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**STUDY TITLE**

Report

**DHDPS**

Repeated-dose 90-day oral toxicity study in Wistar rats  
Administration by gavage

**TEST GUIDELINE(S)**

OECD 408  
Commission Regulation (EC) No 440/2008

**AUTHOR(S)**

[REDACTED]

**STUDY COMPLETION DATE**

16 Oct 2014

**TEST FACILITY**

BASF SE  
Experimental Toxicology and Ecology  
67056 Ludwigshafen, Germany

**TEST FACILITY PROJECT IDENTIFICATION**

Project No. 50C0066/05S019

**SPONSORS**

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**PART I OF III (REPORT SECTION AND SUMMARY TABLES)**

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The Chemical Company

Report; Project No.: 50C0066/05S019

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Submitter: ..... Date: .....

Typed Name of Signer:

Typed Name of Company: BASF Corporation, Agricultural Products  
P.O. Box 13528  
Research Triangle Park, NC 27709-3528

**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.

Study Director: .

Date:

Typed name of Study Director:

Typed name of Laboratory:

BASF SE  
Experimental Toxicology and Ecology  
67056 Ludwigshafen  
Germany

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### FLAGGING CRITERIA

I have applied the criteria of 40 CFR 158.34/40 CFR 161.34 for flagging studies for potential adverse effects to the results of the attached study. This study neither meets nor exceeds any of the applicable criteria.

Submitter: .....

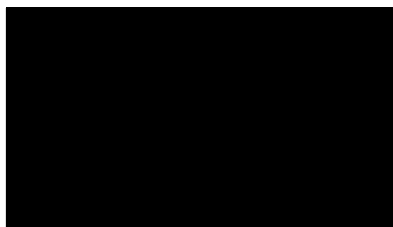
.....  
Date

Typed Name of Signer:

Typed Name of Company: BASF Corporation, Agricultural Products  
P.O. Box 13528  
Research Triangle Park, NC 27709-3528

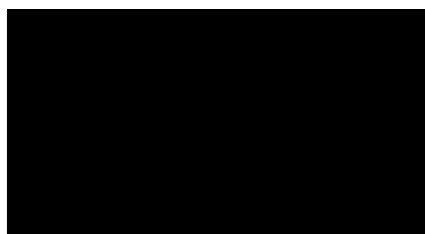
**SIGNATURE PAGE**

Study Director:



16 Oct 2014

Clinical Pathology:



9 Oct 2014

Pathology:



13 Oct 2014

Analytical Chemistry:



14 Oct 2014

Test Facility Management:



15 Oct 2014

**CONTRIBUTORS TO THE STUDY/ SUPERVISORY LABORATORY PERSONNEL**

Head of Experimental Toxicology and Ecology:



Study Director:



Clinical Pathology:



Pathology:



Analytical Chemistry:



Data Processing:



Statistics:



Quality Assurance Unit (QAU):



Coordination QAU:



Laboratory Analytical Chemistry:



Laboratory Subchron./Chron. Tox. Rodent:



Clinical Pathology/ Hematology:



Pathology:



Histopathology:



**STATEMENT OF THE QUALITY ASSURANCE UNIT**

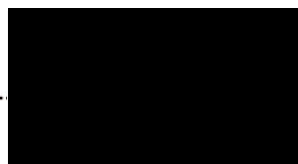
The Quality Assurance Unit (QAU) inspected the study and reported any inspection results to the Study Director and to Management.

The final report reflects the raw data.

| Phase of study    | Date of inspection<br>(mm-dd-yyyy) | Reported to Study Director<br>and to Test Facility Management<br>(mm-dd-yyyy) |
|-------------------|------------------------------------|---|
| Study Plan:       | 08-02-2013                         | 08-02-2013  |
| Conduct of study: | 08-28-2013                         | 08-28-2013  |
|                   | 09-03-2013                         | 09-03-2013  |
|                   | 11-14-2013                         | 11-14-2013  |
|                   | 11-15-2013                         | 11-15-2013  |
| Report:           | 07-16-2014                         | 07-16-2014  |

Ludwigshafen,

16 Oct 2014





## GLP CERTIFICATE (FROM THE COMPETENT AUTHORITY)



Rheinland-Pfalz

LANDESAMT FÜR UMWELT,  
WASSERWIRTSCHAFT UND  
GEWERBEAUFICHT

### 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 bzw. 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)

03. bis 05.09.2013

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

Auf der Grundlage des Inspektionsberichts 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

*Pia Hirsch* 18.12.2013

**Dr.-Ing. Pia Hirsch - Stellvertretende Präsidentin**

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

**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)

MESSEN  
BEWERTEN  
BERATEN



**CONTENTS OF PART I (REPORT SECTION AND SUMMARY TABLES)**

TITLE PAGE

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

GLP COMPLIANCE STATEMENT

FLAGGING CRITERIA

SIGNATURE PAGE

CONTRIBUTORS TO THE STUDY/ SUPERVISORY LABORATORY PERSONNEL

STATEMENT OF THE QUALITY ASSURANCE UNIT

GLP CERTIFICATE (FROM THE COMPETENT AUTHORITY)

**CONTENTS OF PART I (REPORT SECTION AND SUMMARY TABLES)**

- 1. SUMMARY
  - 1.1. METHODS
  - 1.2. OBSERVATIONS
  - 1.3. RESULTS
    - 1.3.1. Analytics
    - 1.3.2. Findings
  - 1.4. CONCLUSION
- 2. INTRODUCTION
  - 2.1. OBJECTIVES
  - 2.2. SELECTION OF DOSES
  - 2.3. TEST GUIDELINES
  - 2.4. STUDY DATES
  - 2.5. RETENTION OF RECORDS
  - 2.6. ANIMAL WELFARE
- 3. MATERIAL AND METHODS
  - 3.1. TEST ITEM

- 3.2. TEST SYSTEM
- 3.3. HOUSING AND DIET
- 3.4. TEST GROUPS AND DOSES/ CONCENTRATIONS
- 3.5. TEST SUBSTANCE PREPARATIONS AND PREPARATION FREQUENCY
- 3.6. ANALYSES
  - 3.6.1. Analyses of the test-substance preparations
  - 3.6.2. Analytical methods
  - 3.6.3. Food analyses
  - 3.6.4. Drinking water analyses
  - 3.6.5. Bedding and enrichment analyses
- 3.7. EXPERIMENTAL PROCEDURE
- 3.8. CLINICAL EXAMINATIONS
  - 3.8.1. Mortality
  - 3.8.2. Clinical observations
  - 3.8.3. Detailed clinical observations
  - 3.8.4. Food consumption
  - 3.8.5. Water consumption
  - 3.8.6. Body weight data
  - 3.8.7. Functional observational battery
  - 3.8.8. Motor activity assessment
  - 3.8.9. Ophthalmoscopy
  - 3.8.10. Statistics of clinical examinations
- 3.9. CLINICAL PATHOLOGY
  - 3.9.1. Hematology
  - 3.9.2. Clinical chemistry
  - 3.9.3. Urinalysis
  - 3.9.4. Statistics of clinical pathology
- 3.10. PATHOLOGY
  - 3.10.1. Necropsy
  - 3.10.2. Organ weights
  - 3.10.3. Organ/tissue fixation
  - 3.10.4. Histopathology
  - 3.10.5. Statistics of pathology
- 4. RESULTS
  - 4.1. ANALYSES
    - 4.1.1. Stability analyses
    - 4.1.2. Homogeneity control analyses
    - 4.1.3. Concentration control analyses
    - 4.1.4. Food analyses

- 4.1.5. Drinking water analyses
- 4.1.6. Bedding and enrichment analyses
- 4.2. CLINICAL EXAMINATIONS
  - 4.2.1. Mortality
  - 4.2.2. Clinical observations
  - 4.2.3. Food consumption
  - 4.2.4. Water consumption
  - 4.2.5. Body weight data
  - 4.2.6. Functional observational battery
  - 4.2.7. Motor activity measurement
  - 4.2.8. Ophthalmological examinations
- 4.3. CLINICAL PATHOLOGY
  - 4.3.1. Hematology
  - 4.3.2. Clinical chemistry
  - 4.3.3. Urinalyses
- 4.4. PATHOLOGY
  - 4.4.1. Weight parameters
  - 4.4.2. Gross lesions
  - 4.4.3. Histopathology
- 5. DISCUSSION
- 6. CONCLUSION
- 7. REFERENCES
- 8. APPENDIX
  - 8.1. LIST OF ABBREVIATIONS USED IN TABLES CLINICAL EXAMINATIONS
  - 8.2. LIST OF ABBREVIATIONS USED IN TABLES CLINICAL PATHOLOGY
  - 8.3. LIST OF ABBREVIATIONS USED IN TABLES PATHOLOGY

**Part A:****CLINICAL EXAMINATIONS (MEAN VALUES AND SUMMARY TABLES)**

## Tables

|                                  |                |
|----------------------------------|----------------|
| Clinical Observations            | IA 1 - IA- 2   |
| Food consumption                 | IA 3 - IA- 6   |
| Body weight                      | IA 7 - IA- 10  |
| Body weight change               | IA 11 - IA- 14 |
| Functional observational battery | IA 15 - IA- 30 |
| Motor activity                   | IA 31 - IA- 34 |
| Ophthalmological Examinations    | IA 35 - IA- 36 |

**Part B:****CLINICAL PATHOLOGY (MEAN VALUES AND SUMMARY TABLES)**

|   |                |
|---|----------------|
| Red blood cell + coagulation parameters | IB- 1 - IB- 2  |
| White blood cell parameters             | IB- 3 - IB- 4  |
| Enzymes                                 | IB- 5 - IB- 6  |
| Substrates                              | IB- 7 - IB- 8  |
| Electrolytes + minerals                 | IB- 9 - IB- 10 |
| Urinalyses                              | IB-11 - IB- 14 |

**Part C:****PATHOLOGY (MEAN VALUES AND SUMMARY TABLES)**

|  |               |
|--|---------------|
| Absolute weights - mean values                                 | IC- 1 - IC- 4 |
| Relative weights - mean values                                 | IC- 5 - IC- 8 |
| Incidence of gross lesions                                     | IC- 9         |
| Incidence of all microscopic findings                          | IC-10 - IC-12 |
| Incidence and grading of microscopic findings in target organs | IC-13 - IC-14 |
| Liver GSTP   | IC-15         |

**CONTENTS OF PART II (TABLES SECTION; INDIVIDUAL VALUES)**

TITLE PAGE

TABLE OF CONTENTS

**Part A:  
CLINICAL EXAMINATIONS (INDIVIDUAL VALUES)**

Tables

|                                      |                   |
|--------------------------------------|-------------------|
| Mortality                            | IIA- 1 - IIA- 12  |
| Detailed Clinical Observations [DCO] | IIA- 13 - IIA- 36 |
| Clinical Observations                | IIA- 37 - IIA-408 |
| Food consumption                     | IIA-409 - IIA-424 |
| Body weight                          | IIA-425 - IIA-440 |
| Functional observational battery     | IIA-441 - IIA-472 |
| Motor activity                       | IIA-473 - IIA-480 |
| Ophthalmological Examinations        | IIA-481 - IIA-486 |

**Part B:  
CLINICAL PATHOLOGY (INDIVIDUAL VALUES)**

|   |                   |
|---|-------------------|
| Red blood cell + coagulation parameters | IIB- 1 - IIB- 2   |
| White blood cell parameters             | IIB- 3 - IIB- 4   |
| Enzymes                                 | IIB- 5 - IIB- 6   |
| Substrates                              | IIB- 7 - IIB- 8   |
| Electrolytes + minerals                 | IIB- 9 - IIB- 10  |
| Urinalyses                              | IIB- 11 - IIB- 26 |

**Part C:  
PATHOLOGY (INDIVIDUAL VALUES)**

|                                      |                   |
|--------------------------------------|-------------------|
| Absolute weights - individual values | IIC- 1 - IIC- 16  |
| Relative weights - individual values | IIC- 17 - IIC- 32 |
| Single animal sheet                  | IIC- 33 - IIC- 85 |

**CONTENTS OF PART III (SUPPLEMENT)**

Title Page

Table of contents

Characterization of "4,4'-Dihydroxydiphenylsulfon"  
Study No. 12L00002

DHDPS

Stability Analysis in 1% Carboxymethylcellulose in Drinking Water  
Study No. 01Y0066/05Y009

Homogeneity and Concentration Control Analysis of DHDPS in  
1% carboxymethylcellulose in drinking water

Functional observational battery (FOB)

Detailed description of examinations, ranking and documentation procedures

Historical control data of clinical pathology testing

Historical control data of pathology

**THIS REPORT CONSISTS OF PART I, II AND III**

## 1. SUMMARY

### 1.1. METHODS

DHDPS was administered by gavage to groups of 10 male and 10 female Wistar rats at dose levels of 0 (test group 0), 100 (test group 1), 300 (test group 2) and 1000 mg/kg bw/d (test group 3) over a period of 3 months. Due to severely impaired body weight development in male animals of test group 3 (1000 mg/kg bw/d), i.e. -20% on study day 63, the male animals were treated at a dose level of 600 mg/kg bw/d from study day 70 onwards. Female animals were continuously treated at the limit dose. Drinking water containing 1% carboxymethylcellulose served as vehicle.

### 1.2. OBSERVATIONS

Food consumption and body weights were determined weekly. The animals were examined for signs of toxicity or mortality at least once a day. In addition, the animals were daily examined for any clinically abnormal signs. Detailed clinical examinations in an open field were conducted prior to the start of the administration period and weekly thereafter. Ophthalmological examinations were performed before the beginning and at the end of the administration period. Beside this, a functional observational battery (FOB) as well as measurement of motor activity (MA) were carried out at the end of the administration period. Clinicochemical and hematological examinations as well as urinalyses were performed towards the end of the administration period. After the administration period all rats were sacrificed and assessed by gross pathology. Organ weights were determined followed by histopathological examinations.

### 1.3. RESULTS

#### 1.3.1. Analytics

The various analyses confirmed

- the stability of the test-substance preparations over a period of 7 days in the refrigerator,
- the homogenous distribution of the test substance in the vehicle,
- the correctness of the prepared concentrations.



