.5	1,034.5	1,040.0

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), Wilcoxon test (one-sided+), * p<=0.05, ** p <=0.01, X = Group excluded from statistics

k=KRUSKALL-WALLIS; NA=No Test Applicable

Study

90R0066/05R034_K

IB 18

25-Sep-2018 09:45

Ascentos™ 1.3

Urinalysis

Sex: **Female** - Phase: **In-life**

		G 00 / F 0 mg/kg bw/d	G 01 / F 20 mg/kg bw/d	G 02 / F 60 mg/kg bw/d	G 03 / F 180mg/kg bw/d
CRYST_C [---] day 120	Mean	2.80 x+	2.80	2.30	2.50
	S.d.	0.42	0.42	0.48	0.53
	N	10	10	10	10
	Median	3.00	3.00	2.00	2.50
RENAL EC_C [---] day 120	Mean	1.00 NA	1.00	1.00	1.00
	S.d.	0.00	0.00	0.00	0.00
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
TRANS EC_C [---] day 120	Mean	1.10 x+	1.10	1.10	1.10
	S.d.	0.32	0.32	0.32	0.32
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
SQUAM EC_C [---] day 120	Mean	1.00 NA	1.00	1.00	1.00
	S.d.	0.00	0.00	0.00	0.00
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
CASTS_C [---] day 120	Mean	0.00 x+	0.00	0.10	0.00
	S.d.	0.00	0.00	0.32	0.00
	N	10	10	10	10
	Median	0.00	0.00	0.00	0.00
ERY_C [---] day 120	Mean	1.10 x+	1.00	1.00	1.10
	S.d.	0.32	0.00	0.00	0.32
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00
LEUCO_C [---] day 120	Mean	1.00 x+	1.10	1.30	1.10
	S.d.	0.00	0.32	0.67	0.32
	N	10	10	10	10
	Median	1.00	1.00	1.00	1.00

Statistic Profile = Wilcoxon test (one-sided+), Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics

x=WILCOX; NA=No Test Applicable

Study 90R0066/05R034_K

IB 19

25-Sep-2018 15:06

Ascentos™ 1.3

Spermanalysis

Sex: **Male** - Phase: **In-life**

		G 00 / M 0 mg/kg bw/d	G 01 / M 20 mg/kg bw/d	G 02 / M 60 mg/kg bw/d	G 03 / M 180 mg/kg bw/d
MOTILE_C [%] week 15	Mean	88 x-	84 *	85 *	86 *
	S.d.	5	7	8	4
	N	24	24	24	24
	Median	90	84	86	87
	Deviation Vs Control [%]		-5	-4	-3
TS/gT [Mio/g] week 15	Mean	100 x-	X	X	104
	S.d.	14			18
	N	24	0	0	24
	Median	96			98
	Deviation Vs Control [%]	0			4
TS/gC [Mio/g] week 15	Mean	732 x-	X	X	728
	S.d.	112			98
	N	24	0	0	24
	Median	730			725
	Deviation Vs Control [%]	0			-1
ABNORMAL5_C [%; Cut off 5%] week 15	Mean	5.6 x+	X	X	5.5
	S.d.	1.4			0.9
	N	23	0	0	24
	Median	5.0			5.0
	Deviation Vs Control [%]	0.0			-1.9

Statistic Profile = Wilcoxon with Bonferroni-Holm (one-sided+), Wilcoxon with Bonferroni-Holm (one-sided-), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
x=WILCOX

Study

90R0066/05R034_K

IB 20

18-Jun-2019 06:42

Ascentos™ 1.3

Red blood cell + coagulation parameters

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
RBC [tera/L] day 90	Mean	7.91 k	7.91	7.99	8.12
	S.d.	0.33	0.42	0.30	0.27
	N	10	10	10	10
	Median	7.85	7.83	8.00	8.10
	Deviation Vs Control [%]		-0.04	1.00	2.67
HGB [mmol/L] day 90	Mean	8.7 v	8.6	8.7	9.0 *
	S.d.	0.2	0.3	0.2	0.3
	N	10	10	10	10
	Median	8.6	8.6	8.6	9.0
	Deviation Vs Control [%]		-1.6	0.0	3.3
HCT [L/L] day 90	Mean	0.412 v	0.403	0.411	0.423
	S.d.	0.015	0.013	0.006	0.013
	N	10	10	10	10
	Median	0.412	0.400	0.410	0.424
	Deviation Vs Control [%]		-2.017	-0.194	2.843
MCV [fL] day 90	Mean	52.1 k	51.0	51.5	52.1
	S.d.	1.6	2.2	2.0	1.7
	N	10	10	10	10
	Median	52.2	51.3	51.7	51.9
	Deviation Vs Control [%]		-2.0	-1.1	0.2
MCH [fmol] day 90	Mean	1.10 k	1.08	1.09	1.11
	S.d.	0.04	0.05	0.05	0.03
	N	10	10	10	10
	Median	1.12	1.08	1.09	1.10
	Deviation Vs Control [%]		-1.81	-0.91	0.45
MCHC [mmol/L] day 90	Mean	21.18 k	21.24	21.17	21.24
	S.d.	0.32	0.35	0.38	0.21
	N	10	10	10	10
	Median	21.15	21.29	21.14	21.16
	Deviation Vs Control [%]		0.27	-0.08	0.27
RETA [giga/L] day 90	Mean	183.1 k	205.4	201.8	179.8
	S.d.	21.7	34.8	42.7	23.0
	N	10	10	10	10
	Median	183.9	194.6	192.2	184.1
	Deviation Vs Control [%]		12.2	10.2	-1.8
PLT [giga/L] day 90	Mean	952 k	913	869	879
	S.d.	225	128	107	160
	N	10	10	10	10
	Median	899	872	876	855
	Deviation Vs Control [%]		-4	-9	-8
HQT [sec] day 90	Mean	34.2 v	34.3	34.0	37.4 *
	S.d.	2.8	1.7	1.8	2.7
	N	10	10	10	10
	Median	34.6	33.8	34.2	36.2
	Deviation Vs Control [%]		0.1	-0.8	9.1

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS; v=KRUSKALL-WALLIS-WILCOX

Study

90R0066/05R034_K

IB 21

18-Jun-2019 06:42

Ascentos™ 1.3

Red blood cell + coagulation parameters

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
RBC [tera/L] day 90	Mean	7.54 k	7.51	7.60	7.34
	S.d.	0.33	0.28	0.29	0.39
	N	10	10	10	10
	Median	7.50	7.58	7.54	7.34
	Deviation Vs Control [%]		-0.50	0.80	-2.76
HGB [mmol/L] day 90	Mean	8.7 k	8.6	8.8	8.6
	S.d.	0.3	0.2	0.3	0.4
	N	10	10	10	10
	Median	8.7	8.6	8.9	8.6
	Deviation Vs Control [%]		-0.8	2.1	-1.3
HCT [L/L] day 90	Mean	0.397 k	0.393	0.401	0.388
	S.d.	0.012	0.010	0.015	0.016
	N	10	10	10	10
	Median	0.396	0.392	0.402	0.389
	Deviation Vs Control [%]		-0.957	1.058	-2.317
MCV [fL] day 90	Mean	52.6 k	52.4	52.8	52.9
	S.d.	1.4	1.3	0.8	1.4
	N	10	10	10	10
	Median	52.7	52.4	52.8	53.2
	Deviation Vs Control [%]		-0.4	0.2	0.5
MCH [fmol] day 90	Mean	1.15 k	1.14	1.16	1.17
	S.d.	0.05	0.03	0.02	0.04
	N	10	10	10	10
	Median	1.16	1.14	1.16	1.17
	Deviation Vs Control [%]		-0.69	1.13	1.30
MCHC [mmol/L] day 90	Mean	21.86 k	21.83	22.07	22.07
	S.d.	0.34	0.30	0.39	0.22
	N	10	10	10	10
	Median	21.98	21.88	22.11	22.08
	Deviation Vs Control [%]		-0.16	0.95	0.95
RETA [giga/L] day 90	Mean	149.9 k	171.2	167.0	163.7
	S.d.	34.0	35.0	28.3	33.2
	N	10	10	10	10
	Median	147.0	166.5	169.5	167.8
	Deviation Vs Control [%]		14.2	11.4	9.2
PLT [giga/L] day 90	Mean	859 k	878	884	954
	S.d.	87	75	120	141
	N	10	10	10	10
	Median	866	880	852	994
	Deviation Vs Control [%]		2	3	11
HQT [sec] day 90	Mean	31.0 k	31.8	31.9	31.1
	S.d.	1.3	1.3	2.0	1.7
	N	10	10	10	10
	Median	30.5	31.8	32.1	31.6
	Deviation Vs Control [%]		2.5	3.0	0.3

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKAL-WALLIS

Study

90R0066/05R034_K

IB 22

18-Jun-2019 06:44

Ascentos™ 1.3

Total white and differential blood cell count

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
WBC [giga/L] day 90	Mean	10.19 k	10.11	9.93	8.92
	S.d.	1.75	2.59	1.79	1.55
	N	10	10	10	10
	Median	10.15	10.10	10.27	8.54
	Deviation Vs Control [%]		-0.73	-2.55	-12.43
NEUTA [giga/L] day 90	Mean	1.27 k	1.19	1.24	1.20
	S.d.	0.41	0.34	0.50	0.27
	N	10	10	10	10
	Median	1.08	1.14	1.12	1.23
	Deviation Vs Control [%]		-5.98	-2.20	-5.59
LYMPHA [giga/L] day 90	Mean	8.43 k	8.44	8.23	7.24
	S.d.	1.58	2.40	1.50	1.60
	N	10	10	10	10
	Median	8.46	8.16	8.54	7.02
	Deviation Vs Control [%]		0.05	-2.38	-14.11
MONOA [giga/L] day 90	Mean	0.25 k	0.24	0.21	0.26
	S.d.	0.05	0.10	0.08	0.09
	N	10	10	10	10
	Median	0.24	0.23	0.21	0.24
	Deviation Vs Control [%]		-3.23	-16.53	2.82
EOSA [giga/L] day 90	Mean	0.14 k	0.13	0.15	0.14
	S.d.	0.03	0.04	0.04	0.04
	N	10	10	10	10
	Median	0.13	0.14	0.14	0.15
	Deviation Vs Control [%]		-0.74	11.85	4.44
BASOA [giga/L] day 90	Mean	0.03 k	0.03	0.03	0.02
	S.d.	0.01	0.01	0.01	0.01
	N	10	10	10	10
	Median	0.03	0.03	0.02	0.02
	Deviation Vs Control [%]		0.00	-16.13	-19.35
LUCA [giga/L] day 90	Mean	0.06 k	0.07	0.07	0.06
	S.d.	0.02	0.04	0.04	0.03
	N	10	10	10	10
	Median	0.06	0.05	0.06	0.05
	Deviation Vs Control [%]		12.50	9.38	-10.94

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

Study

90R0066/05R034_K

IB 23

18-Jun-2019 06:44

Ascentos™ 1.3

Total white and differential blood cell count

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
NEUT [%] day 90	Mean	12.6 k	12.3	12.4	13.8
	S.d.	3.7	3.6	3.9	3.8
	N	10	10	10	10
	Median	12.0	11.8	11.2	13.5
	Deviation Vs Control [%]		-2.3	-1.0	9.9
LYMPH [%] day 90	Mean	82.7 k	82.9	83.0	80.7
	S.d.	4.1	4.2	4.1	4.3
	N	10	10	10	10
	Median	83.9	83.2	84.8	80.0
	Deviation Vs Control [%]		0.3	0.4	-2.4
MONO [%] day 90	Mean	2.4 k	2.4	2.1	2.9
	S.d.	0.4	0.8	0.8	1.1
	N	10	10	10	10
	Median	2.5	2.6	2.0	2.7
	Deviation Vs Control [%]		-0.4	-12.8	21.0
EOS [%] day 90	Mean	1.4 k	1.4	1.5	1.6
	S.d.	0.4	0.6	0.4	0.6
	N	10	10	10	10
	Median	1.4	1.2	1.6	1.6
	Deviation Vs Control [%]		-0.7	8.5	16.3
BASO [%] day 90	Mean	0.3 k	0.3	0.3	0.3
	S.d.	0.1	0.1	0.1	0.1
	N	10	10	10	10
	Median	0.3	0.3	0.2	0.3
	Deviation Vs Control [%]		-15.6	-18.8	-9.4
LUC [%] day 90	Mean	0.6 k	0.7	0.7	0.6
	S.d.	0.2	0.3	0.3	0.3
	N	10	10	10	10
	Median	0.6	0.6	0.6	0.5
	Deviation Vs Control [%]		9.4	4.7	-6.3

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKAL-WALLIS

Study

90R0066/05R034_K

IB 24

18-Jun-2019 06:44

Ascentos™ 1.3

Total white and differential blood cell count

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
WBC [giga/L] day 90	Mean	7.78 k	7.23	7.09	7.99
	S.d.	1.06	3.06	1.69	1.82
	N	10	10	10	10
	Median	7.61	6.06	6.78	7.80
	Deviation Vs Control [%]		-7.09	-8.97	2.70
NEUTA [giga/L] day 90	Mean	0.71 k	0.64	0.89	0.62
	S.d.	0.20	0.26	0.93	0.22
	N	10	10	10	10
	Median	0.72	0.58	0.61	0.56
	Deviation Vs Control [%]		-9.17	25.53	-12.83
LYMPHA [giga/L] day 90	Mean	6.74 k	6.27	5.84	7.04
	S.d.	1.16	2.77	1.10	1.80
	N	10	10	10	10
	Median	6.51	5.28	5.86	6.81
	Deviation Vs Control [%]		-6.97	-13.30	4.46
MONOA [giga/L] day 90	Mean	0.15 k	0.15	0.17	0.15
	S.d.	0.03	0.08	0.11	0.03
	N	10	10	10	10
	Median	0.15	0.12	0.13	0.14
	Deviation Vs Control [%]		2.74	18.49	0.68
EOSA [giga/L] day 90	Mean	0.12 k	0.09	0.12	0.11
	S.d.	0.04	0.04	0.05	0.04
	N	10	10	10	10
	Median	0.11	0.08	0.11	0.11
	Deviation Vs Control [%]		-23.73	1.69	-5.08
BASOA [giga/L] day 90	Mean	0.02 k	0.02	0.02	0.02
	S.d.	0.01	0.01	0.01	0.01
	N	10	10	10	10
	Median	0.02	0.02	0.02	0.02
	Deviation Vs Control [%]		5.00	-5.00	5.00
LUCA [giga/L] day 90	Mean	0.05 k	0.06	0.04	0.05
	S.d.	0.02	0.04	0.03	0.02
	N	10	10	10	10
	Median	0.05	0.05	0.04	0.05
	Deviation Vs Control [%]		27.66	-14.89	10.64

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

Study

90R0066/05R034_K

IB 25

18-Jun-2019 06:44

Ascentos™ 1.3

Total white and differential blood cell count

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
NEUT [%] day 90	Mean	9.4 k	9.6	11.4	8.0
	S.d.	3.7	4.6	7.6	2.8
	N	10	10	10	10
	Median	9.0	8.2	9.2	8.0
	Deviation Vs Control [%]		1.7	20.8	-15.7
LYMPH [%] day 90	Mean	86.2 k	86.0	83.6	87.6
	S.d.	4.0	5.0	8.8	3.3
	N	10	10	10	10
	Median	86.5	87.4	86.0	87.4
	Deviation Vs Control [%]		-0.3	-3.0	1.6
MONO [%] day 90	Mean	1.9 k	2.0	2.4	2.0
	S.d.	0.4	0.6	1.2	0.7
	N	10	10	10	10
	Median	2.0	1.9	2.0	2.0
	Deviation Vs Control [%]		6.3	26.6	3.1
EOS [%] day 90	Mean	1.5 k	1.3	1.7	1.5
	S.d.	0.6	0.4	0.5	0.7
	N	10	10	10	10
	Median	1.2	1.2	1.6	1.4
	Deviation Vs Control [%]		-13.6	12.9	2.0
BASO [%] day 90	Mean	0.3 k	0.3	0.3	0.3
	S.d.	0.1	0.1	0.1	0.1
	N	10	10	10	10
	Median	0.2	0.3	0.2	0.3
	Deviation Vs Control [%]		15.4	3.8	3.8
LUC [%] day 90	Mean	0.6 k	0.8	0.6	0.6
	S.d.	0.2	0.3	0.4	0.1
	N	10	10	10	10
	Median	0.6	0.8	0.4	0.6
	Deviation Vs Control [%]		30.5	0.0	10.2

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKAL-WALLIS

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Ascentos™ 1.3

Enzymes

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
ALT [µkat/L] day 90	Mean	0.90 k	0.88	0.94	0.97
	S.d.	0.21	0.22	0.36	0.16
	N	10	10	10	10
	Median	0.86	0.87	0.86	1.02
	Deviation Vs Control [%]		-1.67	4.44	7.89
AST [µkat/L] day 90	Mean	2.80 k	2.87	2.58	2.55
	S.d.	0.88	0.81	0.62	0.66
	N	10	10	10	10
	Median	2.68	2.59	2.49	2.42
	Deviation Vs Control [%]		2.32	-8.10	-9.10
ALP [µkat/L] day 90	Mean	2.01 k	1.89	2.18	2.30
	S.d.	0.26	0.37	0.33	0.40
	N	10	10	10	10
	Median	2.00	1.84	2.17	2.31
	Deviation Vs Control [%]		-6.36	8.24	14.00
GGT_C [nkat/L] day 90	Mean	25 NA	25	25	25
	S.d.	0	0	0	0
	N	10	10	10	10
	Median	25	25	25	25
	Deviation Vs Control [%]		0	0	0

Statistic Profile = Wilcoxon test (one-sided+), Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics

k=KRUSKALL-WALLIS; NA=No Test Applicable

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Enzymes

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
ALT [µkat/L] day 90	Mean	0.78 k	0.78	0.70	0.67
	S.d.	0.16	0.12	0.16	0.16
	N	10	10	10	10
	Median	0.71	0.78	0.66	0.64
	Deviation Vs Control [%]		-0.51	-10.26	-14.10
AST [µkat/L] day 90	Mean	2.54 k	2.21	1.94	1.85
	S.d.	0.80	0.41	0.46	0.47
	N	10	10	10	10
	Median	2.22	2.18	1.79	1.84
	Deviation Vs Control [%]		-12.78	-23.58	-27.09
ALP [µkat/L] day 90	Mean	1.30 k	1.48	1.52	1.32
	S.d.	0.35	0.32	0.67	0.30
	N	10	10	10	10
	Median	1.27	1.52	1.46	1.30
	Deviation Vs Control [%]		14.16	17.17	1.46
GGT_C [nkat/L] day 90	Mean	25 NA	25	25	25
	S.d.	0	0	0	0
	N	10	10	10	10
	Median	25	25	25	25
	Deviation Vs Control [%]		0	0	0

Statistic Profile = Wilcoxon test (one-sided+), Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics

k=KRUSKALL-WALLIS; NA=No Test Applicable

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Substrates

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
UREA [mmol/L] day 90	Mean	4.61 k	4.40	4.36	4.68
	S.d.	0.49	0.63	0.50	0.80
	N	10	10	10	10
	Median	4.67	4.49	4.41	4.69
	Deviation Vs Control [%]		-4.62	-5.36	1.65
CREA [mmol/L] day 90	Mean	20.5 k	21.8	20.2	20.0
	S.d.	2.9	1.3	2.1	2.9
	N	10	10	10	10
	Median	20.2	21.5	20.7	19.4
	Deviation Vs Control [%]		6.6	-1.5	-2.2
GLUC [mmol/L] day 90	Mean	5.96 k	5.96	6.10	5.64
	S.d.	0.35	0.62	0.86	0.50
	N	10	10	10	10
	Median	5.94	5.91	5.77	5.84
	Deviation Vs Control [%]		0.02	2.25	-5.48
TBIL_C [μmol/L] day 90	Mean	1.92 k	1.57	2.01	1.94
	S.d.	0.24	0.35	0.33	0.51
	N	10	10	10	10
	Median	2.04	1.52	1.97	1.81
	Deviation Vs Control [%]		-18.39	4.64	1.15
TPROT [g/L] day 90	Mean	63.55 k	61.96	63.20	63.05
	S.d.	2.61	2.45	1.68	2.54
	N	10	10	10	10
	Median	63.18	62.16	62.61	62.66
	Deviation Vs Control [%]		-2.51	-0.56	-0.79
ALB [g/L] day 90	Mean	37.26 k	36.82	37.59	37.30
	S.d.	1.27	1.34	0.91	1.30
	N	10	10	10	10
	Median	36.84	36.43	37.72	37.48
	Deviation Vs Control [%]		-1.18	0.89	0.11
GLOB [g/L] day 90	Mean	26.30 k	25.14	25.61	25.75
	S.d.	1.85	1.96	1.79	1.66
	N	10	10	10	10
	Median	25.94	25.88	25.62	25.48
	Deviation Vs Control [%]		-4.40	-2.62	-2.07
CHOL [mmol/L] day 90	Mean	1.79 v	1.76	1.96	1.42
	S.d.	0.39	0.26	0.39	0.33
	N	10	10	10	10
	Median	1.77	1.66	1.90	1.40
	Deviation Vs Control [%]		-1.62	9.43	-21.08
TRIG [mmol/L] day 90	Mean	0.76 k	0.86	1.09	0.79
	S.d.	0.24	0.20	0.36	0.27
	N	10	10	10	10
	Median	0.72	0.84	1.06	0.72
	Deviation Vs Control [%]		11.91	42.67	2.88

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS; v=KRUSKALL-WALLIS-WILCOX

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Substrates

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
UREA [mmol/L] day 90	Mean	5.17 k	5.34	5.01	4.78
	S.d.	0.66	0.70	0.42	0.56
	N	10	10	10	10
	Median	5.47	5.27	5.10	4.88
	Deviation Vs Control [%]		3.31	-3.07	-7.58
CREA [mmol/L] day 90	Mean	24.7 k	25.3	24.4	24.0
	S.d.	1.7	3.4	3.5	3.6
	N	10	10	10	10
	Median	24.8	24.4	25.9	25.2
	Deviation Vs Control [%]		2.4	-1.2	-2.7
GLUC [mmol/L] day 90	Mean	5.83 k	5.96	6.00	6.05
	S.d.	0.65	0.53	0.77	0.50
	N	10	10	10	10
	Median	5.80	5.85	5.95	5.98
	Deviation Vs Control [%]		2.23	2.95	3.81
TBIL_C [μmol/L] day 90	Mean	1.98 k	1.99	2.08	2.52
	S.d.	0.49	0.59	0.60	0.41
	N	10	10	10	10
	Median	1.95	2.02	1.86	2.45
	Deviation Vs Control [%]		0.39	4.78	26.96
TPROT [g/L] day 90	Mean	65.99 v	65.02	68.41	70.15 *
	S.d.	2.90	3.32	3.46	3.77
	N	10	10	10	10
	Median	65.72	65.98	68.58	69.70
	Deviation Vs Control [%]		-1.47	3.66	6.30
ALB [g/L] day 90	Mean	40.40 v	40.23	40.99	42.83 *
	S.d.	1.55	1.29	3.35	2.43
	N	10	10	10	10
	Median	40.28	39.54	41.60	42.46
	Deviation Vs Control [%]		-0.42	1.46	6.00
GLOB [g/L] day 90	Mean	25.59 k	24.79	27.42	27.32
	S.d.	2.24	2.99	1.64	2.10
	N	10	10	10	10
	Median	24.83	26.12	28.06	27.36
	Deviation Vs Control [%]		-3.14	7.13	6.77
CHOL [mmol/L] day 90	Mean	2.02 k	2.09	2.11	2.00
	S.d.	0.61	0.38	0.34	0.43
	N	10	10	10	10
	Median	1.89	2.04	2.01	1.91
	Deviation Vs Control [%]		3.37	4.70	-1.24
TRIG [mmol/L] day 90	Mean	0.64 k	0.58	0.62	0.63
	S.d.	0.35	0.18	0.24	0.14
	N	10	10	10	10
	Median	0.54	0.52	0.57	0.62
	Deviation Vs Control [%]		-9.23	-2.97	-1.10

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS; v=KRUSKALL-WALLIS-WILCOX

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Electrolytes + minerals

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
NA [mmol/L] day 90	Mean	145.8 k	145.8	146.8	146.6
	S.d.	1.3	1.7	0.9	0.9
	N	10	10	10	10
	Median	146.0	145.4	146.5	146.6
	Deviation Vs Control [%]		0.0	0.7	0.6
K [mmol/L] day 90	Mean	5.45 k	5.45	5.43	5.45
	S.d.	0.37	0.28	0.25	0.19
	N	10	10	10	10
	Median	5.53	5.44	5.49	5.50
	Deviation Vs Control [%]		0.02	-0.29	0.07
CL [mmol/L] day 90	Mean	102.8 k	103.3	103.7	103.0
	S.d.	1.0	1.8	1.4	1.8
	N	10	10	10	10
	Median	102.8	103.4	103.9	102.6
	Deviation Vs Control [%]		0.5	0.9	0.3
INP [mmol/L] day 90	Mean	2.34 k	2.32	2.20	2.40
	S.d.	0.16	0.18	0.14	0.17
	N	10	10	10	10
	Median	2.34	2.32	2.19	2.37
	Deviation Vs Control [%]		-0.77	-5.82	2.74
CA [mmol/L] day 90	Mean	2.57 v	2.49 *	2.58	2.58
	S.d.	0.11	0.05	0.06	0.07
	N	10	10	10	10
	Median	2.56	2.50	2.56	2.59
	Deviation Vs Control [%]		-3.27	0.16	0.39

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS; v=KRUSKALL-WALLIS-WILCOX

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Electrolytes + minerals

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
NA [mmol/L] day 90	Mean	143.5 v	144.8 *	144.8 **	144.6 *
	S.d.	0.8	1.4	0.6	1.0
	N	10	10	10	10
	Median	143.7	144.6	145.0	144.9
	Deviation Vs Control [%]		0.8	0.9	0.7
K [mmol/L] day 90	Mean	5.02 k	4.81	4.82	5.02
	S.d.	0.31	0.25	0.41	0.29
	N	10	10	10	10
	Median	4.96	4.86	4.70	4.99
	Deviation Vs Control [%]		-4.22	-3.85	0.08
CL [mmol/L] day 90	Mean	102.9 k	104.0	102.8	102.2
	S.d.	1.3	2.5	2.0	1.8
	N	10	10	10	10
	Median	103.2	103.4	102.2	102.1
	Deviation Vs Control [%]		1.1	-0.1	-0.7
INP [mmol/L] day 90	Mean	1.93 k	1.84	1.89	1.92
	S.d.	0.16	0.23	0.19	0.18
	N	10	10	10	10
	Median	1.88	1.86	1.84	1.92
	Deviation Vs Control [%]		-4.45	-1.97	-0.73
CA [mmol/L] day 90	Mean	2.58 v	2.53	2.61	2.66 *
	S.d.	0.06	0.10	0.07	0.07
	N	10	10	10	10
	Median	2.58	2.57	2.62	2.66
	Deviation Vs Control [%]		-1.78	1.16	3.34

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
v=KRUSKALL-WALLIS-WILCOX; k=KRUSKALL-WALLIS

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Thyroid hormones

Sex: **Male** - Phase: **In-life**

		G 00 / M 0 mg/kg bw/d	G 01 / M 20 mg/kg bw/d	G 02 / M 60 mg/kg bw/d	G 03 / M 180 mg/kg bw/d
T4 [nmol/L] day 4	Mean	27.47 k	23.48	25.49	25.64
	S.d.	5.82	4.23	2.77	3.59
	N	10	9	10	10
	Median	27.78	24.53	25.48	26.76
	Deviation Vs Control [%]		-14.53	-7.23	-6.66
TSH [µg/L] day 4	Mean	3.87 k	3.67	3.79	3.98
	S.d.	0.57	0.48	0.71	0.91
	N	10	9	10	10
	Median	3.74	3.64	3.56	3.95
	Deviation Vs Control [%]		-5.24	-2.25	2.81

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

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Thyroid hormones

Sex: **Female** - Phase: **In-life**

		G 00 / F 0 mg/kg bw/d	G 01 / F 20 mg/kg bw/d	G 02 / F 60 mg/kg bw/d	G 03 / F 180mg/kg bw/d
T4 [nmol/L] day 4	Mean	24.54 k	28.17	24.80	24.85
	S.d.	4.16	5.03	4.74	5.04
	N	10	10	10	10
	Median	24.26	29.12	24.62	25.77
	Deviation Vs Control [%]		14.78	1.07	1.26
TSH [µg/L] day 4	Mean	4.15 v	3.54 **	3.85	3.95 *
	S.d.	0.44	0.59	0.64	1.38
	N	10	10	10	10
	Median	4.11	3.51	3.89	3.54
	Deviation Vs Control [%]		-14.85	-7.34	-5.01

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS; v=KRUSKALL-WALLIS-WILCOX

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Ascentos™ 1.3

Thyroid hormones

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
T4 [nmol/L] day 22	Mean	51.13 k	54.45	55.55	57.49
	S.d.	6.25	6.01	7.54	7.09
	N	10	10	10	10
	Median	53.08	54.54	52.23	57.03
	Deviation Vs Control [%]		6.50	8.65	12.45
TSH [µg/L] day 22	Mean	4.35 k	4.56	5.38	4.17
	S.d.	0.87	1.08	2.46	0.95
	N	10	10	10	10
	Median	4.30	4.30	4.90	4.20
	Deviation Vs Control [%]		4.78	23.78	-4.02

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

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Thyroid hormones

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
T4 [nmol/L] day 22	Mean	56.09 k	55.98	49.75	51.07
	S.d.	8.59	5.84	8.55	6.07
	N	10	10	10	10
	Median	54.78	57.54	48.62	51.52
	Deviation Vs Control [%]		-0.21	-11.31	-8.95
TSH [µg/L] day 22	Mean	4.35 k	4.48	4.39	4.59
	S.d.	1.94	1.17	1.04	1.25
	N	10	10	10	10
	Median	3.64	4.37	4.46	4.46
	Deviation Vs Control [%]		2.94	0.78	5.45

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

Study 90R0066/05R034_K

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Thyroid hormones

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
T4 [nmol/L] day 90	Mean	72.40 k	64.16	63.47	60.64
	S.d.	7.43	12.59	10.45	10.77
	N	10	10	10	10
	Median	70.96	62.30	60.28	63.63
	Deviation Vs Control [%]		-11.38	-12.34	-16.24
TSH [µg/L] day 90	Mean	9.61 k	7.08	8.61	6.48
	S.d.	4.58	2.78	3.00	3.02
	N	10	10	10	10
	Median	8.15	7.14	8.92	5.54
	Deviation Vs Control [%]		-26.33	-10.41	-32.62

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

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Thyroid hormones

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
T4 [nmol/L] day 90	Mean	38.39 k	37.84	38.58	39.88
	S.d.	9.46	7.64	6.76	10.59
	N	10	10	10	10
	Median	34.46	36.82	39.58	38.30
	Deviation Vs Control [%]		-1.46	0.49	3.85
TSH [µg/L] day 90	Mean	3.23 k	3.64	3.49	3.93
	S.d.	0.63	0.90	0.33	1.00
	N	10	10	10	10
	Median	3.19	3.59	3.53	3.89
	Deviation Vs Control [%]		12.53	7.86	21.50

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

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T-cell dependent antibody response (SRBC) [U/mL]Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
day 63	Mean	3,738 k	3,727	4,414	3,599
	S.d.	2,918	2,408	1,710	2,808
	N	10	10	10	10
	Median	2,614	3,372	4,418	2,876
	Deviation Vs Control [%]		0	18	-4

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * $p \leq 0.05$, ** $p \leq 0.01$, X = Group excluded from statistics
k=KRUSKALL-WALLIS

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T-cell dependent antibody response (SRBC) [U/mL]

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
day 63	Mean	13,647 k	8,239	9,598	14,555
	S.d.	12,787	5,678	8,936	11,711
	N	10	9	10	10
	Median	6,652	6,552	5,526	9,162
	Deviation Vs Control [%]		-40	-30	7

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

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Ascentos™ 1.3

T-cell dependent antibody response (SRBC) [U/mL]Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 14 / M 4-5 mg/kg bw/d positive control
day 63	Mean	3,738 x	927
	S.d.	2,918	564
	N	10	10
	Median	2,614	785
	Deviation Vs Control [%]		-75