### 1.3.2. Findings

The following test substance-related, relevant findings were noted:

#### **Test group 3: 1000 mg/kg bw/d (male animals received 600 mg/kg bw/d from study day 70 onwards)**

##### Clinical Examinations

- Soft (and discolored) feces were observed in all male and female animals towards the end of the administration period.
- Slightly reduced food consumption for male animals during the entire treatment period (max. of -18% on study days 7 and 63).
- Significantly lower mean body weights in male animals were observed during the entire administration period (max. of -20% on study day 70)
- Significantly lower body weight change values in male animals were observed during the entire administration period (max. of -33% from study day 0 to 63)

##### Clinical Pathology

- Decreased red blood cell (RBC) counts and hemoglobin values in rats of both sexes
- Decreased hematocrit levels and absolute eosinophil counts in females
- Increased mean corpuscular volume (MCV) and relative reticulocyte counts in males
- Prolonged prothrombin time in females
- Decreased chloride levels in both sexes
- Increased alkaline phosphatase (ALP) activities in females
- Increased creatinine and triglyceride levels in males
- Decreased cholesterol and total bilirubin levels in males

##### Pathology

- Increased absolute and relative weight of the adrenal glands in males (abs. +40%, rel. +77%) and females (abs. +23%, rel. +31%)
- Increased absolute and relative liver weights in female animals (abs. +38%, rel. +49%)
- Increased relative liver weight in male animals (+18%)
- Increased relative ovarian weights in female animals (+30%)
- Hypertrophy/hyperplasia in the adrenal cortex of male animals
- Centrilobular hepatocellular hypertrophy in all female animals
- Mainly eosinophilic foci of hepatocellular alteration in females
- Increased extramedullary hematopoiesis in the spleen of male and female animals
- Multifocal atrophy in the mammary gland in all male animals
- Squamous metaplasia in the uterus in 5 of 10 female animals

**Test group 2: 300 mg/kg bw/d****Clinical Examinations**

- Soft (and discolored) feces were observed in all male and female animals towards the end of the administration period.
- Lower mean body weights (not significantly) in male animals were observed during the entire administration period (max. of -20% on study day 70)
- Significantly lower body weight change values in male animals were observed during the last third of the administration period (max. of -15% from study day 0 to 84)

**Clinical Pathology**

- No treatment-related, adverse effects were observed.

**Pathology**

- Multifocal atrophy in the mammary gland in 7 of 10 male animals

**Test group 1: 100 mg/kg bw/d****Clinical Examinations, Clinical Pathology and Pathology**

- No treatment-related, adverse effects were observed.

**1.4. CONCLUSION**

The administration of DHDPS by gavage to male and female Wistar rats for 3 months caused test substance-related adverse signs of systemic toxicity at a dose level of 300 mg/kg bw/d and above in male animals and at a dose level of 1000 mg/kg bw/d in female Wistar rats. Therefore, under the conditions of the present study the no observed adverse effect level (NOAEL) was 100 mg/kg bw/d in male and 300 mg/kg bw/d in female Wistar rats.

## 2. INTRODUCTION

### 2.1. OBJECTIVES

The aim of the study was to assess the toxicological profile of DHDPS including the target organs and the “no observed adverse effect level” (NOAEL) after 3-month administration by gavage.

### 2.2. SELECTION OF DOSES

At the request of the sponsor, the following dose levels were selected for the present study:

|                               |   |
|-------------------------------|---|
| 1000 mg/kg bw/d <sup>a)</sup> | as high dose for male (until study day 69) and female animals |
| 600 mg/kg bw/d                | as high dose in male animals, from study day 70 onwards       |
| 300 mg/kg bw/d                | as intermediate dose  |
| 100 mg/kg bw/d                | as low dose   |

<sup>a)</sup> mg/kg body weight/day

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

### 2.3. TEST GUIDELINES

The study was conducted according to the following test guidelines:

- Commission Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), Part B: Subchronic oral toxicity test repeated dose 90-day oral toxicity study in rodents; Official Journal of the European Union, No. L 142
- OECD Guidelines for Testing of Chemicals; Method No. 408: Subchronic Oral Toxicity - Rodent: 90-Day Study; adopted 21 Sep 1998

## 2.4. STUDY DATES

In the following table, the relevant intervals for certain study phases are given:

| Males               | Females                                   | Phase of study/ Examination  | Study day |
|---------------------|---|--|-----------|
| 02 Aug 2013         |   | Study initiation date: signature of study director   | -19       |
| 13 Aug 2013         |   | Experimental starting date: arrival of the animals and start of the acclimatization period | -8        |
| 19 Aug 2013         |   | Randomization of the animals   | -2        |
| 20 Aug 2013         |   | Sampling for analyses (all dose groups)  | -1        |
| 20 Aug 2013         |   | Ophthalmoscopy   | -1        |
| 21 Aug 2013         |   | Start of the administration period   | 0         |
| 30 Oct 2013         |   | Sampling for analyses (selected dose only)   | 70        |
| 14 Nov 2013         |   | Urinalysis   | 85        |
| 15 Nov 2013         | 16 Nov 2013<br>17 Nov 2013<br>18 Nov 2013 | FOB1; MA1 <sup>a)</sup>  | 86        |
| 17 Nov 2013         |   | FOB2; MA2 <sup>a)</sup>  | 87        |
|                     |   | FOB3; MA3 <sup>b)</sup>  | 88        |
|                     |   | FOB4; MA4 <sup>b)</sup>  | 89        |
| 19 Nov 2013         |   | Sampling for analyses (all dose groups)  | 90        |
| 20 Nov 2013         |   | Ophthalmoscopy   | 91        |
| 20 Nov 2013         |   | Last weighing  | 91        |
| 21 Nov 2013         | 22 Nov 2013                               | Blood sampling and necropsy <sup>c)</sup>  | 92        |
|                     |   |  | 93        |
| Nov 2013 – Apr 2014 |   | Organ fixation, processing and evaluation  |           |
| 19 May 2014         |   | Experimental completion date; draft report to QAU  |           |

a) = first 5 animals of every test group.

b) = second 5 animals of every test group.

c) = Fasting period (withdrawal of food) of about 16 to 20 hours before blood sampling and necropsy

FOB = Functional observational battery

MA = Measurement of motor activity

1...4 = Identification number of the specific examination

## 2.5. RETENTION OF RECORDS

All GLP-relevant documents and materials will be archived at BASF SE, at least for the period of time specified in the GLP regulations. Details of the responsibility and site of archiving can be seen from the specific SOPs or 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) were carried out at Competence Center Analytics, BASF SE, 67056 Ludwigshafen, Germany.

|                         |                                      |
|-------------------------|--------------------------------------|
| Name of test substance: | DHDPS                                |
| CAS No.:                | 80-09-1                              |
| Test substance No.:     | 05/0066-4                            |
| Batch identification:   | 69611767J0                           |
| Purity:                 | 99.4% (study No. 12L00002)           |
| Homogeneity:            | given (visually; study No. 12L00002) |
| Stability:              | stable until 28 Nov 2013             |

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

#### ADDITIONAL TEST-SUBSTANCE INFORMATION

|                              |  |
|------------------------------|--|
| Synonym;                     | 4,4'-Dihydroxydiphenylsulfon               |
| Date of production:          | 28 Nov 2011                                |
| Physical state / appearance: | solid/ white                               |
| Storage conditions:          | room temperature, protect against moisture |

### 3.2. TEST SYSTEM

|  |  |
|--|--|
| Species:                                   | rat  |
| Strain:                                    | CrI:WI(Han)  |
| Supplier:                                  | Charles River Laboratories, Research Models and Services GmbH, Sulzfeld, Germany   |
| Sex:                                       | males / females  |
| Age when supplied:                         | 34 ± 1 days  |
| Age at the start of administration period: | 42 ± 1 days  |
| Reason for the selection:                  | The rat is a frequently used laboratory animal, and there is comprehensive experience with this animal species. Moreover, the rat has been proposed as a suitable animal species by the OECD and the EPA for this type of study. |
| Animal identification:                     | ear tattoo (animal number)   |

### 3.3. HOUSING AND DIET

The animals were housed together (5 animals per cage) in H-Temp polysulfonate cages type 2000P supplied by TECNIPLAST, Hohenpeißenberg, Germany (floor area about 2065 cm<sup>2</sup>). Motor activity measurements were conducted in polycarbonate cages type III (floor area about 800 cm<sup>2</sup>). The cages and wire covers were supplied by TECNIPLAST, Hohenpeissenberg, Germany resp. by Ehret, Emmendingen, Germany. Dust-free wooden bedding was used in this study (the present supplier is documented in the raw data). Wooden gnawing blocks (Typ NGM E-022) supplied by Abedd<sup>®</sup> Lab. and Vet. Service GmbH, Vienna, Austria and large play tunnels (Art. 14153) supplied by PLEXX B.V., Elst, Netherlands were added for environmental enrichment. The animals were accommodated in fully air-conditioned rooms in which central air conditioning guaranteed a range of temperature of 20-24°C, a range of relative humidity of 30-70% and 15 air changes per hour. The day/night cycle was 12 hours (12 hours light from 06.00-18.00 h, 12 hours dark from 18.00-06.00 h). There were no or only minimal deviations from these limits. The animal room was completely disinfected prior to the study using a disinfectant ("AUTEX", fully automatic, formalin-ammonia-based terminal disinfectant). The floor and the walls 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, Kaiseraugst, Switzerland. Food and drinking water (from water bottles) were available ad libitum.

### 3.4. TEST GROUPS AND DOSES/ CONCENTRATIONS

#### Males

| Test group | Dose (mg/kg bw/d) <sup>a)</sup> | Concentration (g/100 mL) | No. of animals | Animal No.         | Cage No. |
|------------|---------------------------------|--------------------------|----------------|--------------------|----------|
| 0          | 0 <sup>b)</sup>                 | -                        | 10             | 1 - 5<br>6 - 10    | 1<br>2   |
| 1          | 100                             | 1.0                      | 10             | 11 - 15<br>16 - 20 | 3<br>4   |
| 2          | 300                             | 3.0                      | 10             | 21 - 25<br>26 - 30 | 5<br>6   |
| 3          | 1000/ 600 <sup>c)</sup>         | 10.0/ 6.0 <sup>c)</sup>  | 10             | 31 - 35<br>36 - 40 | 7<br>8   |

#### Females

| Test group | Dose (mg/kg bw/d) <sup>a)</sup> | Concentration (g/100 mL) | No. of animals | Animal No.         | Cage No. |
|------------|---------------------------------|--------------------------|----------------|--------------------|----------|
| 0          | 0 <sup>b)</sup>                 | -                        | 10             | 41 - 45<br>46 - 50 | 9<br>10  |
| 1          | 100                             | 1.0                      | 10             | 51 - 55<br>56 - 60 | 11<br>12 |
| 2          | 300                             | 3.0                      | 10             | 61 - 65<br>66 - 70 | 13<br>14 |
| 3          | 1000                            | 10.0                     | 10             | 71 - 75<br>76 - 80 | 15<br>16 |

<sup>a)</sup> The dose refers to the body weight determined most recently.

<sup>b)</sup> Vehicle: drinking water containing 1% carboxymethylcellulose

<sup>c)</sup> from study day 70 onwards

### 3.5. TEST SUBSTANCE PREPARATIONS AND PREPARATION FREQUENCY

DHDPS was applied as a suspension. To prepare this suspension, the appropriate amount of test substance was weighed out depending on the desired concentration. Then, drinking water containing 1% carboxymethylcellulose was filled up to the desired volume, subsequently released manually. The test-substance preparations were produced at least weekly and stored at a refrigerator. The administration volume was 10 mL/kg body weight.



### **3.6. ANALYSES**

#### **3.6.1. Analyses of the test-substance preparations**

The analyses of the test-substance preparations have been carried out at the Analytical Chemistry Laboratory of Experimental Toxicology and Ecology of BASF SE, Ludwigshafen, Germany, as a part of this study. The study was carried out in compliance with the Principles of Good Laboratory Practice.

The stability of the test substance in drinking water containing 1% carboxymethylcellulose in the refrigerator for a period of 7 days was demonstrated before the start of the administration period (see PART III, Supplement, project No. 01Y0066/05Y009).

Homogeneity was verified in 3 samples in the highest and lowest concentrations (was used as a concentration control at the same time) at the beginning of the administration period; additional concentration control analyses were verified in 1 sample of the mid concentration at the same time. Since the dose level for male animals of test group 3 was decreased from 1000 to 600 mg/kg bw/d, a sample for concentration control analysis was taken directly on study day 70. Additional concentration control analyses were performed for all concentrations towards the end of the administration period (PART III, Supplement).

#### **3.6.2. Analytical methods**

The methods used for analytical investigations of the test-substance preparations can be found in PART III (Supplement).

#### **3.6.3. Food analyses**

The supplier assayed the food used in the study for chemical and microbiological contaminants.

#### **3.6.4. Drinking water analyses**

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

#### **3.6.5. Bedding and enrichment analyses**

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

### 3.7. EXPERIMENTAL PROCEDURE

On day of arrival, the animals were subjected to an acclimatization period during which they received ground diet and drinking water ad libitum. Prior to the first detailed clinical observation, the animals were distributed according to weight among the individual test groups, separated by sex. The weight variation of the animals used did not exceed 20 percent of the mean weight of each sex. The list of randomization instructions was compiled with a computer.

The test substance was administered daily by gavage for about 3 months. Control animals received the vehicle only. The volume to be administered was 10 mL/kg bw/d (related to the body weight determined most recently in each case). All animals were sacrificed after a fasting period (withdrawal of food) of at least 16 hours.

### 3.8. CLINICAL EXAMINATIONS

#### 3.8.1. Mortality

A check for moribund and dead animals was made twice daily on working days and once daily on Saturdays, Sundays and public holidays. If animals were in a moribund state, they were sacrificed and necropsied.

#### 3.8.2. Clinical observations

All animals were checked daily for any abnormal clinically signs before the administration as well as within 2 hours and within 5 hours after the administration.