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
x=WILCOX

Study 90R0066/05R034_K

IB 41
16-Oct-2018 08:54
Ascentos™ 1.3**T-cell dependent antibody response (SRBC) [U/mL]**Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 14 / F 4.5 mg/kg bw/d positive control
day 63	Mean	13,647 x	1,546
	S.d.	12,787	889
	N	10	10
	Median	6,652	1,340
	Deviation Vs Control [%]		-89

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
x=WILCOX

Study 90R0066/05R034_K

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18-Jun-2019 07:03
Ascentos™ 1.3

Lymphocyte subpopulations in spleen

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
B_SPL [%] day 90	Mean	39.98 k	40.64	40.88	37.97
	S.d.	4.73	7.11	4.22	3.43
	N	10	10	10	10
	Median	40.20	40.54	39.58	37.28
	Deviation Vs Control [%]		1.64	2.25	-5.04
T_SPL [%] day 90	Mean	43.26 k	45.25	44.21	46.90
	S.d.	5.54	8.12	6.74	7.36
	N	10	10	10	10
	Median	44.19	47.08	44.46	45.48
	Deviation Vs Control [%]		4.60	2.20	8.44
B/T_SPL [---] day 90	Mean	0.95 k	0.96	0.95	0.84
	S.d.	0.24	0.41	0.20	0.20
	N	10	10	10	10
	Median	0.90	0.85	0.92	0.82
	Deviation Vs Control [%]		0.85	-0.22	-12.09
CD4_SPL [%] day 90	Mean	40.93 k	42.60	42.08	43.88
	S.d.	7.95	4.76	6.25	6.69
	N	10	10	10	10
	Median	39.88	44.29	43.14	44.78
	Deviation Vs Control [%]		4.08	2.79	7.19
CD8_SPL [%] day 90	Mean	48.79 k	48.52	48.09	47.20
	S.d.	7.46	5.42	5.89	6.58
	N	10	10	10	10
	Median	49.99	46.66	47.47	47.79
	Deviation Vs Control [%]		-0.54	-1.43	-3.26
CD4/CD8_SPL [---] day 90	Mean	0.89 k	0.90	0.90	0.96
	S.d.	0.36	0.18	0.23	0.25
	N	10	10	10	10
	Median	0.81	0.95	0.90	0.93
	Deviation Vs Control [%]		0.85	1.20	8.19
NK_SPL [%] day 90	Mean	6.12 k	5.46	5.64	6.18
	S.d.	1.85	2.29	1.89	2.04
	N	10	10	10	10
	Median	5.50	4.64	5.49	6.77
	Deviation Vs Control [%]		-10.86	-7.85	0.98

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

Study 90R0066/05R034_K

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Ascentos™ 1.3

Lymphocyte subpopulations in spleen

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
BA_SPL [Mio/g] day 90	Mean	21.4 k	19.6	22.4	17.9
	S.d.	4.6	5.1	5.5	4.9
	N	10	10	10	10
	Median	21.9	18.9	20.4	16.0
	Deviation Vs Control [%]		-8.2	5.0	-16.3
TA_SPL [Mio/g] day 90	Mean	23.5 k	23.3	24.8	21.9
	S.d.	7.2	9.8	8.8	5.4
	N	10	10	10	10
	Median	23.7	22.6	24.2	21.2
	Deviation Vs Control [%]		-0.9	5.4	-7.1
CD4A_SPL [Mio/g] day 90	Mean	9.5 k	9.9	10.5	9.6
	S.d.	3.0	4.5	4.7	2.8
	N	10	10	10	10
	Median	8.7	9.4	9.5	9.3
	Deviation Vs Control [%]		4.8	10.9	1.3
CD8A_SPL [Mio/g] day 90	Mean	11.7 k	11.4	11.9	10.4
	S.d.	4.4	5.1	4.3	2.9
	N	10	10	10	10
	Median	11.8	11.4	11.2	10.2
	Deviation Vs Control [%]		-2.0	2.1	-11.3
NKA_SPL [Mio/g] day 90	Mean	3.3 k	2.8	3.2	3.0
	S.d.	1.2	1.8	1.5	1.5
	N	10	10	10	10
	Median	3.3	2.1	2.5	2.8
	Deviation Vs Control [%]		-16.7	-4.3	-8.8

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
k=KRUSKAL-WALLIS

Study 90R0066/05R034_K

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Ascentos™ 1.3

Lymphocyte subpopulations in spleen

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
B_SPL [%] day 90	Mean	35.77 k	37.00	38.15	36.32
	S.d.	5.01	5.60	6.48	4.21
	N	10	10	10	10
	Median	37.04	38.00	39.07	36.04
	Deviation Vs Control [%]		3.44	6.66	1.53
T_SPL [%] day 90	Mean	54.16 k	51.07	51.82	51.48
	S.d.	6.61	5.67	7.96	4.27
	N	10	10	10	10
	Median	51.62	50.82	50.58	52.26
	Deviation Vs Control [%]		-5.71	-4.34	-4.95
B/T_SPL [---] day 90	Mean	0.68 k	0.74	0.77	0.72
	S.d.	0.15	0.18	0.25	0.14
	N	10	10	10	10
	Median	0.73	0.75	0.78	0.68
	Deviation Vs Control [%]		9.49	13.55	5.69
CD4_SPL [%] day 90	Mean	43.52 k	43.29	43.28	39.26
	S.d.	7.82	7.67	5.47	3.83
	N	10	10	10	10
	Median	44.81	44.51	43.72	39.25
	Deviation Vs Control [%]		-0.54	-0.57	-9.81
CD8_SPL [%] day 90	Mean	48.51 k	48.70	49.56	52.67
	S.d.	9.03	7.46	5.76	4.51
	N	10	10	10	10
	Median	48.04	48.73	48.91	52.43
	Deviation Vs Control [%]		0.40	2.17	8.59
CD4/CD8_SPL [---] day 90	Mean	0.95 k	0.93	0.89	0.76
	S.d.	0.35	0.29	0.19	0.14
	N	10	10	10	10
	Median	0.93	0.92	0.90	0.74
	Deviation Vs Control [%]		-2.83	-6.47	-20.85
NK_SPL [%] day 90	Mean	4.35 k	4.99	5.09	5.73
	S.d.	1.17	1.38	2.06	1.59
	N	10	10	10	10
	Median	4.12	5.02	5.12	5.16
	Deviation Vs Control [%]		14.56	16.90	31.53

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
k=KRUSKALL-WALLIS

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Ascentos™ 1.3

Lymphocyte subpopulations in spleen

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
BA_SPL [Mio/g] day 90	Mean	21.1 k	20.2	21.3	18.3
	S.d.	5.5	5.6	7.7	5.1
	N	10	10	10	10
	Median	22.9	20.9	20.9	17.3
	Deviation Vs Control [%]		-4.1	1.1	-12.9
TA_SPL [Mio/g] day 90	Mean	32.2 k	27.4	28.0	25.6
	S.d.	8.6	5.5	5.6	4.9
	N	10	10	10	10
	Median	33.0	25.7	28.5	25.7
	Deviation Vs Control [%]		-14.7	-12.8	-20.3
CD4A_SPL [Mio/g] day 90	Mean	13.9 k	11.8	12.3	10.1
	S.d.	4.3	2.6	3.2	2.3
	N	10	10	10	10
	Median	13.8	12.4	12.3	9.3
	Deviation Vs Control [%]		-15.5	-12.1	-27.7
CD8A_SPL [Mio/g] day 90	Mean	15.7 k	13.5	13.8	13.5
	S.d.	5.6	3.9	2.6	2.8
	N	10	10	10	10
	Median	16.7	14.1	13.9	13.3
	Deviation Vs Control [%]		-14.3	-12.5	-14.4
NKA_SPL [Mio/g] day 90	Mean	2.5 k	2.7	2.9	2.9
	S.d.	0.6	0.8	1.8	1.0
	N	10	10	10	10
	Median	2.5	2.7	2.3	2.6
	Deviation Vs Control [%]		6.6	14.9	14.0

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p<=0.01, X = Group excluded from statistics
k=KRUSKAL-WALLIS

Study

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Ascentos™ 1.3

Urinalysis

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
PH_C [---] week 12	Mean	6.8 k	6.8	6.8	6.6
	S.d.	0.2	0.3	0.3	0.4
	N	10	10	10	10
	Median	7.0	7.0	6.8	6.5
PRO_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
GLU_C [---] week 12	Mean	0.0 NA	0.0	0.0	0.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	0.0	0.0	0.0	0.0
KET_C [---] week 12	Mean	1.1 x+	1.0	1.0	1.0
	S.d.	0.3	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
UBG_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
BIL_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
BLOOD_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
VOL [ml] week 12	Mean	7.2 k	8.1	8.2	8.0
	S.d.	2.7	2.7	3.0	3.9
	N	10	10	10	10
	Median	7.8	7.8	7.8	7.0
SP.GR._C [g/L] week 12	Mean	1,038 k	1,036	1,041	1,041
	S.d.	14	5	11	13
	N	10	10	10	10
	Median	1,036	1,036	1,038	1,038

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), Wilcoxon test (one-sided+), * p<=0.05, ** p <=0.01, X = Group excluded from statistics

k=KRUSKAL-WALLIS; NA=No Test Applicable; x=WILCOX

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Urinalysis

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
CRYST_C [---] week 12	Mean	2.5 x+	2.7	2.8	2.8
	S.d.	0.5	0.5	0.4	0.4
	N	10	10	10	10
	Median	2.5	3.0	3.0	3.0
RENAL EC_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
TRANS EC_C [---] week 12	Mean	1.0 x+	1.1	1.1	1.0
	S.d.	0.0	0.3	0.3	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
SQUAM EC_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
CASTS_C [---] week 12	Mean	0.0 x+	0.1	0.1	0.0
	S.d.	0.0	0.3	0.3	0.0
	N	10	10	10	10
	Median	0.0	0.0	0.0	0.0
ERY_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
LEUCO_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0

Statistic Profile = Wilcoxon test (one-sided+), Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
x=WILCOX; NA=No Test Applicable

Study

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Urinalysis

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
PH_C [---] week 12	Mean	6.4 k	6.2	6.4	6.4
	S.d.	0.3	0.2	0.2	0.4
	N	10	10	10	10
	Median	6.5	6.0	6.5	6.5
PRO_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
GLU_C [---] week 12	Mean	0.0 NA	0.0	0.0	0.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	0.0	0.0	0.0	0.0
KET_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
UBG_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
BIL_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
BLOOD_C [---] week 12	Mean	1.0 x+	1.1	1.0	1.0
	S.d.	0.0	0.3	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
VOL [ml] week 12	Mean	3.8 v	3.6	5.6	5.8 **
	S.d.	1.1	1.3	2.6	1.4
	N	10	10	10	10
	Median	4.0	3.3	5.3	5.4
SP.GR._C [g/L] week 12	Mean	1,053 v	1,060	1,042	1,037 **
	S.d.	15	21	18	5
	N	10	10	10	10
	Median	1,052	1,056	1,038	1,037

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), Wilcoxon test (one-sided+), * p<=0.05, ** p <=0.01, X = Group excluded from statistics

k=KRUSKALL-WALLIS; NA=No Test Applicable; x=WILCOX; v=KRUSKALL-WALLIS-WILCOX

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Ascentos™ 1.3

Urinalysis

Sex: **Female** - Phase: **In-life**

		G 10 / F 0 mg/kg bw/d	G 11 / F 20 mg/kg bw/d	G 12 / F 60 mg/kg bw/d	G 13 / F 180 mg/kg bw/d
CRYST_C [---] week 12	Mean	2.5 x+	2.2	2.1	2.4
	S.d.	0.5	0.4	0.3	0.5
	N	10	10	10	10
	Median	2.5	2.0	2.0	2.0
RENAL EC_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
TRANS EC_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
SQUAM EC_C [---] week 12	Mean	1.0 NA	1.0	1.0	1.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
CASTS_C [---] week 12	Mean	0.0 NA	0.0	0.0	0.0
	S.d.	0.0	0.0	0.0	0.0
	N	10	10	10	10
	Median	0.0	0.0	0.0	0.0
ERY_C [---] week 12	Mean	1.1 x+	1.0	1.0	1.1
	S.d.	0.3	0.0	0.0	0.3
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0
LEUCO_C [---] week 12	Mean	1.1 x+	1.3	1.1	1.0
	S.d.	0.3	0.7	0.3	0.0
	N	10	10	10	10
	Median	1.0	1.0	1.0	1.0

Statistic Profile = Wilcoxon test (one-sided+), Kruskal-Wallis + Wilcoxon test (two-sided), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
x=WILCOX; NA=No Test Applicable

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Ascentos™ 1.3

Spermanalysis

Sex: **Male** - Phase: **In-life**

		G 10 / M 0 mg/kg bw/d	G 11 / M 20 mg/kg bw/d	G 12 / M 60 mg/kg bw/d	G 13 / M 180 mg/kg bw/d
MOTILE_C [%] day 90	Mean	84 x-	83	84	83
	S.d.	10	8	7	8
	N	20	20	20	20
	Median	86	84	86	86
	Deviation Vs Control [%]		-1	1	-1
TS/gT [Mio/g] day 90	Mean	106 x-	X	X	107
	S.d.	10			15
	N	20	0	0	20
	Median	106			105
	Deviation Vs Control [%]	0			2
TS/gC [Mio/g] day 90	Mean	794 x-	X	X	846
	S.d.	173			226
	N	20	0	0	20
	Median	772			909
	Deviation Vs Control [%]	0			6
ABNORMAL5_C [%; Cut off 5%] day 90	Mean	5.2 x+	X	X	5.6
	S.d.	0.4			1.2
	N	20	0	0	20
	Median	5.0			5.0
	Deviation Vs Control [%]	0.0			7.8

Statistic Profile = Wilcoxon with Bonferroni-Holm (one-sided+), Wilcoxon with Bonferroni-Holm (one-sided-), * p<=0.05, ** p <=0.01, X = Group excluded from statistics
x=WILCOX

BASF

PATHOLOGY REPORT

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90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Feb.2019 HAMA

ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

F0 GENERATION, PARENTAL ANIMALS

Sacrifice			F1			
Sex			M			
Group			00	01	02	03
.....						
Terminal body weight	g	M	521.575	514.408	521.35	507.229
		% dev	100	99	100	97
		SD	53.787	71.895	40.003	53.489
		n	24	24	24	24
.....						
Adrenal glands	mg	M	54.0	55.958	58.75 *	60.625*
		% dev	100	104	109	112
		SD	7.126	8.196	6.648	10.425
		n	24	24	24	24
.....						
Brain	g	M	2.293	2.27	2.238	2.256
		% dev	100	99	98	98
		SD	0.108	0.12	0.113	0.112
		n	24	24	24	24
.....						
Cauda epididymis	g	M	0.548	0.559	0.552	0.537
		% dev	100	102	101	98
		SD	0.051	0.064	0.072	0.067
		n	24	24	24	24
.....						
Epididymides	g	M	1.304	1.328	1.3	1.3
		% dev	100	102	100	100
		SD	0.081	0.099	0.122	0.112
		n	24	24	24	24
.....						
Heart	g	M	1.667	1.708	1.698	1.718
		% dev	100	102	102	103
		SD	0.195	0.196	0.158	0.28
		n	24	24	24	24
.....						
Kidneys	g	M	3.543	3.391	3.673	4.124**
		% dev	100	96	104	116
		SD	0.374	0.408	0.375	0.602
		n	24	24	24	24
.....						

*: P <= 0.05, **: P <= 0.01

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Modified extended one-generation reproduction toxicity study
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ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

F0 GENERATION, PARENTAL ANIMALS

Sacrifice			F1			
Sex			M			
Group			00	01	02	03
.....						
Liver	g	M	12.572	13.298	13.003	12.46
	% dev		100	106	103	99
	SD		1.495	2.571	1.771	1.789
	n		24	24	24	24
.....						
Pituitary gland	mg	M	13.542	13.583	13.875	14.417
	% dev		100	100	102	106
	SD		1.865	2.535	1.752	1.666
	n		24	24	24	24
.....						
Prostate	g	M	1.478	1.423	1.454	1.335
	% dev		100	96	98	90
	SD		0.226	0.237	0.193	0.2
	n		24	24	24	24
.....						
Seminal vesicle	g	M	1.924	1.788	1.847	1.834
	% dev		100	93	96	95
	SD		0.306	0.261	0.204	0.202
	n		24	24	24	24
.....						
Spleen	g	M	0.776	0.814	0.828	0.766
	% dev		100	105	107	99
	SD		0.097	0.113	0.11	0.113
	n		24	24	24	24
.....						
Testes	g	M	3.642	3.739	3.53	3.659
	% dev		100	103	97	100
	SD		0.279	0.25	0.337	0.323
	n		24	24	24	24
.....						
Thymus	mg	M	250.167	283.375	283.292*	233.708
	% dev		100	113	113	93
	SD		56.891	81.089	57.613	50.798
	n		24	24	24	24
.....						

*: P ≤ 0.05, **: P ≤ 0.01

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ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

F0 GENERATION, PARENTAL ANIMALS

Sacrifice			F1			
Sex			M			
Group			00	01	02	03
.....						
Thyroid glands	mg	M	24.833	25.625	24.875	25.625
		% dev	100	103	100	103
		SD	3.83	3.573	6.024	4.985
		n	24	24	24	24
.....						

*: P ≤ 0.05, **: P ≤ 0.01

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ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

F0 GENERATION, PARENTAL ANIMALS

Sacrifice			F1			
Sex			F			
Group			00	01	02	03
.....						
Terminal body weight	g	M	272.125	278.826	275.429	273.408
		% dev	100	102	101	100
		SD	18.498	24.349	15.309	20.197
		n	24	23	24	24
.....						
Adrenal glands	mg	M	80.208	70.391	77.208	71.625
		% dev	100	88	96	89
		SD	63.225	7.011	37.792	9.513
		n	24	23	24	24
.....						
Brain	g	M	2.018	2.03	2.036	2.043
		% dev	100	101	101	101
		SD	0.089	0.114	0.093	0.068
		n	24	23	24	24
.....						
Heart	g	M	1.145	1.178	1.198	1.22
		% dev	100	103	105	107
		SD	0.102	0.111	0.086	0.082
		n	24	23	24	24
.....						
Kidneys	g	M	2.083	2.135	2.137	2.148
		% dev	100	102	103	103
		SD	0.148	0.221	0.18	0.182
		n	24	23	24	24
.....						
Liver	g	M	8.08	8.259	8.348	8.695
		% dev	100	102	103	108
		SD	0.747	0.853	0.882	0.87
		n	24	23	24	24
.....						

*: P ≤ 0.05, **: P ≤ 0.01

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ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

F0 GENERATION, PARENTAL ANIMALS

Sacrifice			F1				
Sex			F				
Group			00	01	02	03	
Ovaries	mg	M	102.667	111.13	106.0	104.042	
		% dev	100	108	103	101	
		SD	16.844	20.06	12.452	13.437	
		n	24	23	24	24	
Pituitary gland	mg	M	14.375	15.13	14.833	14.625	
		% dev	100	105	103	102	
		SD	3.474	2.817	1.834	2.601	
		n	24	23	24	24	
Spleen	g	M	0.536	0.564	0.583	0.531	
		% dev	100	105	109	99	
		SD	0.064	0.09	0.216	0.068	
		n	24	23	24	24	
Thymus	mg	M	239.167	224.391	233.625	218.875	
		% dev	100	94	98	92	
		SD	50.496	67.897	42.564	46.807	
		n	24	23	24	24	
Thyroid glands	mg	M	15.625	18.13	17.125	16.542	
		% dev	100	116	110	106	
		SD	3.809	4.104	3.234	2.949	
		n	24	23	24	24	
Uterus	g	M	0.728	0.709	0.75	0.737	
		% dev	100	97	103	101	
		SD	0.361	0.216	0.195	0.228	
		n	24	23	24	24	

*: P ≤ 0.05, **: P ≤ 0.01

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RELATIVE WEIGHTS - MEAN VALUES (MALE)

F0 GENERATION, PARENTAL ANIMALS

Sacrifice			F1			
Sex			M			
Group			00	01	02	03
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		24	24	24	24
.....						
Adrenal glands	%	M	0.01	0.011	0.011*	0.012**
	% dev		100	106	109	116
	SD		0.001	0.002	0.001	0.002
	n		24	24	24	24
.....						
Brain	%	M	0.443	0.448	0.431	0.449
	% dev		100	101	97	101
	SD		0.041	0.058	0.033	0.044
	n		24	24	24	24
.....						
Cauda epididymis	%	M	0.106	0.111	0.106	0.107
	% dev		100	104	100	101
	SD		0.015	0.02	0.015	0.015
	n		24	24	24	24
.....						
Epididymides	%	M	0.252	0.263	0.25	0.258
	% dev		100	104	99	102
	SD		0.03	0.041	0.025	0.023
	n		24	24	24	24
.....						
Heart	%	M	0.32	0.334	0.327	0.338
	% dev		100	104	102	106
	SD		0.022	0.025	0.03	0.038
	n		24	24	24	24
.....						
Kidneys	%	M	0.68	0.663	0.705	0.817**
	% dev		100	97	104	120
	SD		0.046	0.053	0.062	0.123
	n		24	24	24	24
.....						

*: P <= 0.05, **: P <= 0.01

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RELATIVE WEIGHTS - MEAN VALUES (MALE)

F0 GENERATION, PARENTAL ANIMALS

Sacrifice			F1				
Sex			M				
Group			00	01	02	03	
Liver	%	M	2.413	2.575	2.491	2.455	
	% dev		100	107	103	102	
	SD		0.188	0.236	0.249	0.218	
	n		24	24	24	24	
Pituitary gland	%	M	0.003	0.003	0.003	0.003	
	% dev		100	102	102	110	
	SD		0.0	0.0	0.0	0.0	
	n		24	24	24	24	
Prostate	%	M	0.286	0.281	0.281	0.266	
	% dev		100	98	98	93	
	SD		0.05	0.053	0.045	0.051	
	n		24	24	24	24	
Seminal vesicle	%	M	0.37	0.352	0.355	0.365	
	% dev		100	95	96	99	
	SD		0.055	0.055	0.041	0.055	
	n		24	24	24	24	
Spleen	%	M	0.15	0.159	0.159	0.152	
	% dev		100	106	106	101	
	SD		0.022	0.018	0.019	0.021	
	n		24	24	24	24	
Testes	%	M	0.703	0.739	0.679	0.726	
	% dev		100	105	97	103	
	SD		0.072	0.104	0.066	0.07	
	n		24	24	24	24	
Thymus	%	M	0.048	0.056	0.054*	0.046	
	% dev		100	116	112	96	
	SD		0.012	0.017	0.01	0.01	
	n		24	24	24	24	

*: P ≤ 0.05, **: P ≤ 0.01

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RELATIVE WEIGHTS - MEAN VALUES (MALE)

F0 GENERATION, PARENTAL ANIMALS

Sacrifice			F1			
Sex			M			
Group			00	01	02	03
.....						
Thyroid glands	%	M	0.005	0.005	0.005	0.005
	% dev		100	105	100	106
	SD		0.001	0.001	0.001	0.001
	n		24	24	24	24
.....						

*: P ≤ 0.05, **: P ≤ 0.01

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RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

F0 GENERATION, PARENTAL ANIMALS

Sacrifice			F1			
Sex			F			
Group			00	01	02	03
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		24	23	24	24
.....						
Adrenal glands	%	M	0.029	0.025	0.028	0.026
	% dev		100	86	95	89
	SD		0.023	0.002	0.013	0.003
	n		24	23	24	24
.....						
Brain	%	M	0.745	0.732	0.741	0.751
	% dev		100	98	100	101
	SD		0.057	0.062	0.05	0.06
	n		24	23	24	24
.....						
Heart	%	M	0.422	0.424	0.435	0.448
	% dev		100	101	103	106
	SD		0.038	0.041	0.031	0.044
	n		24	23	24	24
.....						
Kidneys	%	M	0.767	0.768	0.776	0.787
	% dev		100	100	101	103
	SD		0.053	0.071	0.045	0.054
	n		24	23	24	24
.....						
Liver	%	M	2.968	2.964	3.029	3.181**
	% dev		100	100	102	107
	SD		0.161	0.21	0.246	0.229
	n		24	23	24	24
.....						

*: P <= 0.05, **: P <= 0.01

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RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

F0 GENERATION, PARENTAL ANIMALS

Sacrifice			F1				
Sex			F				
Group			00	01	02	03	
Ovaries	%	M	0.038	0.04	0.039	0.038	
	% dev		100	106	102	101	
	SD		0.006	0.007	0.004	0.004	
	n		24	23	24	24	
Pituitary gland	%	M	0.005	0.005	0.005	0.005	
	% dev		100	103	103	102	
	SD		0.001	0.001	0.001	0.001	
	n		24	23	24	24	
Spleen	%	M	0.197	0.204	0.213	0.195	
	% dev		100	103	108	99	
	SD		0.023	0.035	0.084	0.025	
	n		24	23	24	24	
Thymus	%	M	0.088	0.081	0.085	0.08	
	% dev		100	92	96	91	
	SD		0.019	0.024	0.015	0.018	
	n		24	23	24	24	
Thyroid glands	%	M	0.006	0.007	0.006	0.006	
	% dev		100	113	108	105	
	SD		0.002	0.001	0.001	0.001	
	n		24	23	24	24	
Uterus	%	M	0.268	0.255	0.274	0.273	
	% dev		100	95	102	102	
	SD		0.133	0.074	0.075	0.094	
	n		24	23	24	24	

*: P ≤ 0.05, **: P ≤ 0.01

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INCIDENCE OF GROSS LESIONS

F0 GENERATION, PARENTAL ANIMALS

Sacrifice	F1							
Sex	M				F			
Group	00	01	02	03	00	01	02	03
Animals in selected group	24	24	24	24	24	24	24	24
No abnormalities	16	19	20	12	18	17	19	19
Adipose tissue
Focus	1
Adrenal cortex
Focus	1	.
Cecum
Enlarged	.	.	.	3
Diaphragm
Deposition	1	.	.
Eyes with opt. nerve
Cloudiness of cornea	.	.	.	1
Glandular stomach
Focus	1	1	2	2	2	1	.	.
Kidneys
Cyst	1	1
Discoloration	.	.	.	1
Enlarged	.	.	.	6
Pelvic dilation	.	.	1	.	.	.	1	1
Retraction	4	2	1	1	2	3	2	.
Liver
Adhesion	1
Discoloration	.	.	.	1
Enlarged	.	1
Focus	1	2	1	.	.	.	1	.
Granular surface	.	.	.	1
Liver lymph node
Enlarged	1	.	.
Lungs
Adhesion	1	.	.
Deposition	1	.	.
Mediastinal lymph n.
Enlarged	1	.	.

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INCIDENCE OF GROSS LESIONS

F0 GENERATION, PARENTAL ANIMALS

Sacrifice	F1							
Sex	M				F			
Group	00	01	02	03	00	01	02	03
Animals in selected group	24	24	24	24	24	24	24	24
.....
Ovaries
Cyst	1	.	.	.
Pancreatic ln
Enlarged	.	.	.	1
Pericard
Effusion	1	.	.
Renal lymph nodes
Enlarged	1	.	.
Tracheobronch. lnn.
Enlarged	1	.	.

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INCIDENCE OF ALL MICROSCOPIC FINDINGS

F0 GENERATION, PARENTAL ANIMALS

Sacrifice		F1							
Sex		M				F			
Group		00	01	02	03	00	01	02	03
Animals in selected group		24	24	24	24	24	24	24	24
Adipose tissue exam.		1
Necrosis, (multi)focal		1
Adrenal cortex exam.		21	2	.	21	21	3	1	21
Hypertrophy, z. fasc., (m)f		.	.	.	1
Accessory cortical tissue		2	.	.	.	3	1	.	.
Hypertrophy, z.glomerul., mf		2	.	.	.
Degeneration, cystic		1	1
Adrenal medulla exam.		21	2	.	21	21	3	.	21
Axillary lymph nodes exam.		20	.	.	20	20	1	.	20
Sinus histiocytosis		1
Bone marrow exam.		20	.	.	20	20	1	.	20
Brain exam.		20	.	.	20	20	1	.	20
Mineralization, (multi)focal		1
Cecum exam.		20	.	.	22	24	24	24	24
Inflamm. c. infiltr., (m)f		.	.	.	1	.	.	.	1
Parasite(s) in lumen		1	.	.	3	.	.	.	2
Cervical cord exam.		19	.	.	20	20	1	.	20
Cervix exam.		21	3	.	21
Coagulating glands exam.		21	2	.	21
Colon exam.		20	.	.	20	20	1	.	20
Parasite(s) in lumen		6	.	.	4	.	.	.	1
Diaphragm exam.		1	.	.
Inflammation, (multi)focal		1	.	.
Ductus deferens exam.		21	2	.	21
Atrophy, diffuse		1	.	.	2
Dilation		1	.	.	1
Duodenum exam.		20	.	.	20	20	1	.	20
Esophagus exam.		20	.	.	20	20	1	.	20

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INCIDENCE OF ALL MICROSCOPIC FINDINGS

F0 GENERATION, PARENTAL ANIMALS

Sacrifice	F1								
Sex	M				F				
Group	00	01	02	03	00	01	02	03	
Animals in selected group	24	24	24	24	24	24	24	24	
.....									
Eyes with opt. nerve exam.	20	.	.	21	20	1	.	20	
Degeneration, retinal, diff.	.	.	.	1	
Degeneration, retinal, focal	.	.	.	1	
Degeneration, lenticular	.	.	.	1	
Inflammation, diffuse	.	.	.	1	
Rosette, retinal	1	.	.	.	
Forestomach exam.	24	24	24	24	20	2	.	20	
Inflammation, (multi)focal	.	2	3	.	.	1	.	.	
Erosion/ulcer	.	.	1	
Glandular stomach exam.	24	24	24	24	21	2	.	20	
Dilation, glands	2	.	2	4	
Erosion/ulcer	1	1	2	3	1	1	.	.	
Inflammation, (multi)focal	.	.	1	2	1	.	.	1	
Metaplasia, basal cell	1	
Hyperemia, (m)f	.	1	1	
Heart exam.	20	.	.	20	20	1	.	20	
Necrosis/fibrosis	9	.	.	7	3	.	.	1	
(Peri-)vasculitis, (m)f	2	
Inflammation, pericard	1	.	.	
Ileum exam.	20	.	.	20	20	1	.	20	
Jejunum exam.	20	.	.	20	20	1	.	20	
Parasite in lumen	.	.	.	1	
Kidneys exam.	24	24	24	24	20	4	3	21	
Mineralization, medulla, (m)f	.	.	1	21	14	2	1	15	
Mineralization, papilla, mf	1	
Nuclear crowding	.	.	.	22	
Tubules, basophilic, (m)f	17	18	16	19	9	4	2	12	
Cast, tubular	2	2	2	3	2	.	.	3	
Dilation, tubular	.	.	.	13	
Eosinophilic droplets	.	1	
Infiltration, lymphoid, (m)f	5	5	8	1	2	1	3	6	
Cyst(s)	6	2	.	.	1	1	1	1	
Dilation, renal pelvis	.	.	1	1	
Scar(s), cortical	.	2	1	.	1	1	2	.	
Proliferation, interst. cell	1	.	.	.	
Inflammation, mf, pelvic	.	.	1	
Hyperplasia, transit., dif	.	.	1	

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INCIDENCE OF ALL MICROSCOPIC FINDINGS