#### 3.8.3. Detailed clinical observations

All animals were subjected to detailed clinical observations (DCO) outside their cages once before the beginning of the administration period (day 0) and subsequently once a week (in the morning). For observation, the animals were therefore removed from their cages and placed in a standard arena (50 × 37.5 × 25 cm). The following parameters were examined:

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
15. Assessment of the feces discharged during the examination (appearance/ consistency)
16. Assessment of the urine discharged during the examination
17. Pupil size

#### **3.8.4. Food consumption**

Food consumption was determined weekly as representative value over a period of 4 days and calculated as mean food consumption in grams per animal and day.

#### **3.8.5. Water consumption**

Drinking water consumption was monitored by daily visual inspection of the water bottles for any changes in volume.

#### **3.8.6. Body weight data**

Body weight was determined before the start of the administration period in order to randomize the animals. During the administration period the body weight was determined on study day 0 (start of the administration period) and thereafter at weekly intervals. The difference between the body weight on the respective day of weighing and the body weight on study day 0 was calculated as body weight change.

#### **3.8.7. Functional observational battery**

A functional observational battery (FOB) was performed in all animals at the end of the administration period starting at about 10:00 h. At least one hour before the start of the FOB the animals were transferred singly to polycarbonate cages. Drinking water was provided ad libitum whereas no food was offered during the measurements. The FOB started with passive observations without disturbing the animals, 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 the degree of severity, if applicable. The observations were performed at random. A detailed description of the methods, the ranking and documentation system can be found in PART III (Supplement).

*Home cage observations:*

The animals were observed in their closed home cages; any disturbing activities (touching the cage or rack, noise) were avoided during these examinations in order not to influence the behavior of the animals. Attention was paid to:

1. Posture
2. Tremors
3. Convulsions
4. Abnormal movements
5. Gait abnormalities

*Open field observations:*

The animals were transferred to a standard arena (50 × 50 cm with sides of 25 cm height) and observed for at least 2 minutes. Following parameters were examined:

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 abnormalities
15. Activity/ arousal level
16. Feces excreted within 2 minutes (number/ appearance/ consistency)
17. Urine excreted within 2 minutes (amount/ color)
18. Rearing within 2 minutes

*Sensory motor tests/ reflexes:*

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

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 (Auditory startle response)
7. Coordination of movements (Righting response)
8. Behavior during handling

9. Vocalization
10. Pain perception (Tail pinch)
11. Grip strength of forelimbs
12. Grip strength of hindlimbs
13. Landing foot-splay test
14. Other findings

### **3.8.8. Motor activity assessment**

Motor activity (MA) was also 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 rats were placed in new 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 was counted over 12 intervals for 5 minutes per interval. The sequence in which the rats were placed in the cages was selected at random. On account of the time needed to place the rats in the cages, the starting time was "staggered" for each animal. The measurement period began when the 1<sup>st</sup> beam was interrupted and finished exactly 1 hour later. No food or water was offered to the rats during these measurements and the measurement room was darkened after the transfer of the last rat. The program requires a file name for the measured data to be stored. This name consists of the reference number and a serial number.

### **3.8.9. Ophthalmoscopy**

The eyes of all animals were examined prior to the start of the administration period. Towards the end of the administration period, i.e. study day 91, the eyes of animals in test groups 0 (control) and 3 (1000 [600 in males from day 70 onwards] mg/kg bw/d) were examined for any changes using an ophthalmoscope (HEINE OPTOTECHNIK, Herrsching, Germany) after administration of a mydriatic agent (Mydrum, Chauvin ankerpharm GmbH, Rudolstadt, Germany).

### 3.8.10. Statistics of clinical examinations

Means and standard deviations of each test group were calculated for several parameters (see tables). Further statistical analyses were performed according to following table:

| Parameters  | Statistical test   | Markers in the tables                       | References  |
|---|--|---|---|
| Body weight, body weight change   | A comparison of each group with the control group was performed using DUNNETT's test (two-sided) for the hypothesis of equal means   | * for $p \leq 0.05$<br>** 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<br><br>DUNNETT, C.W. (1964). New tables for multiple comparisons with a control. Biometrics, Vol. 20, 482-491 |
| Feces, rearing, grip strength forelimbs, grip strength hindlimbs, foot-splay test, motor activity | 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 $p \leq 0.05$<br>** for $p \leq 0.01$ | SIEGEL, S. (1956): Non-parametric statistics for the behavioral sciences. McGraw-Hill New York  |

### 3.9. CLINICAL PATHOLOGY

In the morning blood was taken from the retro-bulbar venous plexus from fasted animals. The animals were anaesthetized using isoflurane. The blood sampling procedure and subsequent analysis of blood and serum samples were carried out in a randomized sequence. For urinalysis the individual animals were transferred to metabolism cages (withdrawal of food and water) and urine was collected overnight. Urine samples were evaluated in a randomized sequence

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 examinations were carried out in all animals per test group and sex at the end of the administration period.

#### 3.9.1. Hematology

The following parameters were determined in blood with EDTA-K<sub>3</sub> 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:<br>MCV x erythrocytes                                |                                       |
| Mean corpuscular volume (MCV)                    | fL           | RBC/PLT method; mean of RBC volume distribution curve (histogram) |                                       |
| Mean corpuscular hemoglobin (MCH)                | fmol         | calculation:<br><u>hemoglobin</u><br>erythrocytes                 |                                       |
| Mean corpuscular hemoglobin concentration (MCHC) | mmol/L       | calculation:<br><u>hemoglobin</u><br>hematocrit                   |                                       |
| Platelet count (PLT)                             | giga/L       | flow cytometric laserlight scattering                             |                                       |
| Differential blood count                         | % and giga/L | cytochemistry coupled with flow cytometry                         |                                       |
| Reticulocytes (RET)                              | %            | 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, 6<sup>th</sup> 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<br>(Hepato Quick's test)<br>(HQT) | seconds | citrated blood with calcium<br>thromboplastin | Fischer, M. and Falkensammer, Ch.,<br>Klin. Wschr. <u>86</u> , 577-583 (1974) |

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



| Blood Chemistry Parameter | Unit   | Method   | References   |
|---------------------------|--------|--|--|
| Sodium (NA)               | mmol/L | ion selective electrodes (ISE)   | Hitachi 917 - working instructions   |
| Potassium (K)             | mmol/L |  |  |
| Chloride (CL)             | mmol/L |  |  |
| Inorganic phosphate (INP) | mmol/L | molybdate reaction   | 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   | 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                                    | Neumann, U. and Ziegenhorn, J.: XVI, Nordiska kongressen för klinisk kemi och klinisk fysiologi 1977, Oulu, Finland; Roche working instructions  |
| Creatinine (CREA)         | μmol/L | enzymatic determination with the creatininase/ creatinase /sarcosinoxidase method                          | 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  | Schmidt, F.H., Klin. Wschr. <u>39</u> , 1244-1247 (1961); Roche working instructions   |
| Total bilirubin (TBIL)    | μmol/L | DPD method   | 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  | Weichselbaum, T.E., Amer. J. Clin. Path. <u>10</u> , 40 (1946); Roche working instructions   |
| Albumin (ALB)             | g/L    | bromocresol green method   | Dumas et al., Clin. Chim. Acta <u>31</u> , 87 (1971); Roche 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   | 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) | Siedel, J. et al., J. Clin. Chem. Clin. Biochem. <u>19</u> , 838 (1981); Roche working instructions  |

### 3.9.3. Urinalysis

The dry chemical reactions on test strips (Combur-10-test M, Roche, Mannheim, Germany) used to determine urine constituents semiquantitatively were evaluated with a reflection photometer (Meditron M; Roche, Mannheim, 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)                    | graduated tubes  |   |

### 3.9.4. Statistics of clinical pathology

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

The following table contains statistical analyses generally used in reports. This report will not necessarily use all statistical methods listed below. Details were explained in the summary tables in PART IB:

| Parameter  | Statistical test  | Markers in the tables                       | References  |
|--|---|---|---|
| Blood parameters   | For parameters with <b>bidirectional</b> changes:<br>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<br>For parameters with <b>unidirectional</b> changes:<br>Pairwise comparison of each dose group with the control group using the WILCOXON-test (one-sided) <b>with Bonferroni-Holm adjustment</b> for the hypothesis of equal medians | * for $p \leq 0.05$<br>** for $p \leq 0.01$ | SIEGEL, S. (1956):<br>Non-parametric statistics for the behavioural sciences.<br>McGraw-Hill New York<br><br>Holm (1979): A Simple Sequentially Rejective Multiple Test Procedure.<br>Scand. J. Statist. 6, 65-70 |
| 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   | * for $p \leq 0.05$<br>** for $p \leq 0.01$ | SIEGEL, S. (1956):<br>Non-parametric statistics for the behavioural sciences.<br>McGraw-Hill New York   |
| Urine pH, volume, specific gravity, color and turbidity                                    | 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. Urine color and turbidity are not evaluated statistically.  | * for $p \leq 0.05$<br>** for $p \leq 0.01$ | SIEGEL, S. (1956):<br>Non-parametric statistics for the behavioural sciences.<br>McGraw-Hill New York   |

### **3.10. PATHOLOGY**

#### **3.10.1. Necropsy**

The animals were sacrificed by decapitation under isoflurane anesthesia. The exsanguinated animals were necropsied and assessed by gross pathology.

#### **3.10.2. Organ weights**

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

1. Anesthetized animals
2. Adrenal glands
3. Brain
4. Epididymides
5. Heart
6. Kidneys
7. Liver
8. Ovaries
9. Spleen
10. Testes
11. Thymus
12. Thyroid glands
13. Uterus with cervix

#### **3.10.3. 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. Aorta
4. Bone marrow (femur)
5. Brain
6. Cecum
7. Cervix
8. Coagulating glands
9. Colon
10. Duodenum
11. Epididymides
12. Esophagus
13. Extraorbital lacrimal glands

14. Eyes with optic nerve (modified Davidson's solution)
15. Femur with knee joint
16. Harderian glands
17. Heart
18. Ileum
19. Jejunum (with Peyer's patches)
20. Kidneys
21. Larynx
22. Liver
23. Lungs
24. Lymph nodes (mesenteric and axillary lymph nodes)
25. Mammary gland (male and female)
26. Nose (nasal cavity)
27. Ovaries
28. Oviducts
29. Pancreas
30. Parathyroid glands
31. Pharynx
32. Pituitary gland
33. Prostate
34. Rectum
35. Salivary glands (mandibular and sublingual glands)
36. Sciatic nerve
37. Seminal vesicles
38. Skeletal muscle
39. Skin
40. Spinal cord (cervical, thoracic and lumbar cord)
41. Spleen
42. Sternum with marrow
43. Stomach (forestomach and glandular stomach)
44. Testes
45. Thymus
46. Thyroid glands
47. Trachea
48. Urinary bladder
49. Uterus
50. Vagina

### 3.10.4. Histopathology

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

| Organs  | Test group |            |            |            |
|---|------------|------------|------------|------------|
|   | 0          | 1          | 2          | 3          |
| 1. All gross lesions                                      | A2         | A2         | A2         | A2         |
| 2. Adrenal glands   | A1         | A1         | A1         | A1         |
| 3. Aorta  | A1         |            |            | A1         |
| 4. Bone marrow (femur)                                    | A1         |            |            | A1         |
| 5. Brain  | A1         |            |            | A1         |
| 6. Cecum  | A1         | A1         | A1         | A1         |
| 7. Cervix   | A1         |            |            | A1         |
| 8. Coagulating glands                                     | A1         |            |            | A1         |
| 9. Colon  | A1         |            |            | A1         |
| 10. Duodenum  | A1         |            |            | A1         |
| 11. Epididymides  | A1         |            |            | A1         |
| 12. Esophagus   | A1         |            |            | A1         |
| 13. Eyes with optic nerve                                 | A1         |            |            | A1         |
| 14. Heart   | A1         |            |            | A1         |
| 15. Ileum   | A1         |            |            | A1         |
| 16. Jejunum   | A1         |            |            | A1         |
| 17. Kidneys   | A1         | A1         | A1         | A1         |
| 18. Liver   | A1, B1, C1 | A1, B1, C1 | A1, B1, C1 | A1, B1, C1 |
| 19. Lung  | A1         |            |            | A1         |
| 20. Lymph nodes<br>(mesenteric and axillary lymph nodes)  | A1         |            |            | A1         |
| 21. Mammary gland, female                                 | A1         |            |            | A1         |
| 22. Mammary gland, male                                   | A1         | A1         | A1         | A1         |
| 23. Ovaries   | A1         |            |            | A1         |
| 24. Pancreas  | A1         |            |            | A1         |
| 25. Parathyroid glands                                    | A1         |            |            | A1         |
| 26. Peyer's patches                                       | A1         |            |            | A1         |
| 27. Pituitary gland                                       | A1         |            |            | A1         |
| 28. Prostate  | A1         |            |            | A1         |
| 29. Rectum  | A1         |            |            | A1         |
| 30. Salivary glands<br>(mandibular and sublingual glands) | A1         |            |            | A1         |

| Organs  | Test group |    |    |    |
|---|------------|----|----|----|
|   | 0          | 1  | 2  | 3  |
| 31. Sciatic nerve                                       | A1         |    |    | A1 |
| 32. Seminal vesicles                                    | A1         |    |    | A1 |
| 33. Skin  | A1         |    |    | A1 |
| 34. Spinal cord<br>(cervical, thoracic and lumbar cord) | A1         |    |    | A1 |
| 35. Spleen  | A1         | A1 | A1 | A1 |
| 36. Stomach<br>(forestomach and glandular stomach)      | A1         |    |    | A1 |
| 37. Testes  | A1         |    |    | 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 |

A = Hematoxylin and Eosin (H&E) stain

B = Cresyl violet stain

C =GSTP (Glutathione-S-Transferase p) immunohistochemical stain

1 = all animals/test group

2 = all animals affected/test group

Cresyl violet stain was used for better classification of basophilic foci and GSTP immunohistochemistry was used to better detect GSTP positive (eosinophilic) hepatocellular foci.

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.