F0 GENERATION, PARENTAL ANIMALS

Sacrifice	F1								
Sex	M				F				
Group	00	01	02	03	00	01	02	03	
Animals in selected group	24	24	24	24	24	24	24	24	
Left epididymis exam.	21	2	.	21	
Infiltration, lymphoid, (m)f	3	.	.	2	
Left testicle exam.	21	2	.	21	
Multinucleated giant cells	.	.	.	1	
Degeneration, tubular, (m)f	2	.	.	2	
Liver exam.	20	3	1	21	20	1	1	20	
Infiltration, lymphoid, (m)f	20	3	1	20	20	1	1	18	
Necrosis, (multi)focal	.	.	1	1	1	1	1	3	
Focus of cellular alteration	.	.	.	1	3	1	.	1	
- Basophilic diffuse	1	.	.	
- Basophilic tigroid	3	.	.	1	
- Eosinophilic	.	.	.	1	
Fatty change, (multi)focal	1	3	.	1	1	.	.	.	
Fibrosis, capsule	1	
Tension lipidosis	2	4	
Peri-/vasculitis	2	1	.	2	1	.	.	.	
Liver lymph node exam.	1	.	.	
Histiocytosis, (multi)focal	1	.	.	
Hyperplasia, lympho-reticul.	1	.	.	
Lumbar cord exam.	20	.	.	20	20	1	.	20	
Lungs exam.	20	.	.	20	20	1	.	21	
Osseous metaplasia, (m)f	1	.	.	1	
Histiocytosis, alv., (m)f	3	.	.	1	4	.	.	3	
Inflammation, diff., pleura	1	.	.	
Mammary gland exam.	19	.	.	21	20	1	.	20	
Atrophy	.	.	.	1	
Mammary gland fatpad exam.	10	.	.	10	10	.	.	10	
Atrophy	.	.	.	1	
Mediastinal lymph n. exam.	1	.	.	
Inflammation, (multi)focal	1	.	.	
Histiocytosis, (multi)focal	1	.	.	
Mesenteric lymph n. exam.	20	.	.	20	20	1	.	20	
Sinus histiocytosis	.	.	.	1	1	.	.	.	
Ovaries exam.	24	2	.	24	
Cyst(s)	3	.	.	1	

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INCIDENCE OF ALL MICROSCOPIC FINDINGS

F0 GENERATION, PARENTAL ANIMALS

Sacrifice		F1							
Sex		M				F			
Group		00	01	02	03	00	01	02	03
Animals in selected group		24	24	24	24	24	24	24	24
Oviducts	exam.	21	3	.	21
Pancreas	exam.	20	.	.	20	20	.	.	20
Inflammation, (multi)focal		3	.	.	5	3	.	.	4
Pigment storage		.	.	.	1
Degeneration, acinar, (m)f		2
Pancreatic ln	exam.	.	.	.	1
Inflammation, mf, granulom		.	.	.	1
Parathyroid glands	exam.	19	.	.	20	20	1	.	20
Peyers patch	exam.	20	.	.	20	20	1	.	20
Inflammation, (m)f, crypt		1	.	.	2	1	.	.	1
Pituitary gland	exam.	21	2	.	21	21	3	.	21
Cyst(s), pars distalis		1
Cyst(s), pars intermedia		1	.	.	2	2	.	.	.
Craniopharyngeal structures		1	.	.	.
Dilation of Rathke's cleft		2	.	.	1	5	.	.	9
Hyperplasia, p. distalis, mf		.	1	.	2	.	.	.	1
Hypertrophy, p. interm., foc		1	.	.	.
Prostate	exam.	21	2	.	21
Inflammation, chronic		12	1	.	2
Inflammation, purulent		4	1	.	8
Rectum	exam.	20	.	.	20	20	1	.	20
Parasite(s) in lumen		4	.	.	6	.	.	.	3
Renal lymph nodes	exam.	1	.	.
Edema		1	.	.
Sciatic nerve	exam.	20	.	.	20	20	1	.	20
Seminal vesicle	exam.	21	2	.	21
Infiltration, lymphoid, (m)f		.	.	.	1
Skeletal muscle	exam.	20	.	.	20	19	1	.	19
Spleen	exam.	20	.	.	20	20	1	.	20
Hematopoiesis, extramedullar		10	.	.	12	1	1	.	1
Pigment storage		13	.	.	14	14	1	.	13
Thoracic cord	exam.	20	.	.	20	20	1	.	20

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INCIDENCE OF ALL MICROSCOPIC FINDINGS

F0 GENERATION, PARENTAL ANIMALS

Sacrifice		F1							
Sex		M				F			
Group		00	01	02	03	00	01	02	03
Animals in selected group		24	24	24	24	24	24	24	24
Thymus	exam.	20	.	.	20	20	1	.	20
Hyperplasia, tub/cords, (m)f		2	.	.	1	11	.	.	12
Ectopia, parathy. tissue		1
Cyst(s)		.	.	.	1	1	.	.	1
Thyroid glands	exam.	20	.	.	20	20	1	.	20
Infiltration, lymphoid, (m)f		1	.	.	.
Trachea	exam.	20	.	.	20	20	1	.	20
Tracheobronch. lnn.	exam.	1	.	.
Histiocytosis, (multi)focal		1	.	.
Inflammation, granulomatous		1	.	.
Urinary bladder	exam.	20	.	.	20	20	1	.	20
Uterus	exam.	21	3	.	21
Inflammation, (multi)focal		1
Metaplasia, squamous, (m)f		1	.	.	.
Vagina	exam.	21	3	.	21

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INCIDENCE AND GRADING OF MICROSCOPIC FINDINGS IN KIDNEYS
F0 GENERATION, PARENTAL ANIMALS

Sacrifice		F1			
Sex		M			
Group		00	01	02	03
Animals in selected group		24	24	24	24
.....					
Kidneys	exam.	24	24	24	24
Mineralization, medulla, (m) f		.	.	1	21
	. 1.	.	.	1	11
	. 2.	.	.	.	7
	. 3.	.	.	.	1
	. 4.	.	.	.	2
Nuclear crowding		.	.	.	22
	. 1.	.	.	.	11
	. 2.	.	.	.	8
	. 3.	.	.	.	3
Dilation, tubular		.	.	.	13
	. 1.	.	.	.	7
	. 2.	.	.	.	6

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ABSOLUTE WEIGHTS - MEAN VALUES (MALE)
F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice			R1			
Sex			M			
Group			10	11	12	13
.....						
Terminal body weight	g	M	455.095	449.15	452.61	433.11
		% dev	100	99	99	95
		SD	35.552	55.562	23.332	37.971
		n	20	20	20	20
.....						
Adrenal glands	mg	M	65.0	63.2	63.6	70.5
		% dev	100	97	98	108
		SD	7.861	6.971	9.517	8.389
		n	20	20	20	20
.....						
Axillary lymph nodes	mg	M	130.4	118.3	107.7	105.8
		% dev	100	91	83	81
		SD	36.265	30.977	23.636	29.57
		n	10	10	10	10
.....						
Brain	g	M	2.219	2.175	2.199	2.196
		% dev	100	98	99	99
		SD	0.104	0.092	0.114	0.103
		n	20	20	20	20
.....						
Cauda epididymis	g	M	0.493	0.49	0.472	0.482
		% dev	100	99	96	98
		SD	0.051	0.058	0.08	0.053
		n	20	20	20	20
.....						
Epididymides	g	M	1.167	1.159	1.14	1.151
		% dev	100	99	98	99
		SD	0.097	0.093	0.147	0.089
		n	20	20	20	20
.....						
Heart	g	M	1.586	1.535	1.515	1.489
		% dev	100	97	95	94
		SD	0.15	0.162	0.085	0.123
		n	20	20	20	20
.....						
Kidneys	g	M	3.224	3.137	3.335	3.599**
		% dev	100	97	103	112
		SD	0.283	0.326	0.308	0.381
		n	20	20	20	20
.....						
Liver	g	M	13.032	13.349	12.923	11.265**
		% dev	100	102	99	86
		SD	1.819	1.951	1.468	1.221
		n	20	20	20	20
.....						

*: P <= 0.05, **: P <= 0.01
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ABSOLUTE WEIGHTS - MEAN VALUES (MALE)
F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice			R1			
Sex			M			
Group			10	11	12	13
Mesenteric lymph n.	mg	M	298.4	318.7	291.6	322.9
		% dev	100	107	98	108
		SD	118.184	134.468	120.832	103.177
		n	10	10	10	10
Pituitary gland	mg	M	13.0	13.05	13.05	13.3
		% dev	100	100	100	102
		SD	2.0	1.849	2.089	2.003
		n	20	20	20	20
Prostate	g	M	1.163	1.118	1.053*	1.046**
		% dev	100	96	91	90
		SD	0.16	0.147	0.181	0.205
		n	20	20	20	20
Seminal vesicle	g	M	1.353	1.254	1.285	1.258
		% dev	100	93	95	93
		SD	0.205	0.193	0.205	0.186
		n	20	20	20	20
Spleen	g	M	0.876	0.817	0.801*	0.726**
		% dev	100	93	91	83
		SD	0.074	0.103	0.101	0.091
		n	20	20	20	20
Testes	g	M	3.655	3.56	3.69	3.63
		% dev	100	97	101	99
		SD	0.315	0.318	0.325	0.296
		n	20	20	20	20
Thymus	mg	M	435.7	418.45	435.35	350.85 *
		% dev	100	96	100	81
		SD	142.531	66.354	111.511	89.957
		n	20	20	20	20
Thyroid glands	mg	M	24.5	26.15	23.75	23.45
		% dev	100	107	97	96
		SD	4.431	5.669	3.401	4.571
		n	20	20	20	20

*: P <= 0.05, **: P <= 0.01

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ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice			R1			
Sex			F			
Group			10	11	12	13
.....						
Terminal body weight	g	M	242.17	240.59	248.375	251.237
		% dev	100	99	103	104
		SD	25.702	21.075	20.088	14.766
		n	20	20	20	19
.....						
Adrenal glands	mg	M	69.05	69.15	71.5	76.737
		% dev	100	100	104	111
		SD	10.59	10.97	7.578	10.418
		n	20	20	20	19
.....						
Axillary lymph nodes	mg	M	68.4	70.5	71.8	73.6
		% dev	100	103	105	108
		SD	15.248	19.795	25.125	19.884
		n	10	10	10	10
.....						
Brain	g	M	2.041	2.013	2.029	2.012
		% dev	100	99	99	99
		SD	0.078	0.093	0.095	0.065
		n	20	20	20	19
.....						
Heart	g	M	0.975	0.924	0.946	0.99
		% dev	100	95	97	102
		SD	0.119	0.098	0.067	0.081
		n	20	20	20	19
.....						
Kidneys	g	M	1.797	1.791	1.86	1.91
		% dev	100	100	103	106
		SD	0.177	0.183	0.238	0.215
		n	20	20	20	19
.....						
Liver	g	M	6.828	6.725	6.906	7.238
		% dev	100	98	101	106
		SD	0.984	0.769	0.686	0.68
		n	20	20	20	19
.....						
Mesenteric lymph n.	mg	M	236.5	221.1	257.4	244.9
		% dev	100	93	109	104
		SD	82.213	69.772	81.976	82.232
		n	10	10	10	10
.....						
Ovaries	mg	M	82.2	82.9	88.2	86.222
		% dev	100	101	107	105
		SD	12.593	13.242	14.972	14.437
		n	20	20	20	18
.....						

*: P <= 0.05, **: P <= 0.01

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ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice			R1				
Sex			F				
Group			10	11	12	13	
Pituitary gland	mg	M	13.55	13.75	14.25	14.947	
		% dev	100	101	105	110	
		SD	2.704	2.489	1.888	2.592	
		n	20	20	20	19	
Spleen	g	M	0.524	0.494	0.529	0.502	
		% dev	100	94	101	96	
		SD	0.088	0.062	0.091	0.064	
		n	20	20	20	19	
Thymus	mg	M	354.05	356.75	381.8	355.158	
		% dev	100	101	108	100	
		SD	88.538	65.725	113.685	82.955	
		n	20	20	20	19	
Thyroid glands	mg	M	16.7	17.35	15.8	16.526	
		% dev	100	104	95	99	
		SD	2.25	3.2	2.419	1.806	
		n	20	20	20	19	
Uterus	g	M	0.707	0.709	0.716	0.823	
		% dev	100	100	101	116	
		SD	0.26	0.218	0.281	0.251	
		n	20	20	20	19	

*: P ≤ 0.05, **: P ≤ 0.01

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RELATIVE WEIGHTS - MEAN VALUES (MALE)

F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice			R1			
Sex			M			
Group			10	11	12	13
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		20	20	20	20
.....						
Adrenal glands	%	M	0.014	0.014	0.014	0.016**
	% dev		100	98	98	113
	SD		0.002	0.001	0.002	0.001
	n		20	20	20	20
.....						
Axillary lymph nodes	%	M	0.028	0.026	0.024	0.025
	% dev		100	90	85	86
	SD		0.008	0.004	0.005	0.006
	n		10	10	10	10
.....						
Brain	%	M	0.491	0.49	0.486	0.51
	% dev		100	100	99	104
	SD		0.049	0.051	0.025	0.035
	n		20	20	20	20
.....						
Cauda epididymis	%	M	0.109	0.11	0.104	0.111
	% dev		100	101	96	102
	SD		0.014	0.012	0.018	0.01
	n		20	20	20	20
.....						
Epididymides	%	M	0.258	0.26	0.252	0.266
	% dev		100	101	98	103
	SD		0.027	0.027	0.034	0.013
	n		20	20	20	20
.....						
Heart	%	M	0.349	0.343	0.335	0.344
	% dev		100	98	96	99
	SD		0.026	0.028	0.019	0.021
	n		20	20	20	20
.....						
Kidneys	%	M	0.712	0.701	0.737	0.832**
	% dev		100	98	103	117
	SD		0.082	0.039	0.058	0.061
	n		20	20	20	20
.....						
Liver	%	M	2.863	2.973	2.858	2.601**
	% dev		100	104	100	91
	SD		0.314	0.262	0.319	0.156
	n		20	20	20	20
.....						

*: P <= 0.05, **: P <= 0.01

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RELATIVE WEIGHTS - MEAN VALUES (MALE)

F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice			R1				
Sex			M				
Group			10	11	12	13	
Mesenteric lymph n.	%	M	0.065	0.07	0.066	0.075	
	% dev		100	107	101	115	
	SD		0.024	0.026	0.026	0.022	
	n		10	10	10	10	
Pituitary gland	%	M	0.003	0.003	0.003	0.003	
	% dev		100	102	101	107	
	SD		0.0	0.0	0.0	0.0	
	n		20	20	20	20	
Prostate	%	M	0.257	0.252	0.233	0.242	
	% dev		100	98	91	94	
	SD		0.039	0.041	0.041	0.043	
	n		20	20	20	20	
Seminal vesicle	%	M	0.3	0.282	0.284	0.291	
	% dev		100	94	95	97	
	SD		0.056	0.047	0.043	0.039	
	n		20	20	20	20	
Spleen	%	M	0.194	0.182	0.177*	0.168**	
	% dev		100	94	92	87	
	SD		0.023	0.017	0.025	0.018	
	n		20	20	20	20	
Testes	%	M	0.807	0.801	0.818	0.842	
	% dev		100	99	101	104	
	SD		0.095	0.095	0.091	0.076	
	n		20	20	20	20	
Thymus	%	M	0.095	0.094	0.096	0.08	
	% dev		100	98	101	84	
	SD		0.028	0.015	0.022	0.016	
	n		20	20	20	20	
Thyroid glands	%	M	0.005	0.006	0.005	0.005	
	% dev		100	108	97	100	
	SD		0.001	0.001	0.001	0.001	
	n		20	20	20	20	

*: P <= 0.05, **: P <= 0.01

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RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice			R1			
Sex			F			
Group			10	11	12	13
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		20	20	20	19
.....						
Adrenal glands	%	M	0.029	0.029	0.029	0.031
	% dev		100	100	101	106
	SD		0.005	0.003	0.003	0.003
	n		20	20	20	19
.....						
Axillary lymph nodes	%	M	0.028	0.03	0.029	0.029
	% dev		100	107	102	103
	SD		0.007	0.009	0.009	0.008
	n		10	10	10	10
.....						
Brain	%	M	0.851	0.841	0.821	0.803
	% dev		100	99	96	94
	SD		0.088	0.068	0.059	0.052
	n		20	20	20	19
.....						
Heart	%	M	0.403	0.385	0.382	0.394
	% dev		100	95	95	98
	SD		0.033	0.036	0.023	0.026
	n		20	20	20	19
.....						
Kidneys	%	M	0.745	0.745	0.747	0.759
	% dev		100	100	100	102
	SD		0.057	0.05	0.058	0.059
	n		20	20	20	19
.....						
Liver	%	M	2.814	2.794	2.78	2.88
	% dev		100	99	99	102
	SD		0.199	0.176	0.158	0.191
	n		20	20	20	19
.....						
Mesenteric lymph n.	%	M	0.098	0.096	0.105	0.098
	% dev		100	98	107	100
	SD		0.035	0.032	0.032	0.037
	n		10	10	10	10
.....						
Ovaries	%	M	0.034	0.034	0.036	0.034
	% dev		100	101	105	101
	SD		0.005	0.004	0.006	0.006
	n		20	20	20	18
.....						

*: P <= 0.05, **: P <= 0.01

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RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice			R1				
Sex			F				
Group			10	11	12	13	
Pituitary gland	%	M	0.006	0.006	0.006	0.006	
	% dev		100	102	102	106	
	SD		0.001	0.001	0.001	0.001	
	n		20	20	20	19	
Spleen	%	M	0.216	0.206	0.213	0.2	
	% dev		100	95	99	93	
	SD		0.028	0.026	0.035	0.027	
	n		20	20	20	19	
Thymus	%	M	0.146	0.148	0.154	0.142	
	% dev		100	101	105	97	
	SD		0.034	0.024	0.046	0.034	
	n		20	20	20	19	
Thyroid glands	%	M	0.007	0.007	0.006	0.007	
	% dev		100	104	92	95	
	SD		0.001	0.001	0.001	0.001	
	n		20	20	20	19	
Uterus	%	M	0.294	0.299	0.288	0.328	
	% dev		100	101	98	112	
	SD		0.109	0.108	0.108	0.103	
	n		20	20	20	19	

*: P <= 0.05, **: P <= 0.01

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INCIDENCE OF GROSS LESIONS

F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice	R1							
Sex	M				F			
Group	10	11	12	13	10	11	12	13
Animals in selected group	20	20	20	20	20	20	20	20
.....
No abnormalities	16	17	14	16	17	19	17	15
Axillary lymph nodes
Enlarged	.	1
Epididymides
Organ size reduced	.	.	1
Esophagus
Dilation	1
Glandular stomach
Focus	2	.	1	3	3	.	2	3
Kidneys
Cyst	1
Dilation	1
Pelvic dilation	1
Retraction	.	2	1	1	.	1	.	.
Liver
Focus	.	.	3
Torsion	.	.	1
Lungs
Deposition	1	.
Discoloration	1
Mediastinal lymph n.
Enlarged	1	1	.
Spleen
Enlarged	1	.
Testes
Discoloration	.	.	1

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INCIDENCE OF ALL MICROSCOPIC FINDINGS

F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice		R1							
Sex		M				F			
Group		10	11	12	13	10	11	12	13
Animals in selected group		20	20	20	20	20	20	20	20
Adrenal cortex	exam.	20	.	.	20	20	.	.	20
Accessory cortical tissue		1	.	.	.
Inflamm. c. infiltr., (m)f		1	.	.	.
Adrenal medulla	exam.	20	.	.	20	20	.	.	20
Axillary lymph nodes	exam.	20	1	.	20	20	.	.	19
Cyst(s), lymphoid		.	1
Bone marrow	exam.	20	.	.	20	20	.	.	20
Brain	exam.	20	.	.	20	20	.	.	20
Cecum	exam.	20	.	.	20	20	.	.	20
Parasite(s) in lumen		.	.	.	1	3	.	.	1
Cervical cord	exam.	20	.	.	20	20	.	.	20
Cervix	exam.	20	20	20	20
Coagulating glands	exam.	20	.	.	20
Colon	exam.	20	.	.	20	20	.	.	20
Parasite(s) in lumen		.	.	.	2	3	.	.	4
Ductus deferens	exam.	20	.	.	20
Debris		.	.	.	1
Duodenum	exam.	20	.	.	20	20	.	.	20
Esophagus	exam.	20	.	.	20	20	.	.	20
Necrosis/granulation tissue		1
Eyes with opt. nerve	exam.	20	.	.	20	20	.	.	20
Rosette, retinal		2	.	.	1	.	.	.	2
Forestomach	exam.	20	20	20	20	20	.	.	20
Inflammation, (multi)focal		1
Glandular stomach	exam.	20	20	20	20	20	.	2	20
Dilation, glands		1	.	2	1	.	.	.	1
Erosion/ulcer		1	1	1	4	2	.	2	3
Inflammation, (multi)focal		.	.	.	2
Metaplasia, basal cell		1	.	1	1
(Peri-)vasculitis, serosal		.	.	1

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INCIDENCE OF ALL MICROSCOPIC FINDINGS

F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice		R1							
Sex		M				F			
Group		10	11	12	13	10	11	12	13
Animals in selected group		20	20	20	20	20	20	20	20
.....									
Heart	exam.	20	.	.	20	20	.	.	20
Necrosis/fibrosis		4	.	.	3	2	.	.	.
(Peri-)vasculitis, (m)f		.	.	.	1	1	.	.	.
Ileum	exam.	20	.	.	20	20	.	.	20
Jejunum	exam.	20	.	.	20	20	.	.	20
Kidneys	exam.	20	20	20	20	20	1	.	20
Mineralization, medulla, (m)f		.	.	1	7	17	.	.	13
Mineralization, papilla, mf		1	.	.	1	2	.	.	.
Nuclear crowding		1	1	.	6
Tubules, basophilic, (m)f		16	15	16	18	12	.	.	10
Cast, tubular		2	1	1	1
Dilation, tubular		.	.	2	7
Eosinophilic droplets		3	3
Infiltration, lymphoid, (m)f		1	12	10	2	3	.	.	.
Cyst(s)		3	2	1	.	1	.	.	2
Dilation, renal pelvis		1	1
Left epididymis	exam.	20	.	1	20
Infiltration, lymphoid, (m)f		3	.	.	2
Oligospermia		.	.	1
Left testicle	exam.	20	.	1	20
Multinucleated giant cells		.	.	.	1
Degeneration, tubular, (m)f		1	.	.	3
Degeneration, tubular, dif.		.	.	1
Liver	exam.	20	.	4	20	20	.	.	20
Infiltration, lymphoid, (m)f		20	.	1	20	20	.	.	20
Necrosis, (multi)focal		.	.	1	2
Focus of cellular alteration		1
- Eosinophilic		1
Fatty change, (multi)focal		.	.	.	3	.	.	.	1
Fatty change, periportal		.	.	.	1	.	.	.	1
Fibrosis, capsule		.	.	1
Tension lipidosis		2
Peri-/vasculitis		1
Fibrosis, focal		1
Torsion of lobe		.	.	1
Lumbar cord	exam.	20	.	.	20	20	.	.	20

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INCIDENCE OF ALL MICROSCOPIC FINDINGS

F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice		R1							
Sex		M				F			
Group		10	11	12	13	10	11	12	13
Animals in selected group		20	20	20	20	20	20	20	20
Lungs	exam.	20	.	.	20	20	.	1	20
Osseous metaplasia, (m)f		3	.	.	1	.	.	.	2
Histiocytosis, alv., (m)f		1	.	.	2	.	.	.	1
Inflamm. c. infiltr., (m)f		.	.	.	3
Inflammation, diff., pleura		1	.
Fibrosis, (m)f, pleural		2
Inflammation, (multi)focal		1
Mammary gland	exam.	20	18	20	20	20	.	.	20
Atrophy		1	.	2	7
Hyperplasia with atypia, (m)		1
Mammary gland fatpad	exam.	10	10	10	10	10	.	.	10
Atrophy		1	.	2	7
Mediastinal lymph n.	exam.	1	1	.
Inflammation, (multi)focal		1	.
Plasmocytosis		1	1	.
Inflammation, perivascular		1
Mesenteric lymph n.	exam.	20	.	.	20	20	.	.	20
Ovaries	exam.	20	.	.	20
Oviducts	exam.	20	.	.	20
Pancreas	exam.	20	.	.	20	20	.	.	20
Inflammation, (multi)focal		3	.	.	2	1	.	.	1
Atrophy, acinar cell (m)f		3	.	.	3	6	.	.	7
Parathyroid glands	exam.	20	.	.	18	19	.	.	19
Peyers patch	exam.	19	.	.	20	20	.	.	20
Pituitary gland	exam.	20	.	.	20	20	.	.	20
Cyst(s), pars distalis		1	1
Craniopharyngeal structures		1	.	.	.	1	.	.	.
Dilation of Rathke's cleft		4	.	.	4	4	.	.	6
Hyperplasia, p.distalis,mf		1
Vacuolization, pars nervosa		1	.	.	.
Prostate	exam.	20	.	.	20
Inflammation, chronic		8	.	.	4
Atrophy, (multi)focal		3	.	.	3
Cell cluster, luminal		1

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INCIDENCE OF ALL MICROSCOPIC FINDINGS

F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice		R1							
Sex		M				F			
Group		10	11	12	13	10	11	12	13
Animals in selected group		20	20	20	20	20	20	20	20
Rectum	exam.	20	.	.	20	20	.	.	20
Parasite(s) in lumen		3	.	.	.	1	.	.	3
Sciatic nerve	exam.	20	.	.	20	20	.	.	20
Seminal vesicle	exam.	20	.	.	20
Infiltration, lymphoid, (m)f		1
Skeletal muscle	exam.	19	.	.	20	19	.	.	19
Spleen	exam.	20	.	.	20	20	.	1	20
Hematopoiesis, extramedullar		16	.	.	16	11	.	1	15
Pigment storage		5	.	.	7	16	.	1	18
Fibrosis, capsule		1
Thoracic cord	exam.	20	.	.	20	20	.	.	20
Thymus	exam.	20	.	.	20	20	.	.	20
Hyperplasia, tub/cords, (m)f		.	.	.	1	8	.	.	9
Ectopia, parathy. tissue		1
Cyst(s)		.	.	.	2
(Peri-)vasculitis, (m)f		1
Thyroid glands	exam.	20	.	.	20	20	.	.	20
Altered colloid		3	.	.	1
Ectopia, thymic tissue		3	.	.	4	2	.	.	.
Hyperplasia, foll. cell, cyst		1
Hypertrophy/hyperplasia foll		1	.	.	1
Trachea	exam.	20	.	.	20	20	.	.	20
Urinary bladder	exam.	20	.	.	20	20	.	.	20
Uterus	exam.	20	20	20	20
Atrophy, diffuse		1
Metaplasia, squamous, (m)f		1	1	2
Vagina	exam.	20	20	20	20

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INCIDENCE AND GRADING OF MICROSCOPIC FINDINGS

F1 GENERATION, REARING ANIMALS, COHORT 1A

Sacrifice		R1			
Sex		M			
Group		10	11	12	13
Animals in selected group		20	20	20	20
.....					
Kidneys	exam.	20	20	20	20
Mineralization, medulla, (m)f	.	.	.	1	7
	. 1.	.	.	1	2
	. 2.	.	.	.	2
	. 3.	.	.	.	3
Nuclear crowding		1	1	.	6
	. 1.	1	1	.	5
	. 2.	.	.	.	1
Dilation, tubular		.	.	2	7
	. 1.	.	.	2	4
	. 2.	.	.	.	3
Mammary gland	exam.	20	18	20	20
Atrophy		1	.	2	7
	. P.	1	.	2	7
Mammary gland fatpad	exam.	10	10	10	10
Atrophy		1	.	2	7
	. P.	1	.	2	7

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Differential Ovarian Follicle Count (DOFC) – Absolute and Mean Values

F1 rearing animals, cohort 1A

Number of animals	Absolute values			
	Group	Primordial	Growing	Primordial + growing
20	10 (0mg/kg bw/d)	6702	220	6922
20	13 (180mg/kg bw/d)	7972	239	8211

Number of animals	Mean values			
	Group	Primordial	Growing	Primordial + growing
20	10 (0mg/kg bw/d)	335.10	11	346.10
20	13 (180 mg/kg bw/d)	398.60	11.95	410.55

Wilcoxon-Test (one-sided) * = $p \leq 0.05$ ** = $p \leq 0.01$

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ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

F1 GENERATION, REARING ANIMALS, COHORT 1B

Sacrifice			R2			
Sex			M			
Group			10	11	12	13
.....						
Terminal body weight	g	M	536.054	530.863	548.279	510.363
		% dev	100	99	102	95
		SD	46.624	45.523	51.443	51.015
		n	24	24	24	24
.....						
Adrenal glands	mg	M	59.792	62.625	67.708**	64.708
		% dev	100	105	113	108
		SD	7.205	7.569	9.831	9.626
		n	24	24	24	24
.....						
Cauda epididymis	g	M	0.542	0.544	0.535	0.525
		% dev	100	100	99	97
		SD	0.064	0.064	0.061	0.066
		n	24	24	24	24
.....						
Epididymides	g	M	1.324	1.347	1.319	1.308
		% dev	100	102	100	99
		SD	0.098	0.098	0.108	0.097
		n	24	24	24	24
.....						
Kidneys	g	M	3.375	3.43	3.807**	4.252**
		% dev	100	102	113	126
		SD	0.257	0.308	0.402	0.689
		n	24	24	24	24
.....						
Liver	g	M	14.813	15.395	14.677	13.272*
		% dev	100	104	99	90
		SD	2.241	2.123	2.185	1.908
		n	24	24	24	24
.....						
Pituitary gland	mg	M	12.917	13.042	12.958	13.167
		% dev	100	101	100	102
		SD	1.248	1.301	1.398	1.341
		n	24	24	24	24
.....						
Prostate	g	M	1.557	1.489	1.47	1.398
		% dev	100	96	94	90
		SD	0.268	0.267	0.213	0.232
		n	24	24	24	24
.....						
Seminal vesicle	g	M	1.808	1.725	1.813	1.74
		% dev	100	95	100	96
		SD	0.201	0.241	0.272	0.23
		n	24	24	24	24
.....						

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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ABSOLUTE WEIGHTS - MEAN VALUES (MALE)
F1 GENERATION, REARING ANIMALS, COHORT 1B

Sacrifice			R2			
Sex			M			
Group			10	11	12	13
.....						
Testes	g	M	3.853	3.954	3.874	3.857
	% dev		100	103	101	100
	SD		0.317	0.314	0.28	0.304
	n		24	24	24	24
.....						

*: P <= 0.05, **: P <= 0.01
Kruskal-Wallis H and Wilcoxon test, two sided

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ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

F1 GENERATION, REARING ANIMALS, COHORT 1B

Sacrifice			R2			
Sex			F			
Group			10	11	12	13
.....						
Terminal body weight	g	M	291.842	284.588	304.817*	308.2
		% dev	100	98	104	106
		SD	24.228	20.968	15.011	30.56
		n	24	24	23	24
.....						
Adrenal glands	mg	M	76.708	72.292	77.435	80.083
		% dev	100	94	101	104
		SD	6.944	8.243	8.333	13.539
		n	24	24	23	24
.....						
Kidneys	g	M	2.158	2.115	2.212	2.31 *
		% dev	100	98	103	107
		SD	0.195	0.12	0.125	0.235
		n	24	24	23	24
.....						
Liver	g	M	9.455	9.326	9.5	9.716
		% dev	100	99	100	103
		SD	1.08	0.955	1.04	1.289
		n	24	24	23	24
.....						
Ovaries	mg	M	109.542	109.5	113.217	106.833
		% dev	100	100	103	98
		SD	14.289	13.587	13.501	12.651
		n	24	24	23	24
.....						
Pituitary gland	mg	M	15.542	15.25	15.714	15.542
		% dev	100	98	101	100
		SD	1.587	1.824	1.821	1.587
		n	24	24	21	24
.....						
Uterus	g	M	0.747	0.669	1.666	0.778
		% dev	100	90	223	104
		SD	0.284	0.25	4.707	0.29
		n	24	24	23	24
.....						