#### Peer review

After completion of the histopathological assessment by the study pathologist an internal peer review was performed by Dr. Karin Küttler (BASF SE, Ludwigshafen, Germany) including cecum and spleen in animals of both sexes; adrenal glands, kidney and mammary gland of male animals and liver and uterus of females. Results presented in this 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 $p \leq 0.05$<br>** for $p \leq 0.01$ | HETTMANNSPERGER, T.P. (1984): Statistical Inference based on Ranks, John Wiley & Sons New York, 132-140.<br>International Mathematical and Statistical Libraries, Inc., 2500 Park West Tower One, Houston, Texas 77042-3020, USA, nakl-1 - nakl-3<br><br>MILLER, R.G. (1981): Simultaneous Statistical Inference, Springer-Verlag New York Inc., 165-167<br><br>NIJENHUIS, A. and S.W. WILF (1978): Combinatorial Algorithms, Academic Press, New York, 32-33 |



## 4. RESULTS

Throughout the chapter "results", the term "significant" implies that the inter-group differences have attained *statistical* significance ( $p \leq 0.05$ ) when compared with the control group.

### 4.1. ANALYSES

#### 4.1.1. Stability analyses

The stability of DHDPS in drinking water containing 1% carboxymethylcellulose in the refrigerator was demonstrated for a period of 7 days.

#### 4.1.2. Homogeneity control analyses

Considering the low relative standard deviation in the homogeneity analysis, it can be concluded that DHDPS was distributed homogeneously in drinking water containing 1% carboxymethylcellulose.

#### 4.1.3. Concentration control analyses

No test substance could be detected in the control samples (samples 2, 11, 14) with a concentration of  $\geq 30\%$  of the lowest calibration solution.

The mean values (samples 3-5 and samples 7-9) and single values (sample 6, sample 12 and samples 15-18) of DHDPS in 1% carboxymethylcellulose in drinking water were found to be in the range of 90-110% of the nominal concentrations.

These results demonstrated the correctness of the concentrations of DHDPS in 1% carboxymethylcellulose in drinking water.

#### 4.1.4. Food analyses

On the basis of duration of use and the analytical findings with respect to chemical and microbiological contaminants 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 number of microorganisms did not exceed  $1 \times 10^5$ /g food. Individual results can be found in the archives of the Experimental Toxicology and Ecology of BASF SE.

#### **4.1.5. Drinking water analyses**

On the basis of the analytical findings the drinking water was found to be suitable. German "Trinkwasserverordnung" (Drinking Water Regulation) served as a guideline for maximum tolerable contaminants. Individual results can be found in the archives of the Experimental Toxicology and Ecology of BASF SE.

#### **4.1.6. Bedding and enrichment analyses**

On the basis of the analytical findings the bedding and the enrichment are found to be suitable. Levels given in Lab. Animal, Nov-Dec 1979, pp. 24-34, served as a guideline for maximum tolerable contaminants. Individual results are to be found in the archives of the Experimental Toxicology and Ecology of BASF SE.

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## 4.2. CLINICAL EXAMINATIONS

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

### 4.2.1. Mortality

(Tables IA-1 - IA-2)

No animal died prematurely in the present study.

### 4.2.2. Clinical observations

(Tables IA-1 - IA-2)

Soft and discolored (light brown) feces were observed in all animals of test groups 3 (1000 mg/kg bw/d [600 mg/kg bw/d in males from day 70 onwards]) and 2 (300 mg/kg bw/d), starting on different days. The discoloration was first observed on study day 15 in male and female animals of test group 3 and on study days 84 and 85 in male and female animals of test group 2, respectively. Soft consistency was observed towards the end of the treatment period, i.e. on study day 83 in male and female animals of test group 3 and on study day 84 in male as well as on study day 85 in female animals of test group 2. These findings were assessed as being treatment-related.

For male animal No. 12 (100 mg/kg bw/d) the following findings were observed for a period of a few days, i.e. piloerection on study days 83 and 84, palpable mass through skin in the left axillary region from study days 83 to 87, and respiratory sounds from study days 83 to 85. These findings were most likely related to a gavage error but not related to the test substance.

Salivation after treatment from slight to moderate was observed in all male and in 9 of 10 female animals of test group 3 (1000 mg/kg bw/d [600 mg/kg bw/d in males from day 70 onwards]), in 9 of 10 male and all female animals of test group 2 (300 mg/kg bw/d) as well as in 6 of 10 male and 4 of 10 female animals of test group 1 (100 mg/kg bw/d). From the temporary, short appearance immediately after dosing (or shortly before) it was concluded that salivation was induced by a bad taste of the test substance or local affection of the upper digestive tract.

Note: For all animals clinical observations before treatment were inadvertently not performed on study days 0 and 7. However, Detailed Clinical Observations (DCO) were performed on the same days before administration.

Also, the examinations of male animal No. 36 study day 19 within 2 hours after treatment were inadvertently not performed. These deviations to the protocol did neither influence the quality nor the outcome of the study.

#### **4.2.3. Food consumption**

(Tables IA-3 - IA-6)

Food consumption in male animals of test group 3 (1000 mg/kg bw/d) was reduced compared to the control group from study day 7 to 70, with a maximum of -18% on study days 7 and 63. After the reduction of the dose (600 mg/kg bw/d from study day 70 onwards) the food consumption was within the usual range. This could clearly be stated as test substance-related. Food consumption of male animals of test groups 1 and 2 (100 and 300 mg/kg bw/d) was not influenced.

No test substance-related effects on food consumption were obtained in all dosed females (test groups 1-3 [100, 300 and 1000 mg/kg bw/d]). All values were within the range typical for animals of this strain and age.

#### **4.2.4. Water consumption**

No test substance-related, adverse changes with regard to water consumption were observed.

#### **4.2.5. Body weight data**

(Tables IA-7 - IA-14; Figures 4.2.5.1. and 4.2.5.2.)

Mean body weight of male animals in test group 3 (1000/ 600 [from day 70 onwards] mg/kg bw/d) was significantly lower compared to the control group during the entire administration period with a maximum of -20% on study day 70. In male animals of test group 2 (300 mg/kg bw/d) mean body weight was also decreased up to nearly -10% on study days 84 and 91. These findings were assessed as being related to treatment.

No deviations of toxicological concern in mean body weight were observed in male animals of test group 1 (100 mg/kg bw/d).

Relevant changes in mean body weight were not observed in female animals of all treatment-groups during the entire administration period.

Mean body weight change values of male animals in test group 3 (1000/ 600 [from day 70 onwards] mg/kg bw/d) were significantly lower during the entire administration period with a maximum of -33% from study day 0 to 63. In male animals of test group 2 (300 mg/kg bw/d) mean body weight change values were also decreased from study day 77 onwards with a maximum of -15% from study day 0 to 84 as well as study days 0 to 91. These findings were assessed as being related to treatment.

No relevant deviations in mean body weight change were observed in male animals of test group 1 (100 mg/kg bw/d).

Relevant changes in mean body weight change were also not observed in female animals of all treatment-groups during the entire administration period.

Figure 4.2.5.1.: Mean body weights of male animals

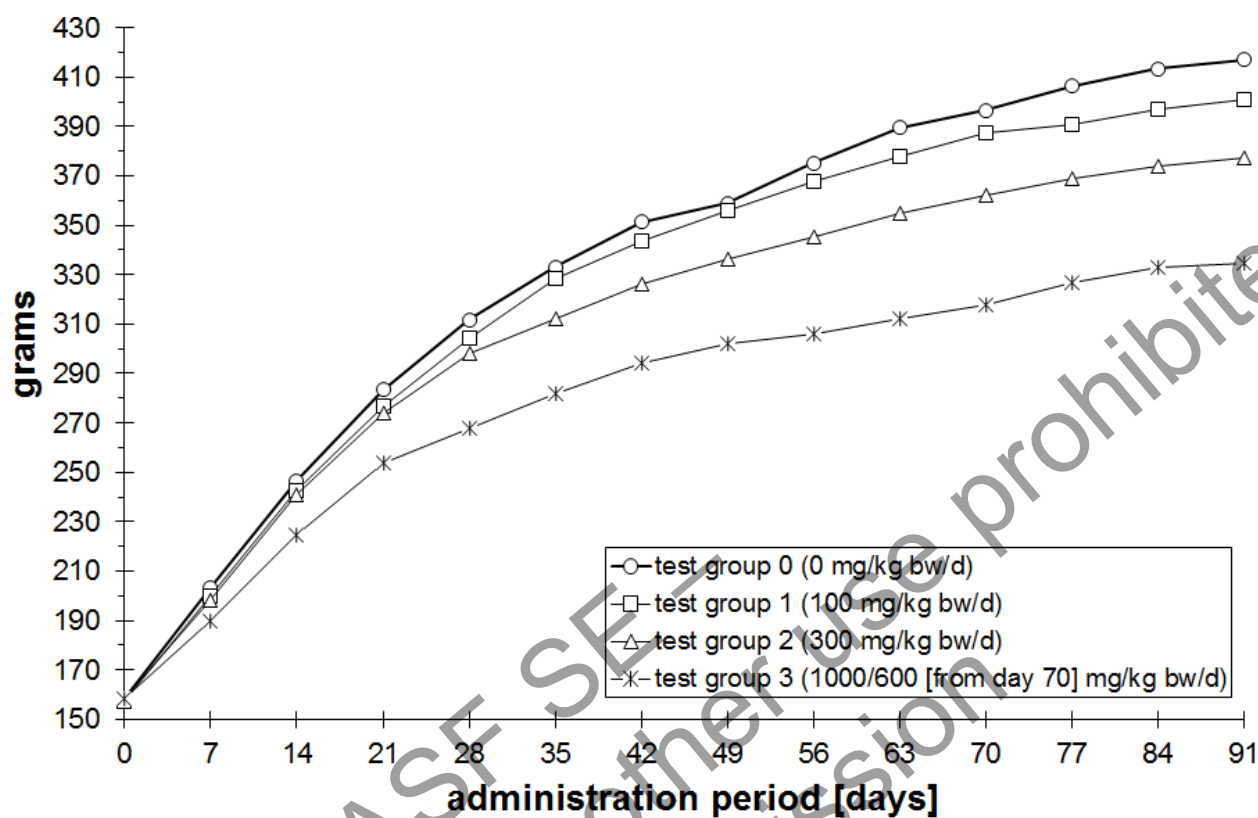
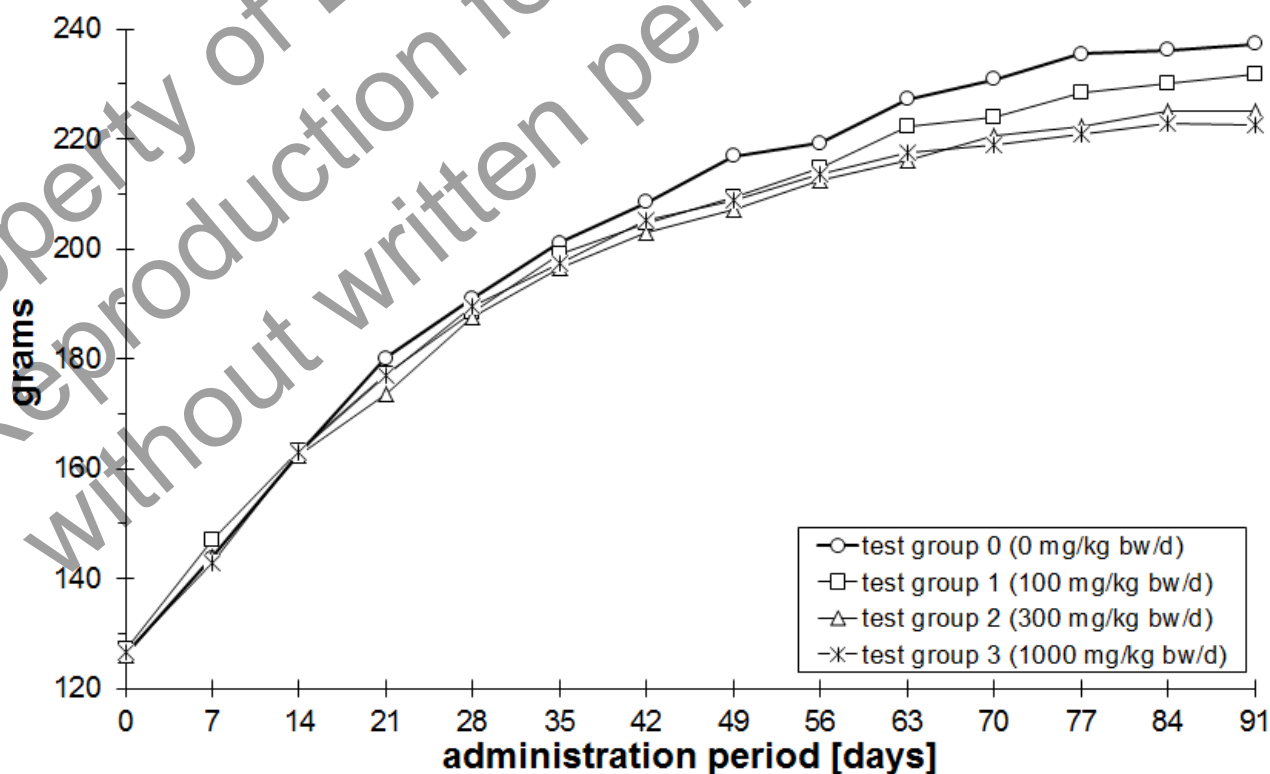


Figure 4.2.5.2.: Mean body weights of female animals



**4.2.6. Functional observational battery**

(Tables IA-15 - IA-30)

Deviations from "zero values" were obtained in several animals. However, as most findings were equally distributed between test-substance treated groups and controls, were without a dose-response relationship or occurred in single animals only, these observations were considered to have been incidental.

The following examinations were performed during FOB and have to be assessed individually:

*Home cage observations:*

(Males: table IA-15; females: table IA-22)

No test substance-related effects were observed in male and female animals of test groups 1-3 (100, 300 and 1000 [600 in males from day 70 onwards] mg/kg bw/d).

*Open field observations:*

(Males: tables IA-16 - IA-19; females: tables IA-23 - IA-26)

Male animal Nos. 25 and 28 of test group 2 (300 mg/kg bw/d) showed soft and light brown discolored feces. These findings were assessed to be test substance-related.