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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RELATIVE WEIGHTS - MEAN VALUES (MALE)

F1 GENERATION, REARING ANIMALS, COHORT 1B

Sacrifice			R2			
Sex			M			
Group			10	11	12	13
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		24	24	24	24
.....						
Adrenal glands	%	M	0.011	0.012	0.012*	0.013**
	% dev		100	105	111	113
	SD		0.002	0.001	0.002	0.002
	n		24	24	24	24
.....						
Cauda epididymis	%	M	0.102	0.103	0.098	0.104
	% dev		100	102	96	102
	SD		0.012	0.015	0.012	0.014
	n		24	24	24	24
.....						
Epididymides	%	M	0.248	0.255	0.242	0.258
	% dev		100	103	98	104
	SD		0.022	0.027	0.023	0.028
	n		24	24	24	24
.....						
Kidneys	%	M	0.632	0.649	0.696**	0.832**
	% dev		100	103	110	132
	SD		0.044	0.059	0.055	0.102
	n		24	24	24	24
.....						
Liver	%	M	2.758	2.902	2.669	2.6 *
	% dev		100	105	97	94
	SD		0.302	0.33	0.243	0.246
	n		24	24	24	24
.....						
Pituitary gland	%	M	0.002	0.002	0.002	0.003
	% dev		100	102	98	107
	SD		0.0	0.0	0.0	0.0
	n		24	24	24	24
.....						
Prostate	%	M	0.293	0.283	0.269	0.274
	% dev		100	97	92	94
	SD		0.056	0.057	0.035	0.04
	n		24	24	24	24
.....						
Seminal vesicle	%	M	0.34	0.327	0.332	0.342
	% dev		100	96	98	100
	SD		0.052	0.052	0.052	0.04
	n		24	24	24	24
.....						

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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RELATIVE WEIGHTS - MEAN VALUES (MALE)
F1 GENERATION, REARING ANIMALS, COHORT 1B

Sacrifice			R2			
Sex			M			
Group			10	11	12	13
.....						
Testes	%	M	0.723	0.75	0.712	0.764
		% dev	100	104	98	106
		SD	0.076	0.087	0.074	0.11
		n	24	24	24	24
.....						

*: P <= 0.05, **: P <= 0.01
Kruskal-Wallis H and Wilcoxon test, two sided

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RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

F1 GENERATION, REARING ANIMALS, COHORT 1B

Sacrifice			R2			
Sex			F			
Group			10	11	12	13
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		24	24	23	24
.....						
Adrenal glands	%	M	0.026	0.026	0.025	0.026
	% dev		100	97	97	99
	SD		0.003	0.003	0.003	0.005
	n		24	24	23	24
.....						
Kidneys	%	M	0.741	0.746	0.726	0.752
	% dev		100	101	98	102
	SD		0.055	0.054	0.032	0.07
	n		24	24	23	24
.....						
Liver	%	M	3.237	3.28	3.119	3.175
	% dev		100	101	96	98
	SD		0.212	0.279	0.33	0.488
	n		24	24	23	24
.....						
Ovaries	%	M	0.038	0.039	0.037	0.035
	% dev		100	102	99	93
	SD		0.005	0.005	0.005	0.005
	n		24	24	23	24
.....						
Pituitary gland	%	M	0.005	0.005	0.005	0.005
	% dev		100	101	97	95
	SD		0.001	0.001	0.0	0.001
	n		24	24	21	24
.....						
Uterus	%	M	0.255	0.235	0.538	0.255
	% dev		100	92	211	100
	SD		0.09	0.086	1.495	0.099
	n		24	24	23	24
.....						

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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INCIDENCE OF GROSS LESIONS

F1 GENERATION, REARING ANIMALS, COHORT 1B

Sacrifice	R2							
Sex	M				F			
Group	10	11	12	13	10	11	12	13
Animals in selected group	24	24	24	24	24	24	24	24
.....								
No abnormalities	22	20	17	11	21	15	15	19
General Observations
Cannibalism	1	.
Infertile animal	.	.	1	1
Not pregnant	1	1
Cecum
Organ not detectable/missing	1	.
Epididymides
Organ size reduced	.	.	1
Glandular stomach
Focus	.	.	1	.	2	7	6	2
Kidneys
Cyst	.	.	1	1
Enlarged	.	.	1	10
Pelvic dilation	1	1
Retraction	2	1	1	1	1	2	.	1
Liver
Focal constriction	1
Focus	.	1	1
Mediastinal lymph n.
Discoloration	1	.	.
Enlarged	1	.	.
Ovaries
Cyst	1	.
Pericard
Adhesion	1	.
Focus	1	.
Renal lymph nodes
Enlarged	.	1
Testes
Organ size reduced	.	.	1

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PATHOLOGY REPORT

IC 41/58

90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Feb.2019 HAMA

INCIDENCE OF ALL MICROSCOPIC FINDINGS

F1 GENERATION, REARING ANIMALS, COHORT 1B

Sacrifice		R2							
Sex		M				F			
Group		10	11	12	13	10	11	12	13
Animals in selected group		24	24	24	24	24	24	24	24
.....									
Adrenal cortex	exam.	.	.	1	1	.	.	1	1
Adrenal medulla	exam.	.	.	1	1	.	.	1	1
Cervix	exam.	24	24	24	24
Dilation		1	.
Coagulating glands	exam.	.	.	1	1
Mammary gland	exam.	24	24	24	24	.	.	1	1
Atrophy		1	1	1	1
Mammary gland fatpad	exam.	10	10	10	10
Ovaries	exam.	1	1
Oviducts	exam.	1	1
Pituitary gland	exam.	.	.	1	1	.	.	1	1
Cyst(s), pars distalis		.	.	1
Prostate	exam.	.	.	1	1
Inflammation, purulent		.	.	.	1
Seminal vesicle	exam.	.	.	1	1
Uterus	exam.	24	24	24	24
Dilation of horn(s)		1	.
Vagina	exam.	24	24	24	24

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PATHOLOGY REPORT

IC 42/58

90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Feb.2019 HAMA

INCIDENCE AND GRADING OF MICROSCOPIC FINDINGS

F1 GENERATION, REARING ANIMALS, COHORT 1B

Sacrifice		R2			
Sex		M			
Group		10	11	12	13
Animals in selected group		24	24	24	24
.....					
Mammary gland	exam.	24	24	24	24
Atrophy		1	1	1	1
	. P.	1	1	1	1
.....					
Mammary gland fatpad	exam.	10	10	10	10

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Modified extended one-generation reproduction toxicity study
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05.Feb.2019 HAMA

ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

F1 GENERATION, REARING ANIMALS, COHORT 3 (IMMUNOTOXICITY)

COMPARISON OF TEST GROUP 10 TO TEST GROUPS 11, 12, and 13

Sacrifice			R3			
Sex			M			
Group			10	11	12	13
.....						
Terminal body weight	g	M	332.29	345.04	345.59	349.43
		% dev	100	104	104	105
		SD	24.495	32.796	18.704	23.982
		n	10	10	10	10
.....						
Spleen	g	M	0.717	0.705	0.668	0.677
		% dev	100	98	93	94
		SD	0.095	0.107	0.073	0.095
		n	10	10	10	10
.....						
Thymus	mg	M	620.4	602.6	645.7	530.1
		% dev	100	97	104	85
		SD	120.156	101.941	87.407	76.275
		n	10	10	10	10
.....						

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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PATHOLOGY REPORT

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90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

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ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

F1 GENERATION, REARING ANIMALS, COHORT 3 (IMMUNOTOXICITY)

COMPARISON OF TEST GROUP 10 TO TEST GROUPS 11, 12 and 13

Sacrifice			R3			
Sex			F			
Group			10	11	12	13
.....						
Terminal body weight	g	M	198.92	200.711	198.8	211.29
		% dev	100	101	100	106
		SD	21.915	12.199	22.892	15.813
		n	10	9	10	10
.....						
Spleen	g	M	0.465	0.479	0.416	0.478
		% dev	100	103	89	103
		SD	0.084	0.058	0.05	0.06
		n	10	9	10	10
.....						
Thymus	mg	M	478.1	467.222	488.1	486.6
		% dev	100	98	102	102
		SD	120.298	137.673	70.749	50.661
		n	10	9	10	10
.....						

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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PATHOLOGY REPORT

IC 45/58

90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Feb.2019 HAMA

RELATIVE WEIGHTS - MEAN VALUES (MALE)

F1 GENERATION, REARING ANIMALS, COHORT 3 (IMMUNOTOXICITY)

COMPARISON OF TEST GROUP 10 TO TEST GROUPS 11, 12 AND 13

Sacrifice			R3			
Sex			M			
Group			10	11	12	13
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		10	10	10	10
					
Spleen	%	M	0.217	0.205	0.193	0.193
	% dev		100	94	89	89
	SD		0.032	0.028	0.018	0.019
	n		10	10	10	10
.....						
Thymus	%	M	0.187	0.176	0.187	0.152*
	% dev		100	94	100	81
	SD		0.037	0.032	0.023	0.021
	n		10	10	10	10
.....						

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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PATHOLOGY REPORT

IC 46/58

90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Feb.2019 HAMA

RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

F1 REARING ANIMALS, COHORT 3 (IMMUNOTOXICITY)

COMPARISON OF TEST GROUP 10 TO TEST GROUPS 11, 12, AND 13

Sacrifice			R3			
Sex			F			
Group			10	11	12	13
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		10	9	10	10
.....						
Spleen	%	M	0.233	0.239	0.211	0.227
	% dev		100	102	91	97
	SD		0.026	0.026	0.029	0.033
	n		10	9	10	10
.....						
Thymus	%	M	0.239	0.231	0.247	0.231
	% dev		100	97	103	97
	SD		0.041	0.06	0.037	0.024
	n		10	9	10	10
.....						

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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PATHOLOGY REPORT

IC 47/58

90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Feb.2019 HAMA

ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

F1 GENERATION, REARING ANIMALS, COHORT 3 (IMMUNOTOXICITY)

COMPARISON OF TEST GROUP 10 TO TEST GROUP 14

Sacrifice			R3	
Sex			M	
Group			10	14
.....				
Terminal body weight	g	M	332.29	323.71
		% dev	100	97
		SD	24.495	25.292
		n	10	10
.....				
Spleen	g	M	0.717	0.467**
		% dev	100	65
		SD	0.095	0.063
		n	10	10
.....				
Thymus	mg	M	620.4	529.6
		% dev	100	85
		SD	120.156	139.137
		n	10	10
.....				

*: P <= 0.05, **: P <= 0.01

Wilcoxon test, two sided

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PATHOLOGY REPORT

IC 48/58

90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Feb.2019 HAMA

ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

F1 GENERATION, REARING ANIMALS, COHORT 3 (IMMUNOTOXICITY)

COMPARISON OF TEST GROUP 10 TO TEST GROUP 14

Sacrifice			R3	
Sex			F	
Group			10	14
.....				
Terminal body weight	g	M	198.92	197.48
		% dev	100	99
		SD	21.915	17.376
		n	10	10
.....				
Spleen	g	M	0.465	0.324**
		% dev	100	70
		SD	0.084	0.079
		n	10	10
.....				
Thymus	mg	M	478.1	399.8
		% dev	100	84
		SD	120.298	81.543
		n	10	10
.....				

*: P ≤ 0.05, **: P ≤ 0.01

Wilcoxon test, two sided

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PATHOLOGY REPORT

IC 49/58

90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

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RELATIVE WEIGHTS - MEAN VALUES (MALE)

F1 GENERATION, REARING ANIMALS, COHORT 3 (IMMUNOTOXICITY)

COMPARISON OF TEST GROUP 10 TO TEST GROUP 14

Sacrifice			R3	
Sex			M	
Group			10	14
.....				
Terminal body weight	%	M	100.0	100.0
	% dev		100	100
	n		10	10
			
Spleen	%	M	0.217	0.144**
	% dev		100	67
	SD		0.032	0.018
	n		10	10
.....				
Thymus	%	M	0.187	0.166
	% dev		100	88
	SD		0.037	0.053
	n		10	10
.....				

*: P <= 0.05, **: P <= 0.01

Wilcoxon test, two sided

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PATHOLOGY REPORT

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Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Feb.2019 HAMA

RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

F1 GENERATION, REARING ANIMALS, COHORT 3 (IMMUNOTOXICITY)

COMPARISON OF TEST GROUP 10 TO TEST GROUP 14

Sacrifice			R3	
Sex			F	
Group			10	14
.....				
Terminal body weight	%	M	100.0	100.0
	%	dev	100	100
		n	10	10
			
Spleen	%	M	0.233	0.164**
	%	dev	100	70
		SD	0.026	0.034
		n	10	10
.....				
Thymus	%	M	0.239	0.204
	%	dev	100	85
		SD	0.041	0.047
		n	10	10
.....				

*: P <= 0.05, **: P <= 0.01

Wilcoxon test, two sided

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PATHOLOGY REPORT

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90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Feb.2019 HAMA

INCIDENCE OF GROSS LESIONS

F1 GENERATION, REARING ANIMALS, COHORT 3 (IMMUNOTOXICITY)

COMPARISON OF TEST GROUP 10 TO TEST GROUPS 11, 12 AND 13

Sacrifice	R3							
Sex	M				F			
Group	10	11	12	13	10	11	12	13
Animals in selected group	10	10	10	10	10	10	10	10
.....
No abnormalities	9	9	9	10	10	10	9	8
Glandular stomach
Focus	1	1	1	.	.	.	1	2

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PATHOLOGY REPORT

IC 52/58

90R0066/05R034

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INCIDENCE OF GROSS LESIONS

F1 GENERATION, REARING ANIMALS, COHORT3 (IMMUNOTOXICITY)

COMPARISON OF TEST GROUP 10 TO TEST GROUP 14

Sacrifice	R3			
Sex	M		F	
Group	10	14	10	14
Animals in selected group	10	10	10	10
.....				
No abnormalities	9	8	10	10
Glandular stomach
Focus	1	1	.	.

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ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

F1 GENERATION, PUPS PND 22, NOT SELECTED FOR COHORTS

Sacrifice			R4			
Sex			M			
Group			10	11	12	13
.....						
Terminal body weight	g	M	56.91	58.94	62.79	61.83
		% dev	100	104	110	109
		SD	5.805	5.305	4.752	3.062
		n	10	10	10	10
.....						
Brain	g	M	1.554	1.567	1.628**	1.596
		% dev	100	101	105	103
		SD	0.045	0.072	0.057	0.057
		n	9	10	10	10
.....						
Spleen	g	M	0.238	0.293	0.284	0.285
		% dev	100	123	119	120
		SD	0.044	0.051	0.036	0.058
		n	10	10	10	10
.....						
Thymus	mg	M	228.6	284.2 **	267.2 *	247.8
		% dev	100	124	117	108
		SD	36.761	35.045	31.233	35.593
		n	10	10	10	10
.....						

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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PATHOLOGY REPORT

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90R0066/05R034

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in Sprague-Dawley Rats, Oral Administration (gavage)

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ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

F1 GENERATION, PUPS PND 22, NOT SECTED FOR COHORTS

Sacrifice			R4			
Sex			F			
Group			10	11	12	13
.....						
Terminal body weight	g	M	56.35	60.05	60.32	57.09
		% dev	100	107	107	101
		SD	3.437	5.382	3.439	5.221
		n	10	10	10	10
.....						
Brain	g	M	1.543	1.564	1.512	1.522
		% dev	100	101	98	99
		SD	0.048	0.053	0.043	0.071
		n	10	10	10	10
.....						
Spleen	g	M	0.242	0.267	0.276	0.266
		% dev	100	110	114	110
		SD	0.029	0.042	0.042	0.053
		n	10	10	10	10
.....						
Thymus	mg	M	260.7	265.1	273.5	258.5
		% dev	100	102	105	99
		SD	32.452	45.752	34.744	34.645
		n	10	10	10	10
.....						

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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PATHOLOGY REPORT

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90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Feb.2019 HAMA

RELATIVE WEIGHTS - MEAN VALUES (MALE)

F1 GENERATION, PUPS PND 22, NOT SELECTED FOR COHORTS

Sacrifice			R4			
Sex			M			
Group			10	11	12	13
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		10	10	10	10
.....						
Brain	%	M	2.742	2.672	2.606	2.585
	% dev		100	97	95	94
	SD		0.249	0.19	0.212	0.124
	n		9	10	10	10
.....						
Spleen	%	M	0.416	0.495**	0.453	0.462
	% dev		100	119	109	111
	SD		0.04	0.064	0.058	0.096
	n		10	10	10	10
.....						
Thymus	%	M	0.402	0.483**	0.425	0.401
	% dev		100	120	106	100
	SD		0.055	0.052	0.028	0.058
	n		10	10	10	10
.....						

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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PATHOLOGY REPORT

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90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Feb.2019 HAMA

RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

F1 GENERATION, PUPS PND 22, NOT SELECTED FOR COHORTS

Sacrifice			R4			
Sex			F			
Group			10	11	12	13
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		10	10	10	10
.....						
Brain	%	M	2.747	2.617	2.513**	2.677
	% dev		100	95	91	97
	SD		0.178	0.17	0.138	0.144
	n		10	10	10	10
.....						
Spleen	%	M	0.429	0.447	0.457	0.465
	% dev		100	104	107	108
	SD		0.044	0.074	0.064	0.073
	n		10	10	10	10
.....						
Thymus	%	M	0.465	0.44	0.453	0.454
	% dev		100	95	98	98
	SD		0.069	0.055	0.053	0.054
	n		10	10	10	10
.....						

*: P <= 0.05, **: P <= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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PATHOLOGY REPORT

IC 57/58

90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Feb.2019 HAMA

INCIDENCE OF GROSS LESIONS

F1 GENERATION, PUPS PND 22, NOT SELECTED FOR COHORTS

Sacrifice	R4							
Sex	M				F			
Group	10	11	12	13	10	11	12	13
Animals in selected group	10	10	10	10	10	10	10	10
.....								
No abnormalities	10	10	10	9	10	10	10	10
Liver lymph node	:	:	:	:	:	:	:	:
Enlarged	:	:	:	1	:	:	:	:

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BASF	PATHOLOGY REPORT	IC 58/58
		90R0066/05R034
Modified extended one-generation reproduction toxicity study in Sprague-Dawley Rats, Oral Administration (gavage)		05.Feb.2019 HAMA

INCIDENCE OF ALL MICROSCOPIC FINDINGS
F1 GENERATION, PUPS PND22, NOT SELECTED FOR COHORTS

Sacrifice		R4							
Sex		M				F			
Group		10	11	12	13	10	11	12	13
Animals in selected group		10	10	10	10	10	10	10	10
.....									
Mammary gland	exam.	6	.	.	5	8	.	.	7
.....									
Mammary gland fatpad	exam.	10	.	.	10	10	.	.	10

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90R0066/05R034
Modified extended one-generation reproduction toxicity study 05.Mar.2019 SIGR
in Sprague-Dawley Rats, Oral Administration (gavage)

ABSOLUTE BRAIN WEIGHTS - MEAN VALUES (MALE)
F1 GENERATION, REARING ANIMALS, COHORT 2A (ADULTS)

Sacrifice			I1					
Sex			M					
Group			10	11	12	13		
Terminal body weight			g	M	394.72	394.66	408.31	402.59
			%	dev	100	100	103	102
				SD	42.07	25.739	24.1	14.674
				n	10	10	10	10
Brain			g	M	2.262	2.166	2.223	2.242
			%	dev	100	96	98	99
				SD	0.12	0.074	0.092	0.117
				n	10	10	10	10

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90R0066/05R034
Modified extended one-generation reproduction toxicity study 05.Mar.2019 SIGR
in Sprague-Dawley Rats, Oral Administration (gavage)

ABSOLUTE BRAIN WEIGHTS - MEAN VALUES (FEMALE)
F1 GENERATION, REARING ANIMALS, COHORT 2A (ADULTS)

Sacrifice				I1			
Sex				F			
Group				10	11	12	13
.....							
Terminal body weight	g	M	236.19	227.32	233.66	248.19	
	% dev		100	96	99	105	
	SD		21.896	25.011	11.367	25.302	
	n		10	10	10	10	
.....							
Brain	g	M	2.047	2.02	2.033	2.077	
	% dev		100	99	99	101	
	SD		0.119	0.073	0.058	0.084	
	n		10	10	10	10	
.....							

*: P <= 0.05, **: P <= 0.01
Kruskal-Wallis H and Wilcoxon test, two sided

BASF NEUROPATHOLOGY REPORT ID 3/16
90R0066/05R034
Modified extended one-generation reproduction toxicity study 05.Mar.2019 SIGR
in Sprague-Dawley Rats, Oral Administration (gavage)

RELATIVE BRAIN WEIGHTS - MEAN VALUES (MALE)
F1 GENERATION, REARING ANIMALS, COHORT 2A (ADULTS)

Sacrifice			I1			
Sex			M			
Group			10	11	12	13
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		10	10	10	10
.....						
Brain	%	M	0.579	0.55	0.546	0.557
	% dev		100	95	94	96
	SD		0.072	0.022	0.031	0.025
	n		10	10	10	10
.....						

*: P <= 0.05, **: P <= 0.01
Kruskal-Wallis H and Wilcoxon test, two sided

BASF NEUROPATHOLOGY REPORT ID 4/16
90R0066/05R034
Modified extended one-generation reproduction toxicity study 05.Mar.2019 SIGR
in Sprague-Dawley Rats, Oral Administration (gavage)

RELATIVE BRAIN WEIGHTS - MEAN VALUES (FEMALES)
F1 GENERATION, REARING ANIMALS, COHORT 2A (ADULTS)

Sacrifice			I1			
Sex			F			
Group			10	11	12	13
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		10	10	10	10
.....						
Brain	%	M	0.871	0.897	0.872	0.842
	% dev		100	103	100	97
	SD		0.064	0.086	0.044	0.067
	n		10	10	10	10
.....						

*: P <= 0.05, **: P <= 0.01
Kruskal-Wallis H and Wilcoxon test, two sided

NEUROPATHOLOGY REPORT

ID 5/16

90R0066/05R034

Length and width of brain (mean values)

F1 Generation, rearing animals, Cohort 2A (adults)

Male (adults):

Group	Brain			
	Length (cm)	%	Width (cm)	%
10	2.20	100	1.62	100
11	2.17	99	1.61	100
12	2.21	100	1.63	100
13	2.22	101	1.60	99

Female (adults):

Group	Brain			
	Length (cm)	%	Width (cm)	%
10	2.12	100	1.58	100
11	2.12	100	1.58	100
12	2.13	100	1.57	100
13	2.13	100	1.59	101

* $p \leq 0,05$ Wilcoxon + Bonferroni-Holm adjustment (two-sided)** $p \leq 0,01$

BASF	NEUROPATHOLOGY REPORT	ID 6/16
		90R0066/05R034
Modified extended one-generation reproduction toxicity study in Sprague-Dawley Rats, Oral Administration (gavage)		05.Mar.2019 SIGR

INCIDENCE OF GROSS LESIONS
F1 GENERATION, REARING ANIMALS, COHORT 2A (ADULTS)

Sacrifice	I1							
Sex	M				F			
Group	10	11	12	13	10	11	12	13
Animals in selected group	10	10	10	10	10	10	10	10
.....								
No abnormalities	10	10	10	9	10	10	10	10
Skin	:	:	:	:	:	:	:	:
Focus	:	:	:	1	:	:	:	:

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NEUROPATHOLOGY REPORT

ID 7/16

90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Mar.2019 SGR

INCIDENCE OF ALL MICROSCOPIC FINDINGS

F1 GENERATION, REARING ANIMALS, COHORT 2A (ADULTS)

Sacrifice		I1							
Sex		M				F			
Group		10	11	12	13	10	11	12	13
Animals in selected group		10	10	10	10	10	10	10	10
Cerebellum	exam.	10	.	.	10	10	.	.	10
Cervical cord	exam.	10	.	.	10	10	.	.	10
Cervical ganglia	exam.	10	.	.	10	10	.	.	10
Distal tibial nerve	exam.	10	.	.	10	10	.	.	10
Degeneration, (multi)focal		2	1
Dorsal root, cerv.	exam.	10	.	.	10	10	.	.	10
Dorsal root, lumb.	exam.	10	.	.	10	10	.	.	10
Eyes with opt. nerve	exam.	10	.	.	10	10	.	.	10
Frontal lobe	exam.	10	.	.	10	10	.	.	10
Lumbar cord	exam.	10	.	.	10	10	.	.	10
Degeneration, axonal		1
Lumbar ganglia	exam.	10	.	.	10	10	.	.	10
M. gastrocnemius	exam.	10	.	.	10	10	.	.	10
Medulla oblongata	exam.	10	.	.	10	10	.	.	10
Midbrain	exam.	10	.	.	10	10	.	.	10
Nasal cavity, III	exam.	10	.	.	10	10	.	.	10
Olfactory bulb	exam.	10	.	.	10	10	.	.	10
Parietal lobe	exam.	10	.	.	10	10	.	.	10
Pituitary gland	exam.	10	.	.	10	10	.	.	10
Pons	exam.	10	.	.	10	10	.	.	10
Prox. sciatic nerve	exam.	10	.	.	10	10	.	.	10
Degeneration, (multi)focal		.	.	.	1	.	.	.	1
Prox.tibial nerve	exam.	10	.	.	10	10	.	.	10
Skin	exam.	.	.	.	1

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ID 8/16

90R0066/05R034

Modified extended one-generation reproduction toxicity study
in Sprague-Dawley Rats, Oral Administration (gavage)

05.Mar.2019 SIGR

INCIDENCE OF ALL MICROSCOPIC FINDINGS

F1 GENERATION, REARING ANIMALS, COHORT 2A (ADULTS)

Sacrifice		I1							
Sex		M				F			
Group		10	11	12	13	10	11	12	13
Animals in selected group		10	10	10	10	10	10	10	10
.....									
Thoracic cord	exam.	10	.	.	10	10	.	.	10
Degeneration, axonal		6	.	.	4	3	.	.	2
Trigeminal ganglia	exam.	10	.	.	10	10	.	.	10
Ventral root, cerv.	exam.	10	.	.	10	10	.	.	10
Ventral root, lumb.	exam.	10	.	.	10	10	.	.	10

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Morphometry - Measurements of brain sections (mean values)
F1 Generation, rearing animals, Cohort 2A (adults)

Male:

Group	Measurement (mm)																			
	1	%	2	%	3	%	4	%	5	%	6	%	7	%	8	%	9	%	10	%
10	1.97	100	1.96	100	4.28	100	4.26	100	2.00	100	2.03	100	0.88	100	1.45	100	1.49	100	0.99	100
13	1.89	96	1.85	94	3.84	**	90	3.93	92	1.96	98	1.99	98	0.73	*	83	1.59	110	1.59	107

Female:

Group	Measurement (mm)																			
	1	%	2	%	3	%	4	%	5	%	6	%	7	%	8	%	9	%	10	%
10	1.85	100	1.84	100	3.90	100	4.04	100	1.85	100	1.91	100	0.79	100	1.52	100	1.55	100	0.98	100
13	1.88	102	1.86	101	4.25	**	109	4.21	104	1.88	102	1.95	102	0.69	87	1.47	97	1.48	95	0.99

1 Frontal cortex left
4 Nucleus caudatus width right
7 Corpus callosum width
10 Base of lobus vermis cerebelli No 8

2 Frontal cortex right
5 Parietal cortex left
8 Hippocampus left

3 Nucleus caudatus width left
6 Parietal cortex right
9 Hippocampus right

* $p \leq 0.05$ WILCOXON test (two-sided)

** $p \leq 0.01$ WILCOXON test (two-sided)

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Modified extended one-generation reproduction toxicity study 05.Mar.2019 SIGR
in Sprague-Dawley Rats, Oral Administration (gavage)

ABSOLUTE BRAIN WEIGHTS - MEAN VALUES (MALE)
F1 GENERATION, REARING ANIMALS, COHORT 2B (WEANLINGS)

Sacrifice				I2			
Sex				M			
Group				10	11	12	13
.....							
Terminal body weight	g	M		59.88	57.64	60.29	60.71
		% dev		100	96	101	101
		SD		3.889	4.935	3.753	3.808
		n		10	10	10	10
.....							
Brain	g	M		1.828	1.783	1.855	1.819
		% dev		100	98	101	100
		SD		0.065	0.065	0.057	0.063
		n		10	10	10	10
.....							

*: P <= 0.05, **: P <= 0.01
Kruskal-Wallis H and Wilcoxon test, two sided

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Modified extended one-generation reproduction toxicity study 05.Mar.2019 SIGR
in Sprague-Dawley Rats, Oral Administration (gavage)

ABSOLUTE BRAIN WEIGHTS - MEAN VALUES (FEMALE)
F1 GENERATION, REARING ANIMALS, COHORT 2B (WEANLINGS)

Sacrifice			I2			
Sex			F			
Group			10	11	12	13
.....						
Terminal body weight	g	M	56.1	57.39	58.25	59.61
		% dev	100	102	104	106
		SD	3.893	3.898	4.03	2.517
		n	10	10	10	10
.....						
Brain	g	M	1.757	1.74	1.751	1.801
		% dev	100	99	100	103
		SD	0.043	0.082	0.062	0.111
		n	10	10	10	10
.....						

*: P <= 0.05, **: P <= 0.01
Kruskal-Wallis H and Wilcoxon test, two sided

BASF NEUROPATHOLOGY REPORT ID 12/16
90R0066/05R034
Modified extended one-generation reproduction toxicity study 05.Mar.2019 SIGR
in Sprague-Dawley Rats, Oral Administration (gavage)

RELATIVE BRAIN WEIGHTS - MEAN VALUES (MALE)
F1 GENERATION, REARING ANIMALS, COHORT 2B (WEANLINGS)

Sacrifice			I2				
Sex			M				
Group			10	11	12	13	
Terminal body weight	%	M	100.0	100.0	100.0	100.0	
	% dev		100	100	100	100	
	n		10	10	10	10	
Brain	%	M	3.063	3.109	3.087	3.004	
	% dev		100	102	101	98	
	SD		0.183	0.23	0.184	0.165	
	n		10	10	10	10	

*: P <= 0.05, **: P <= 0.01
Kruskal-Wallis H and Wilcoxon test, two sided

BASF NEUROPATHOLOGY REPORT ID 13/16
90R0066/05R034
Modified extended one-generation reproduction toxicity study 05.Mar.2019 SIGR
in Sprague-Dawley Rats, Oral Administration (gavage)

RELATIVE BRAIN WEIGHTS - MEAN VALUES (FEMALE)
F1 GENERATION, REARING ANIMALS, COHORT 2B (WEANLINGS)

Sacrifice			I2			
Sex			F			
Group			10	11	12	13
.....						
Terminal body weight	%	M	100.0	100.0	100.0	100.0
	% dev		100	100	100	100
	n		10	10	10	10
.....						
Brain	%	M	3.146	3.041	3.016	3.023
	% dev		100	97	96	96
	SD		0.254	0.182	0.186	0.178
	n		10	10	10	10
.....						

*: P <= 0.05, **: P <= 0.01
Kruskal-Wallis H and Wilcoxon test, two sided

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Length and width of brain (mean values)
F1 Generation, rearing animals, Cohort 2B (weanlings)

Male (weanlings):

Group	Brain			
	Length (cm)	%	Width (cm)	%
10	1.95	100	1.53	100
11	1.91	98	1.53	100
12	1.94	99	1.53	100
13	1.95	100	1.55	101

Female (weanlings):

Group	Brain			
	Length (cm)	%	Width (cm)	%
10	1.91	100	1.51	100
11	1.91	100	1.52	101
12	1.92	100	1.52	101
13	1.92	100	1.51	100

* $p \leq 0,05$ Wilcoxon + Bonferroni-Holm adjustment (two-sided)

** $p \leq 0,01$

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INCIDENCE OF GROSS LESIONS
F1 GENERATION, REARING ANIMALS, COHORT 2B (WEANLINGS)

Sacrifice	I2							
Sex	M				F			
Group	10	11	12	13	10	11	12	13
Animals in selected group	10	10	10	10	10	10	10	10
.....								
No abnormalities	10	10	10	10	10	10	10	10

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NEUROPATHOLOGY REPORT

ID 16/16

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INCIDENCE OF ALL MICROSCOPIC FINDINGS

F1 GENERATION, REARING ANIMALS, COHORT 2B (WEANLINGS)

Sacrifice		I2							
Sex		M				F			
Group		10	11	12	13	10	11	12	13
Animals in selected group		10	10	10	10	10	10	10	10
.....								
Cerebellum	exam.	10	.	.	10	10	.	.	10
Frontal lobe	exam.	10	.	.	10	10	.	.	10
Medulla oblongata	exam.	10	.	.	10	10	.	.	10
Midbrain	exam.	10	.	.	10	10	.	.	10
Olfactory bulb	exam.	10	.	.	10	10	.	.	10
Parietal lobe	exam.	10	.	.	10	10	.	.	10
Pituitary gland	exam.	10	.	.	10	10	.	.	10
Pons	exam.	10	.	.	9	10	.	.	10
Trigeminal ganglia	exam.	10	.	.	10	10	.	.	10