No test substance-related effects were observed in all other male and female animals of test groups 1-3 (100, 300 and 1000 mg/kg bw/d).

*Sensorimotor tests/ reflexes:*

(Males: tables IA-20 - IA-21; females: tables IA-27 - IA-28)

No test substance-related effects were observed in male and female animals of test groups 1-3 (100, 300 and 1000 [600 in males from day 70 onwards] mg/kg bw/d).

*Quantitative parameters:*

(Males: table IA-29; females: table IA-30)

Grip strength of forelimbs was significantly reduced in male animals of test group 3 (1000/600 [from day 70 onwards] mg/kg bw/d). As grip strength of hindlimbs as well as foot-splay test were not significantly altered, the finding was assessed as being incidental.

No significant changes were observed in male animals of test groups 1 and 2 (100 and 300 mg/kg bw/d) as well as in female animals of test groups 1-3 (100, 300 and 1000 mg/kg bw/d).

#### 4.2.7. Motor activity measurement

(Tables IA-31 - IA-34; Figures 4.2.7.1. and 4.2.7.2.)

Regarding the overall motor activity, no test substance-related deviations to the control were noted for male and female animals of test groups 1-3 (100, 300 and 1000 [600 in males from day 70 onwards] mg/kg bw/d).

Single interval No. 12 of male animals in test groups 3 (1000/600 [from day 70 onwards] mg/kg bw/d) and 2 (300 mg/kg bw/d) was significantly increased. Single interval No. 1 of female animals in test groups 2 and 3 (300 and 1000 mg/kg bw/d) was significantly decreased.

These individual changes were assessed as being incidental and not related to treatment as no other single intervals as well as the overall motor activity were affected.

Figure 4.2.7.1.: Motor activity measurement in male animals

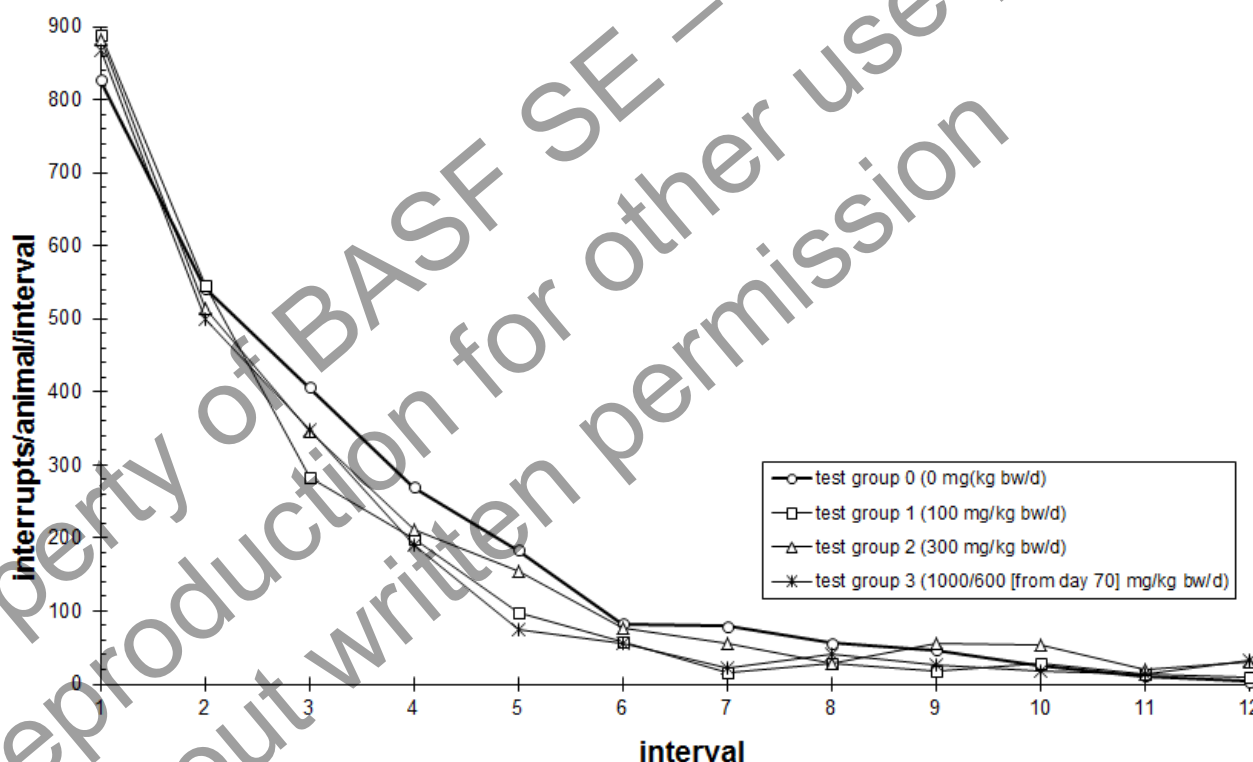
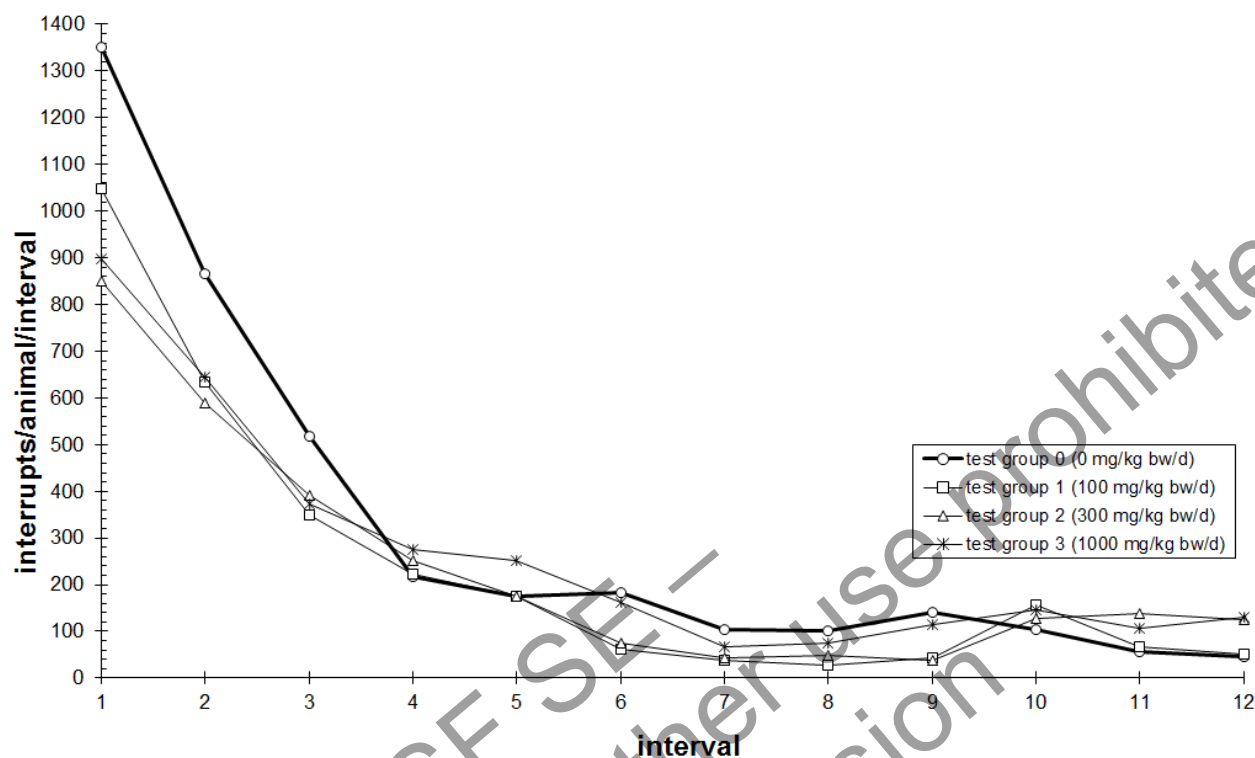


Figure 4.2.7.2.: Motor activity measurement in female animals



#### 4.2.8. Ophthalmological examinations (Tables IA-35 - IA-36)

No treatment-related findings were observed.

All apparent findings were assessed as being incidental in nature since they occurred in individual animals only and did not show a dose-response relationship.



### 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.

#### 4.3.1. Hematology

(Tables IB-1 - IB-2 Red blood cell + coagulation parameters)

(Tables IB-3 - IB-4 White blood cell parameters)

At the end of the administration period in rats of both sexes of test group 3 (females 1000, males 1000/600 mg/kg bw/d), red blood cell (RBC) counts and hemoglobin values were decreased. Additionally, in females of this test group hematocrit values were decreased and in males mean corpuscular volume (MCV) and relative reticulocyte counts were increased. In females of test groups 2 and 3 (300 and 1000 mg/kg bw/d), mean corpuscular hemoglobin concentration (MCHC) was decreased, but the values were within the historical control range (MCHC 20.77-23.82 mmol/L; PART III, Supplement) and therefore, this alteration was regarded as incidental and not treatment-related.

In females of test group 3 (1000 mg/kg bw/d) prothrombin time (Hepatoquick's test, HQT) was prolonged.

In males of test groups 2 and 3 (300 and 1000/600 mg/kg bw/d) total white blood cell (WBC) counts, absolute and relative lymphocyte counts and absolute large unstained cell (LUCA) counts were decreased whereas relative neutrophil counts were increased. All values were within historical control ranges or marginally beyond this range (relative neutrophil counts 26.0%; relative lymphocyte counts 69.6%; historical control ranges WBC 3.71-6.49 Giga/L, absolute lymphocytes 2.68-5.11 Giga/L, relative lymphocytes 69.8-81.8%, absolute large unstained cells 0.01-0.04 Giga/L, relative neutrophils 13.3-25.5%; PART III, Supplement) and therefore, the changes were regarded as incidental and not treatment-related.

In females of test group 3 (1000 mg/kg bw/d) absolute eosinophil counts and relative basophil counts were decreased. There exists no patho-physiological correlate to decreased basophil counts. Therefore, at least lower relative basophil cell counts were regarded as being not toxicologically relevant.

#### 4.3.2. Clinical chemistry

(Tables IB-5 - IB-6 Enzymes)

(Tables IB-7 - IB-8 Substrates)

(Tables IB-9 - IB-10 Electrolytes + minerals)

At the end of the administration period, in males of test groups 2 and 3 (300 and 1000/600 mg/kg bw/d) cholesterol levels were decreased and triglyceride levels were increased, and additionally in males of test group 1 (100 mg/kg bw/d) triglyceride levels were increased. However triglyceride levels of test groups 1 and 2 were not dose-dependently changed and

cholesterol values in test group 2 were the only relevantly changed parameter in this test group. Therefore, triglyceride level changes in test group 1 and 2 were regarded as incidental and cholesterol level alterations in test group 2 were regarded as treatment-related, but not adverse (ECETOC Technical Report No. 85, 2002). In males of test group 3 (1000/600 mg/kg bw/d) creatinine values were increased and total bilirubin values were decreased. In males of test group 1 (100 mg/kg bw/d) creatinine levels were decreased, but this alteration was regarded as being not toxicologically relevant. In rats of both sexes of test group 3 (females 1000, males 1000/600 mg/kg bw/d) chloride levels were decreased. This was also true for males of test group 1 (100 mg/kg bw/d), but this parameter was not dose-dependently changed and, therefore, the decrease in test group 1 was regarded as incidental and not treatment-related. In females of test group 3 (1000 mg/kg bw/d) alkaline phosphatase activities were slightly increased.

Some other parameters were altered but the means were within historical control ranges: alanine aminotransferase (ALT) activity increases in males of test group 2 (300 mg/kg bw/d); glucose level decreases in males of test groups 2 and 3 (300 and 1000/600 mg/kg bw/d) and glucose values increases in females of test group 3 (1000 mg/kg bw/d); inorganic phosphate level increases in males of test group 3 (1000/600 mg/kg bw/d); historical control ranges males: ALT 0.46-0.94  $\mu$ kat/L; glucose 5.11-7.16 mmol/L; inorganic phosphate 1.36-1.96 mmol/L; females: glucose 4.93-6.22 mmol/L; PART III, Supplement. In males of test group 2 (300 mg/kg bw/d) urea levels were decreased, but this alteration was not dose-dependent. Therefore, all mentioned changes were regarded as incidental and not treatment-related.

#### 4.3.3. Urinalyses

(Table IB-11 - IB-14)

No treatment-related changes among urinalysis parameters were observed.

In males of test groups 1, 2 and 3 (100, 300 and 1000/600 mg/kg bw/d), pH values of the urine were lower than in controls. In females of test group 3 (1000 mg/kg bw/d) urine volume was higher compared to controls. Both alterations per se without any other changes in urine or kidney parameters were regarded as not toxicologically relevant.

#### 4.4. PATHOLOGY

Summary tables of the results can be found in Part C of PART I; individual tables can be found in Part C of PART II.

##### 4.4.1. Weight parameters (Tables IC-1 - IC-8)

###### Absolute weights

When compared with the control group 0 (set to 100%), the following mean absolute weights were significantly increased or decreased in one or more test groups (statistically significant changes printed in bold):

| Test group<br>(mg/kg bw/d) | Male animals |              |                 | Female animals |            |               |
|----------------------------|--------------|--------------|-----------------|----------------|------------|---------------|
|                            | 1<br>(100)   | 2<br>(300)   | 3<br>(1000/600) | 1<br>(100)     | 2<br>(300) | 3<br>(1000)   |
| Terminal body weight       | 96%          | <b>91%**</b> | <b>79%**</b>    |                |            |               |
| Adrenal glands             | 92%          | 99%          | <b>140%**</b>   | 98%            | 114%       | <b>123%**</b> |
| Brain                      | <b>95%**</b> | <b>94%**</b> | <b>94%**</b>    | 99%            | 99%        | <b>95%*</b>   |
| Epididymides               | 96%          | 93%          | <b>89%**</b>    |                |            |               |
| Heart                      | 93%          | <b>92%*</b>  | <b>86%**</b>    |                |            |               |
| Kidneys                    |              |              |                 | 99%            | 106%       | <b>110%*</b>  |
| Liver                      |              |              |                 | 106%           | 111%       | <b>138%**</b> |
| Spleen                     | 93%          | <b>85%**</b> | 95%             |                |            |               |
| Testes                     | 99%          | <b>93%*</b>  | <b>92%*</b>     |                |            |               |
| Thymus                     | 82%          | 83%          | <b>69%**</b>    | 96%            | 81%        | <b>73%**</b>  |

\*:  $p \leq 0.05$ , \*\*:  $p \leq 0.01$

All other mean absolute weight parameters did not show significant differences when compared to the control group 0.

###### Relative organ weights

When compared with the control group 0 (set to 100%), the following mean relative organ weights were significantly increased or decreased in one or more test groups (statistically significant changes printed in bold):

| Test group<br>(mg/kg bw/d) | Male animals |               |                 | Female animals |               |               |
|----------------------------|--------------|---------------|-----------------|----------------|---------------|---------------|
|                            | 1<br>(100)   | 2<br>(300)    | 3<br>(1000/600) | 1<br>(100)     | 2<br>(300)    | 3<br>(1000)   |
| Adrenal glands             | 96%          | 109%          | <b>177%**</b>   | 101%           | <b>121%*</b>  | <b>131%**</b> |
| Brain                      | 100%         | 103%          | <b>120%**</b>   |                |               |               |
| Epididymides               | 101%         | 103%          | <b>112%**</b>   |                |               |               |
| Heart                      | 98%          | 101%          | <b>109%*</b>    | 101%           | 107%          | <b>109%*</b>  |
| Kidneys                    | <b>110%*</b> | <b>122%**</b> | <b>125%**</b>   | 102%           | <b>113%*</b>  | <b>118%**</b> |
| Liver                      | 98%          | 104%          | <b>118%**</b>   | 109%           | <b>120%**</b> | <b>149%**</b> |
| Ovaries                    |              |               |                 | 102%           | 109%          | <b>130%*</b>  |

| Test group<br>(mg/kg bw/d) | Male animals |            |                 | Female animals |               |               |
|----------------------------|--------------|------------|-----------------|----------------|---------------|---------------|
|                            | 1<br>(100)   | 2<br>(300) | 3<br>(1000/600) | 1<br>(100)     | 2<br>(300)    | 3<br>(1000)   |
| Spleen                     | 97%          | 94%        | <b>119%**</b>   | 105%           | <b>113%**</b> | <b>111%*</b>  |
| Testes                     | 104%         | 102%       | <b>116%**</b>   |                |               |               |
| Thymus                     |              |            |                 | 100%           | 87%           | <b>79%*</b>   |
| Thyroid glands             | 89%          | 104%       | <b>116%*</b>    | 92%            | 105%          | <b>121%**</b> |

\*:  $p \leq 0.05$ , \*\*:  $p \leq 0.01$

All other mean relative weight parameters did not show significant differences when compared to the control group 0.

The decrease in terminal body weight was dose-dependent and considered treatment-related in male animals.

The increase in absolute (test group 3) and relative (test groups 2 and 3) liver weights was regarded as treatment-related in females and correlated with histopathology. In males, the increase in relative liver weights in test group 3 (1000/600 [from day 70 onwards] mg/kg bw/d) was not accompanied by histopathologic findings but was outside the historical control range (this study: 2.676%, range of historical controls: 2.063 - 2.39%).

Weight increases (absolute and relative) in the adrenal gland of test group 3 animals of both sexes were likely treatment-related although a histopathological correlate was only detected in males of test group 3. The increase in absolute (not significantly) and relative weights in test group 2 females were assessed to be incidental as the weights were within the historical control range (absolute weight - this study: 74.6 mg, range of historical controls: 63.7 – 83.2 mg; relative weight - this study: 0.036%, range of historical controls: 0.03 – 0.037%).

In the spleen, relative weights were increased in test group 3 males and test group 2 and 3 females, which correlated histopathologically with increased extramedullary hematopoiesis and were therefore considered treatment-related. The decrease of absolute spleen weight in test group 2 males was not dose-dependent and was considered to be incidental.

The decrease in thymus weight was not accompanied by histopathologic findings in females and was of questionable significance. The decrease in absolute thymus weights in males of all treatment groups was considered to be secondary to the body weight reduction; there were no significant changes in relative weights.

The statistically significant decrease in absolute and increase in relative weights of brain, epididymis, heart and testis in male animals of one or more treatment groups and decrease of absolute brain and increase of relative heart weights in females of test group 3 was likely due to the decrease in terminal body weight (not significant in females (-6% test group 2 and -7% in test group 3).

The weight changes in the kidney were most likely also related to the decreased terminal body weight in males of all treatment groups as the histopathologically observed mineralization at the medulla/cortical junction was not believed to correlate with the weight change. In females, there was no histopathological correlate to the increased kidney weights in test groups 2 and 3, therefore this was considered of equivocal significance.

The increased weights of the ovaries of test group 3 females were assessed as treatment-related as both absolute and relative weights were outwith the historical control range (this study absolute / relative 126 mg / 0.061%, historical control range absolute / relative 80.7 - 113.8 mg / 0.036 - 0.051%). There were no correlating histopathological findings.

There were no histopathological findings in the thyroid glands of test group 3 male and female animals. The weight change was therefore regarded as incidental.

#### 4.4.2. Gross lesions

(Table IC-9)

The cecum was dilated in all male animals of test group 3 (1000/600 [from day 70 onwards] mg/kg bw/d).

The liver was enlarged in 8 of 10 females of test group 3 (1000 mg/kg bw/d).

All other findings were considered to be incidental or spontaneous in origin and without any relation to treatment.

#### 4.4.3. Histopathology

(Tables IC-10 - IC-15)

Treatment-related findings were observed in cecum and spleen in animals of both sexes; in adrenal glands, kidney and mammary gland in male animals and in the liver in females. A possibly treatment-related finding was noted in the uterus of females.

#### Cecum

Both male and female animals of test group 3 (1000/600 or 1000 mg/kg bw/d, respectively) showed dilation of the cecum, characterized by a greater circumference of the cecal wall as compared to controls. A minimally increased number of apoptotic bodies were observed in the mucosa of treated animals.

| Test group<br>(mg/kg bw/d) | Male animals |            |            |                     | Female animals |            |            |             |
|----------------------------|--------------|------------|------------|---------------------|----------------|------------|------------|-------------|
|                            | 0<br>(0)     | 1<br>(100) | 2<br>(300) | 3<br>(1000/<br>600) | 0<br>(0)       | 1<br>(100) | 2<br>(300) | 3<br>(1000) |
| No. of animals             | 10           | 10         | 10         | 10                  | 10             | 10         | 10         | 10          |
| Dilation                   |              |            |            | 10                  |                |            | 1          | 10          |
| • Present                  |              |            |            | 10                  |                |            | 1          | 10          |
| Apoptosis,<br>increased    |              | 3          | 4          | 7                   |                | 1          | 4          | 7           |
| • Grade 1                  |              | 3          | 4          | 7                   |                | 1          | 4          | 7           |

### Spleen

Increased extramedullary hematopoiesis (mainly with reticulocytes) was observed in the spleen of both male and female animals with incidence and grading as shown in the table below:

|                                  | Male animals |            |            |                     | Female animals |            |            |             |
|----------------------------------|--------------|------------|------------|---------------------|----------------|------------|------------|-------------|
| Test group<br>(mg/kg bw/d)       | 0<br>(0)     | 1<br>(100) | 2<br>(300) | 3<br>(1000/<br>600) | 0<br>(0)       | 1<br>(100) | 2<br>(300) | 3<br>(1000) |
| No. of animals                   | 10           | 10         | 10         | 10                  | 10             | 10         | 10         | 10          |
| Hematopoiesis,<br>extramedullary |              |            |            | 8                   | 2              | 1          | 4          | 10          |
| • Grade 1                        |              |            |            | 5                   | 2              | 1          | 4          | 3           |
| • Grade 2                        |              |            |            | 3                   |                |            |            | 7           |

### Adrenal glands

Male animals of test group 3 (1000/600 [from day 70 onwards] mg/kg bw/d) showed an increased thickness of the cortex of the adrenal gland, which was attributed to both hypertrophy and hyperplasia of cortical cells. This finding was assumed to have caused the weight increase of the adrenal glands in this test group.

|                                   | Male animals |            |            |                 |
|-----------------------------------|--------------|------------|------------|-----------------|
| Test group<br>(mg/kg bw/d)        | 0<br>(0)     | 1<br>(100) | 2<br>(300) | 3<br>(1000/600) |
| No. of animals                    | 10           | 10         | 10         | 10              |
| Hypertrophy/hyperplasia, cortical |              |            |            | 8               |
| • Present                         |              |            |            | 8               |

### Kidneys

Male animals of all test groups showed multifocal mineralization of tubules in the junction between cortex and medulla (termed “mineralization, medulla” in the incidence tables).

Incidence and grading are shown in the table below.

|                            | Male animals |            |            |                 |
|----------------------------|--------------|------------|------------|-----------------|
| Test group<br>(mg/kg bw/d) | 0<br>(0)     | 1<br>(100) | 2<br>(300) | 3<br>(1000/600) |
| No. of animals             | 10           | 10         | 10         | 10              |
| Mineralization, medulla    |              | 7          | 9          | 6               |
| • Grade 1                  |              | 4          | 6          | 6               |
| • Grade 2                  |              | 3          | 2          |                 |
| • Grade 3                  |              |            | 1          |                 |

### Mammary gland

The mammary gland of test group 2 and 3 males showed a change from the physiological lobulo-alveolar morphology to a tubulo-alveolar appearance with smaller, more basophilic epithelial lining cells diagnosed as “atrophy” as described in Rudmann et al. (2012).

|                            | Male animals |            |            |                 |
|----------------------------|--------------|------------|------------|-----------------|
| Test group<br>(mg/kg bw/d) | 0<br>(0)     | 1<br>(100) | 2<br>(300) | 3<br>(1000/600) |
| No. of animals             | 10           | 10         | 10         | 10              |
| Atrophy, (multi)focal      |              |            | 7          | 10              |
| • Grade 1                  |              |            | 7          |                 |
| • Grade 2                  |              |            |            | 4               |
| • Grade 3                  |              |            |            | 2               |
| • Grade 4                  |              |            |            | 3               |
| • Grade 5                  |              |            |            | 1               |

### Liver

On examination of HE stained slides of the liver of female animals, a dose-dependent increase in incidence and severity of centrilobular hypertrophy was noted as shown in the table below.

| HE                         | Female animals |            |            |             |
|----------------------------|----------------|------------|------------|-------------|
| Test group<br>(mg/kg bw/d) | 0<br>(0)       | 1<br>(100) | 2<br>(300) | 3<br>(1000) |
| No. of animals             | 10             | 10         | 10         | 10          |
| Hypertrophy, centrilobular |                | 2          | 5          | 10          |
| • Grade 1                  |                | 1          | 1          |             |
| • Grade 2                  |                | 1          | 3          |             |
| • Grade 3                  |                |            | 1          | 10          |

Furthermore, there was an increased incidence of foci of hepatocellular alteration (especially the eosinophilic type) in test group 3 females, which was also confirmed by an increased incidence of GSTP positive foci in immunohistochemistry. Incidence and grading are given in the tables below.

| HE                           | Female animals |            |            |             |
|------------------------------|----------------|------------|------------|-------------|
| Test group (mg/kg bw/d)      | 0<br>(0)       | 1<br>(100) | 2<br>(300) | 3<br>(1000) |
| No. of animals               | 10             | 10         | 10         | 10          |
| Focus of cellular alteration | 1              | 1          | 1          | 6           |
| -Eosinophilic                |                | 1          |            | 6           |
| • Present                    |                | 1          |            | 6           |
| -Basophilic (NOS)            |                |            |            | 1           |
| • Present                    |                |            |            | 1           |
| - Basophilic diffuse         |                |            |            | 2           |
| • Present                    |                |            |            | 2           |
| - Basophilic tigroid         | 1              |            | 1          |             |
| • Present                    | 1              |            | 1          |             |

With an immunohistochemical stain against GSTP, both single scattered positive cells in a centrilobular distribution and positive foci (distinct aggregates of positive hepatocytes) were detected with incidence and grading as shown in the table below:

| GSTP stain                 | Female animals |            |            |             |
|----------------------------|----------------|------------|------------|-------------|
| Test group (mg/kg bw/d)    | 0<br>(0)       | 1<br>(100) | 2<br>(300) | 3<br>(1000) |
| No. of animals             | 10             | 10         | 10         | 10          |
| GSTP+ cells, centrilobular | 1              | 2          | 4          | 9           |
| • Grade 1                  |                |            | 2          | 4           |
| • Grade 2                  |                |            | 1          |             |
| • Grade 3                  | 1              | 1          | 1          | 5           |
| • Grade 4                  |                | 1          |            |             |
| GSTP+ focus, (multi)focal  | 1              | 1          | 1          | 6           |
| • Present                  | 1              | 1          | 1          | 6           |

No treatment-related findings were observed histopathologically in the liver of male animals.



**Uterus**

Focal squamous metaplasia of the uterine glandular epithelium was noted with an increased incidence in treated female animals, which might be treatment-related.

|                                    | Female animals |            |            |             |
|------------------------------------|----------------|------------|------------|-------------|
| Test group<br>(mg/kg bw/d)         | 0<br>(0)       | 1<br>(100) | 2<br>(300) | 3<br>(1000) |
| No. of animals                     | 10             | 10         | 10         | 10          |
| Metaplasia, squamous, (multi)focal |                | 2          | 2          | 5           |
| • Grade 1                          |                | 2          | 2          | 4           |
| • Grade 2                          |                |            |            | 1           |

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.

## 5. DISCUSSION

DHDPS was administered by gavage to groups of 10 male and 10 female Wistar rats at dose levels of 0 (test group 0), 100 (test group 1), 300 (test group 2) and 1000 mg/kg bw/d (test group 3) over a period of 3 months. Due to severely impaired body weight development in male animals of test group 3 (1000 mg/kg bw/d), i.e. -20% on study day 63, the male animals were treated at a dose level of 600 mg/kg bw/d from study day 70 onwards. Female animals were continuously treated at limit dose. Drinking water containing 1% carboxymethylcellulose served as vehicle.

With regard to clinical examinations, signs of general systemic toxicity were observed in male animals of test group 3 (1000 [600 in males from day 70 onwards] mg/kg bw/d) indicated by significantly lower mean body weights and body weight change values in parallel to a slightly decreased food consumption between study days 0 and 70. In addition, male animals of test groups test group 2 (300 mg/kg bw/d) showed significantly impaired body weight parameter whereas no affection was observed in male animals of test group 1 (100 mg/kg bw/d). No clinical signs with regard to body weights or food consumption were observed in female animals of test groups 1-3 (100, 300 and 1000 mg/kg bw/d).

Soft and discolored (light brown) feces were observed in all animals of test groups 2 and 3 (300 and 1000 mg/kg bw/d [600 mg/kg bw/d in males from day 70 onwards]) starting on different days. These findings were assessed as being treatment-related.

Salivation after treatment was observed in most animals of test group 2 and 3 (300 and 1000 mg/kg bw/d [600 mg/kg bw/d in males from day 70 onwards]) as well as in 6 of 10 male and 4 of 10 female animals of test group 1 (100 mg/kg bw/d). From the temporary, short appearance immediately after dosing (or shortly before) it was concluded that salivation was induced by a bad taste of the test substance or local affection of the upper digestive tract. The effect was assessed to be non-adverse.

Regarding clinical pathology decreased red blood cell parameters in rats of both sexes of test group 3 (1000 mg/kg bw/d [600 mg/kg bw/d in males from day 70 onwards]); in both sexes decreased red blood cell (RBC) counts and hemoglobin values and additionally in females decreased hematocrit values) indicated an anemia. A regenerative anemia could be assumed by higher relative reticulocyte counts at least in males. Low total bilirubin levels in males of this test group could be due to the anemic status.

Secondly, an affection of the liver cell metabolism was indicated by decreased synthesis of coagulation factors (leading to a prolonged prothrombin time) and marginally higher alkaline phosphatase (ALP) activities in females as well as lower cholesterol and higher triglyceride levels in males of test group 3 (1000 mg/kg bw/d [600 mg/kg bw/d in males from day 70 onwards]). Lower chloride levels in males and females of this test group were due to a metabolic alkalosis. At least in males of test group 3 higher creatinine levels may be a hint of a functional renal insufficiency, although a higher skeletal muscle activity can also be the cause of this alteration. Low absolute eosinophil counts in females of test group 3 reflect a stress situation in these individuals.

Regarding pathology, target organs were adrenal glands, cecum, liver, and spleen in animals of both sexes; kidney and mammary gland in male animals and uterus and ovaries in females.

In the **cecum**, dilation was noted macroscopically in all males in test group 3 and histologically in all males and females in test group 3 (1000 mg/kg bw/d [600 mg/kg bw/d in males from day 70 onwards]) and in one female in test group 2 (300 mg/kg bw/d). Slightly dose-dependently increased incidence of apoptosis in the mucosa of the cecum was seen in all test groups in both sexes. The functional consequences of this are not clear; a contribution to the decreased body weight in males cannot be excluded.

Increased extramedullary hematopoiesis in the **spleen** was noted in males of test group 3 (1000 mg/kg bw/d [600 mg/kg bw/d in males from day 70 onwards]) and females of test groups 1, 2 and 3 (100, 300 and 1000 mg/kg bw/d). Correlating this finding with clinical pathology, this was assessed as a regenerative anemia in animals of test group 3 and, therefore, regarded to be adverse.

A weight increase was noted for the **adrenal glands** of male and female animals in test group 3 (1000 mg/kg bw/d [600 mg/kg bw/d in males from day 70 onwards]), which correlated with hypertrophy/hyperplasia in the cortex of male animals only. These findings in the adrenal glands were regarded as treatment-related and adverse.

Multifocal mineralization of **kidney** tubules in the junction between cortex and medulla was noted in males of all treatment groups. This is a very rare finding in males but occurs frequently in female animals. Because there were no degenerative findings in these kidneys, and in females it is also not associated with degenerative findings, it was regarded as non-adverse.

In the **mammary gland** of treated male animals of test groups 2 and 3, a change from the physiological lobulo - alveolar morphology to a tubulo-alveolar appearance with smaller more basophilic epithelial lining cells (atrophy) was seen. In the literature (Rudmann et al., 2012), the occurrence of atrophy has been correlated to altered hormone levels (increased prolactin or decreased androgen) or with emaciation in male animals. This finding was regarded as adverse.

In the **liver** of female animals, a dose-dependent centrilobular hypertrophy was seen in 2/10, 5/10, and 10/10 animals in test group 1, 2 and 3 respectively, graded minimal in test group 1 to moderate in test group 3 animals correlating with the macroscopic finding "enlarged" in test group 3 and with increased liver weights in test groups 2 and 3.

In the livers of test group 3 females, there was also an increased incidence of mainly eosinophilic foci of hepatocellular alteration, which were confirmed by GSTP immunohistochemistry, and considered to be adverse. The hypertrophy in the liver in combination with the increased liver weight of test group 3 females was assessed as adverse due to the presence of these foci. The hypertrophy alone in test groups 1 and 2 was assessed as non-adverse as no concurrent findings in clinical pathology were noted.

The increased relative liver weight in test group 3 males was assessed as adverse together with clinical pathology findings.

In the **uterus**, focal squamous cell metaplasia of glandular epithelium was observed in 2 females of each test groups 1 and 2 and in 5 of 10 females of test group 3. This finding was assessed as possibly treatment-related and adverse due to the higher incidence in test group 3 females. For test group 1 and 2 animals the finding was assessed as non-adverse as it can occur in single animals in control groups.

The increased weights of the **ovaries** of test group 3 females were assessed as treatment-related although there were no correlating histopathological findings. This finding was regarded as adverse.

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.

## 6. CONCLUSION

The administration of DHDPS by gavage to male and female Wistar rats for 3 months caused test substance-related adverse signs of systemic toxicity at a dose level of 300 mg/kg bw/d and above in male animals and at a dose level of 1000 mg/kg bw/d in female Wistar rats. Therefore, under the conditions of the present study the no observed adverse effect level (NOAEL) was 100 mg/kg bw/d in male and 300 mg/kg bw/d in female Wistar rats.

## 7. REFERENCES

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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 CLINICAL EXAMINATIONS

|                      |   |  |
|----------------------|---|--|
| %                    | = | percent                                    |
| %dev                 | = | deviation in percent                       |
| Animal No.           | = | animal number                              |
| anm                  | = | animal                                     |
| AT                   | = | after treatment                            |
| BT                   | = | before treatment                           |
| Bw or bw             | = | body weight                                |
| cm                   | = | centimeter                                 |
| Control              | = | control animals                            |
| d                    | = | day  |
| DCO                  | = | detailed clinical observation              |
| Deviation Vs Control | = | deviation versus control in percent        |
| F                    | = | female animals                             |
| FST                  | = | landing foot-splay test                    |
| g                    | = | weight in gram                             |
| GS F                 | = | grip strength forelimbs                    |
| GS H                 | = | grip strength hindlimbs                    |
| h                    | = | hour                                       |
| Interr.              | = | beam Interrupts                            |
| Interv.              | = | Interval                                   |
| kg or KG             | = | kilogram                                   |
| M                    | = | male animals or mean value                 |
| mg/kg bw/d           | = | milligrams per kilogram bodyweight per day |
| mg or MG             | = | milligram                                  |
| min.                 | = | minute                                     |
| N                    | = | number of animals for determining M and SD |
| NaCl                 | = | sodium chloride                            |
| NAD                  | = | nothing abnormal detected                  |
| NM                   | = | not measured                               |
| ppm                  | = | parts per million                          |
| Rear                 | = | rearing                                    |
| S.d. or SD           | = | standard deviation                         |
| Vs                   | = | versus                                     |

Abbreviations/ ranking described in the tables of functional observational batteries are explained in PART III (Supplement): "Functional Observational Battery (FOB): Detailed description of examinations, ranking and documentation procedures".

## 8.2. LIST OF ABBREVIATIONS USED IN TABLES CLINICAL PATHOLOGY

### CLINICAL PATHOLOGY:

|    |                      |
|----|----------------------|
| SD | = standard deviation |
| N  | = number of values   |

### HEMATOLOGY:

|        |   |
|--------|---|
| WBC    | = white blood cells (leukocytes)            |
| RBC    | = red blood cells (erythrocytes)            |
| HGB    | = hemoglobin                                |
| HCT    | = hematocrit                                |
| MCV    | = mean corpuscular volume                   |
| MCH    | = mean corpuscular hemoglobin               |
| MCHC   | = mean corpuscular hemoglobin concentration |
| PLT    | = platelets                                 |
| RETI   | = reticulocytes                             |
| NEUT   | = polymorphonuclear neutrophils             |
| LYMPH  | = lymphocytes                               |
| MONO   | = monocytes                                 |
| EOS    | = eosinophils                               |
| BASO   | = basophils                                 |
| LUC    | = large unstained cells                     |
| NEUTA  | = polymorphonuclear neutrophils (absolute)  |
| LYMPHA | = lymphocytes (absolute)                    |
| MONOA  | = monocytes (absolute)                      |
| EOSA   | = eosinophils (absolute)                    |
| BASOA  | = basophils (absolute)                      |
| LUCA   | = large unstained cells (absolute)          |
| ANISO  | = anisocytosis                              |
| MICRO  | = microcytosis                              |
| MACRO  | = macrocytosis                              |
| VAR    | = anisochromasia                            |
| HYPO   | = hypochromasia                             |
| HYPER  | = hyperchromasia                            |
| HQT    | = prothrombin time (Hepato Quick's test)    |

### CLINICAL CHEMISTRY:

|      |  |
|------|--|
| ALT  | = alanine aminotransferase             |
| AST  | = aspartate aminotransferase           |
| ALP  | = alkaline phosphatase                 |
| SGGT | = serum- $\gamma$ -glutamyltransferase |
| NA   | = sodium                               |

|       |                       |
|-------|-----------------------|
| K     | = potassium           |
| CL    | = chloride            |
| INP   | = inorganic phosphate |
| CA    | = calcium             |
| UREA  | = urea                |
| CREA  | = creatinine          |
| GLUC  | = glucose             |
| TBIL  | = total bilirubin     |
| TPROT | = total protein       |
| ALB   | = albumin             |
| GLOB  | = globulins           |
| TRIG  | = triglycerides       |
| CHOL  | = cholesterol         |
| MG    | = magnesium           |
| BILE  | = bile acids          |

**URINALYSIS:****Protein:**

|   |                      |
|---|----------------------|
| 0 | = negative 0.15 g/l  |
| 1 | = 0.30 g/l, 0.60 g/l |
| 2 | = 1.00 g/l, 3.00 g/l |
| 3 | = > 5.00 g/l         |

**Glucose:**

|   |                              |
|---|------------------------------|
| 0 | = normal                     |
| 1 | = 2.8 mmol/l                 |
| 2 | = 5.6 mmol/l                 |
| 3 | = 11.1 mmol/l, > 16.7 mmol/l |

**Ketones:**

|   |               |
|---|---------------|
| 0 | = negative    |
| 1 | = 1 mmol/l    |
| 2 | = 5 mmol/l    |
| 3 | = > 15 mmol/l |

## Urobilinogen:

|   |   |
|---|---|
| 0 | = normal  |
| 1 | = 17 $\mu\text{mol/l}$                            |
| 2 | = 68 $\mu\text{mol/l}$                            |
| 3 | = 135 $\mu\text{mol/l}$ , > 270 $\mu\text{mol/l}$ |

## Bilirubin:

|   |  |
|---|--|
| 0 | = negative   |
| 1 | = 9 $\mu\text{mol/l}$  |
| 2 | = 25 $\mu\text{mol/l}$   |
| 3 | = 50 $\mu\text{mol/l}$ , 100 $\mu\text{mol/l}$ , > 200 $\mu\text{mol/l}$ |

## Blood (erythrocytes):

|   |   |
|---|---|
| 0 | = negative  |
| 1 | = 10 ery/ $\mu\text{l}$                             |
| 2 | = 50 ery/ $\mu\text{l}$                             |
| 3 | = 150 ery/ $\mu\text{l}$ , > 250 ery/ $\mu\text{l}$ |

## Spec.

gravity = specific gravity

## SEDIMENT:

|       |                                     |
|-------|-------------------------------------|
| P     | = triple phosphate                  |
| O     | = calcium oxalates                  |
| C     | = crystals of unknown origin        |
| T     | = tyrosine-like crystals            |
| GCE   | = granulated casts/epithelial casts |
| GC    | = granulated casts                  |
| CE    | = epithelial casts                  |
| V     | = clusters                          |
| ERY   | = erythrocytes                      |
| LEUCO | = leukocytes                        |
| 0     | = none                              |
| 1     | = few                               |
| 2     | = many                              |
| 3     | = masses                            |

## COLOR, TURBIDITY:

|      |                       |
|------|-----------------------|
| yc   | = yellow, clear       |
| ycl  | = yellow, cloudy      |
| dyc  | = dark yellow, clear  |
| dycl | = dark yellow, cloudy |



## UNITS:

|          |                                 |
|----------|---------------------------------|
| mmol/l   | = millimole/liter               |
| μmol/l   | = micromole/liter               |
| nmol/l   | = nanomole/liter                |
| g/l, G/L | = gram/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              |
| nkat/l   | = nanokatal/liter               |
| PPM      | = parts per million             |
| mg/kg    | = mg/kilogram                   |
| μl       | = microliter                    |
| ML       | = ml (milliliter)               |

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### 8.3. LIST OF ABBREVIATIONS USED IN TABLES PATHOLOGY

|              |   |  |
|--------------|---|--|
| A.-nos.      | = | Animal numbers   |
| exam         | = | examined   |
| dev          | = | deviation  |
| F            | = | female animals   |
| F1           | = | final sacrifice group  |
| g            | = | weight determination in grams  |
| M            | = | male animals (under sex); mean value (on weight level)                               |
| mg           | = | weight determination in milligrams   |
| mg/kg bw/day | = | milligram per kilogram body weight and day   |
| n            | = | number of values measured for the determination of mean value and standard deviation |
| ppm          | = | parts per million  |
| SD           | = | standard deviation   |
| %            | = | percentage related to the reference weight in relative organ weight calculations     |

#### Codes for the status at necropsy:

1 (P) = planned sacrifice

#### 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           | 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  
17-Feb-2014 14:53  
ToxData© System 3.0

Study 50C0066/05S019

### Summary - Clinical Observation

Sex: **Male** - Phase: **In-life**

|                       |   | 0 / M        | 1 / M          | 2 / M          | 3 / M               |
|-----------------------|---|--------------|----------------|----------------|---------------------|
|                       |   | 0 mg/kg bw/d | 100 mg/kg bw/d | 300 mg/kg bw/d | 1000/600 mg/kg bw/d |
| Animals examined      | N | 10           | 10             | 10             | 10                  |
| Animals with signs    | % | 0.0          | 60.0           | 100.0          | 100.0               |
| dead                  | N | 10           | 10             | 10             | 10                  |
| sacrificed scheduled  | % | 100.0        | 100.0          | 100.0          | 100.0               |
| feces                 | N | 0            | 0              | 10             | 10                  |
|                       | % | 0.0          | 0.0            | 100.0          | 100.0               |
| soft feces            | N | 0            | 0              | 10             | 10                  |
|                       | % | 0.0          | 0.0            | 100.0          | 100.0               |
| discolored feces      | N | 0            | 0              | 10             | 10                  |
|                       | % | 0.0          | 0.0            | 100.0          | 100.0               |
| head                  | N | 0            | 6              | 9              | 10                  |
| salivation            | % | 0.0          | 60.0           | 90.0           | 100.0               |
| mass                  | N | 0            | 1              | 0              | 0                   |
| palpable through skin | % | 0.0          | 10.0           | 0.0            | 0.0                 |
| respiration           | N | 0            | 1              | 1              | 0                   |
| sounds                | % | 0.0          | 10.0           | 10.0           | 0.0                 |
| fur                   | N | 0            | 1              | 0              | 0                   |
| piloerection          | % | 0.0          | 10.0           | 0.0            | 0.0                 |
| normal                | N | 10           | 10             | 10             | 10                  |
| NAD                   | % | 100.0        | 100.0          | 100.0          | 100.0               |

day 0 [DCO] -> day 92 [00:00 - 24:00]

IA- 2  
17-Feb-2014 14:55  
ToxData© System 3.0

Study 50C0066/05S019

### Summary - Clinical Observation

Sex: **Female** - Phase: **In-life**

|                      |   | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|----------------------|---|-----------------------|-------------------------|-------------------------|--------------------------|
| Animals examined     | N | 10                    | 10                      | 10                      | 10                       |
| Animals with signs   | % | 0                     | 4                       | 10                      | 10                       |
| dead                 | % | 0.0                   | 40.0                    | 100.0                   | 100.0                    |
| sacrificed scheduled | % | 100.0                 | 100.0                   | 100.0                   | 100.0                    |
| feces                | % | 0                     | 0                       | 10                      | 10                       |
| soft feces           | % | 0.0                   | 0.0                     | 100.0                   | 100.0                    |
| discolored feces     | % | 0                     | 0                       | 10                      | 10                       |
| head                 | % | 0.0                   | 0.0                     | 100.0                   | 100.0                    |
| salivation           | % | 0                     | 4                       | 10                      | 9                        |
| normal               | % | 0.0                   | 40.0                    | 100.0                   | 90.0                     |
| NAD                  | % | 10                    | 10                      | 10                      | 10                       |
|                      | % | 100.0                 | 100.0                   | 100.0                   | 100.0                    |

day 0 [DCO] -> day 93 [00:00 - 24:00]

IA- 3  
21-Nov-2013 14:09  
ToxData© System 3.0

Study 50C0066/05S019

# Summary Food Consumption Per Day

Sex: Male - Phase: In-life

|            |                      | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|------------|----------------------|-----------------------|-------------------------|-------------------------|------------------------------|
| d 3 -> 7   | Mean [g]             | 18.5                  | 17.8                    | 18.4                    | 15.1                         |
|            | S.d.                 | 0.0                   | 0.9                     | 0.9                     | 0.1                          |
|            | N                    | 2                     | 2                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | -4.1                    | -0.8                    | -18.1                        |
| d 10 -> 14 | Mean [g]             | 21.6                  | 20.6                    | 22.6                    | 19.4                         |
|            | S.d.                 | 0.1                   | 1.0                     | 1.5                     | 2.8                          |
|            | N                    | 2                     | 2                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | -4.6                    | 4.9                     | -10.4                        |
| d 17 -> 21 | Mean [g]             | 23.5                  | 21.8                    | 24.4                    | 21.5                         |
|            | S.d.                 | 1.6                   | 0.4                     | 1.1                     | 0.5                          |
|            | N                    | 2                     | 2                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | -7.4                    | 3.6                     | -8.3                         |
| d 24 -> 28 | Mean [g]             | 23.1                  | 22.7                    | 25.9                    | 19.7                         |
|            | S.d.                 | 1.0                   | 0.4                     | 1.3                     | 1.3                          |
|            | N                    | 2                     | 2                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | -1.7                    | 11.9                    | -14.7                        |
| d 31 -> 35 | Mean [g]             | 22.5                  | 23.7                    | 24.9                    | 20.8                         |
|            | S.d.                 | 0.9                   | 1.0                     | 1.6                     | 1.2                          |
|            | N                    | 2                     | 2                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | 5.1                     | 10.2                    | -8.0                         |
| d 38 -> 42 | Mean [g]             | 23.6                  | 27.0                    | 22.9                    | 19.9                         |
|            | S.d.                 | 2.5                   | 1.6                     | 0.8                     | 0.4                          |
|            | N                    | 2                     | 2                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | 14.4                    | -2.8                    | -15.7                        |
| d 45 -> 49 | Mean [g]             | 20.7                  | 21.0                    | 20.1                    | 19.6                         |
|            | S.d.                 | 0.1                   | 1                       | 0.1                     | 1.2                          |
|            | N                    | 2                     | 1                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | 1.4                     | -3.1                    | -5.1                         |
| d 52 -> 56 | Mean [g]             | 20.7                  | 22.6                    | 21.4                    | 19.9                         |
|            | S.d.                 | 0.3                   | 0.6                     | 1.3                     | 1.1                          |
|            | N                    | 2                     | 2                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | 9.2                     | 3.4                     | -4.1                         |
| d 59 -> 63 | Mean [g]             | 22.4                  | 23.0                    | 24.9                    | 18.3                         |
|            | S.d.                 | 0.4                   | 3.3                     | 2.1                     | 2.1                          |
|            | N                    | 2                     | 2                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | 2.7                     | -2.0                    | -18.3                        |

d = day

IA- 4  
21-Nov-2013 14:09  
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### Summary Food Consumption Per Day

Sex: **Male** - Phase: **In-life**

|            |                      | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|------------|----------------------|-----------------------|-------------------------|-------------------------|------------------------------|
| d 66 -> 70 | Mean [g]             | 22.5                  | 22.2                    | 22.8                    | 19.2                         |
|            | S.d.                 | 0.4                   | 1.8                     | 0.4                     | 2.3                          |
|            | N                    | 2                     | 2                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | -1.3                    | 1.3                     | -14.7                        |
| d 73 -> 77 | Mean [g]             | 21.1                  | 20.2                    | 22.1                    | 24.5                         |
|            | S.d.                 | 1.1                   | 0.6                     | 1.8                     | 5.9                          |
|            | N                    | 2                     | 2                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | -4.0                    | 4.5                     | 16.1                         |
| d 80 -> 84 | Mean [g]             | 21.1                  | 22.2                    | 21.1                    | 22.7                         |
|            | S.d.                 | 0.5                   | 0.4                     | 2.1                     | 4.4                          |
|            | N                    | 2                     | 2                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | 5.0                     | -0.2                    | 7.3                          |
| d 87 -> 91 | Mean [g]             | 22.1                  | 20.9                    | 21.5                    | 22.9                         |
|            | S.d.                 | 1.1                   | 0.8                     | 0.5                     | 4.1                          |
|            | N                    | 2                     | 2                       | 2                       | 2                            |
|            | Deviation Vs Control |                       | -5.6                    | -2.7                    | 3.4                          |

d = day

IA- 5  
21-Nov-2013 14:09  
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### Summary Food Consumption Per Day

Sex: Female - Phase: In-life

|            |                      | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|------------|----------------------|-----------------------|-------------------------|-------------------------|--------------------------|
| d 3 -> 7   | Mean [g]             | 12.9                  | 12.8                    | 12.6                    | 11.3                     |
|            | S.d.                 | 0.2                   | 0.3                     | 0.0                     | 1.1                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -1.2                    | -2.7                    | -12.4                    |
| d 10 -> 14 | Mean [g]             | 14.7                  | 14.0                    | 14.5                    | 22.5                     |
|            | S.d.                 | 0.4                   | 0.1                     | 0.7                     | 4.7                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -4.4                    | -1.0                    | 53.2                     |
| d 17 -> 21 | Mean [g]             | 14.9                  | 14.4                    | 15.1                    | 14.9                     |
|            | S.d.                 | 0.2                   | 0.0                     | 0.1                     | 0.5                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -3.7                    | 0.7                     | 0.0                      |
| d 24 -> 28 | Mean [g]             | 16.4                  | 14.9                    | 15.6                    | 16.2                     |
|            | S.d.                 | 0.2                   | 0.5                     | 0.8                     | 0.4                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -8.6                    | -4.3                    | -0.9                     |
| d 31 -> 35 | Mean [g]             | 15.2                  | 14.6                    | 14.9                    | 15.5                     |
|            | S.d.                 | 0.1                   | 0.1                     | 1.0                     | 0.7                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -3.9                    | -2.0                    | 2.0                      |
| d 38 -> 42 | Mean [g]             | 15.6                  | 14.8                    | 15.0                    | 15.7                     |
|            | S.d.                 | 0.3                   | 0.1                     | 0.1                     | 0.2                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -5.4                    | -3.8                    | 0.3                      |
| d 45 -> 49 | Mean [g]             | 14.7                  | 13.4                    | 16.9                    | 15.1                     |
|            | S.d.                 | 0.2                   | 0.3                     | 4.6                     | 0.2                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -8.5                    | 15.0                    | 2.7                      |
| d 52 -> 56 | Mean [g]             | 16.2                  | 13.5                    | 14.1                    | 22.3                     |
|            | S.d.                 | 1.3                   | 0.1                     | 0.1                     | 9.9                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -16.7                   | -13.0                   | 37.7                     |
| d 59 -> 63 | Mean [g]             | 16.3                  | 14.4                    | 15.3                    | 16.0                     |
|            | S.d.                 | 0.8                   | 0.2                     | 2.4                     | 4.0                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -11.3                   | -6.1                    | -1.5                     |

d = day

IA- 6  
21-Nov-2013 14:09  
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### Summary Food Consumption Per Day

Sex: Female - Phase: In-life

|            |                      | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|------------|----------------------|-----------------------|-------------------------|-------------------------|--------------------------|
| d 66 -> 70 | Mean [g]             | 17.0                  | 15.1                    | 14.8                    | 17.9                     |
|            | S.d.                 | 1.1                   | 0.0                     | 0.5                     | 2.4                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -11.2                   | -12.6                   | 5.3                      |
| d 73 -> 77 | Mean [g]             | 16.2                  | 14.9                    | 15.1                    | 18.2                     |
|            | S.d.                 | 1.0                   | 1.5                     | 0.6                     | 5.3                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -8.3                    | -6.5                    | 12.7                     |
| d 80 -> 84 | Mean [g]             | 15.7                  | 14.4                    | 14.9                    | 16.8                     |
|            | S.d.                 | 1.0                   | 0.2                     | 0.1                     | 0.6                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -8.0                    | -5.1                    | 6.7                      |
| d 87 -> 91 | Mean [g]             | 15.1                  | 13.8                    | 14.6                    | 15.4                     |
|            | S.d.                 | 0.3                   | 0.3                     | 0.1                     | 0.4                      |
|            | N                    | 2                     | 2                       | 2                       | 2                        |
|            | Deviation Vs Control |                       | -8.6                    | -3.6                    | 2.3                      |

d = day



IA- 7  
21-Nov-2013 14:11  
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### Summary Body Weights BW / Body Weights [g]

Sex: Male - Phase: In-life

|        |                      | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|--------|----------------------|-----------------------|-------------------------|-------------------------|------------------------------|
| day 0  | Mean                 | 158.4 n               | 157.1                   | 158.1                   | 158.2                        |
|        | S.d.                 | 6.4                   | 6.6                     | 5.5                     | 5.7                          |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -0.8                    | -0.2                    | -0.1                         |
| day 7  | Mean                 | 203.3 n               | 199.9                   | 198.0                   | 189.9 **                     |
|        | S.d.                 | 9.5                   | 9.4                     | 9.4                     | 10.0                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -1.6                    | -2.6                    | -6.6                         |
| day 14 | Mean                 | 246.7 n               | 242.8                   | 240.6                   | 224.6 **                     |
|        | S.d.                 | 12.6                  | 14.9                    | 11.9                    | 15.4                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -1.6                    | -2.5                    | -9.0                         |
| day 21 | Mean                 | 283.3 n               | 276.7                   | 274.1                   | 253.7 **                     |
|        | S.d.                 | 16.9                  | 21.1                    | 11.4                    | 18.4                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -2.3                    | -3.3                    | -10.5                        |
| day 28 | Mean                 | 311.7 n               | 304.2                   | 298.1                   | 267.6 **                     |
|        | S.d.                 | 20.0                  | 26.3                    | 14.8                    | 20.1                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -2.4                    | -4.4                    | -14.1                        |
| day 35 | Mean                 | 333.0 n               | 328.6                   | 312.2                   | 282.1 **                     |
|        | S.d.                 | 23.8                  | 30.4                    | 17.2                    | 22.8                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -1.3                    | -6.3                    | -15.3                        |
| day 42 | Mean                 | 351.4 n               | 343.8                   | 326.0                   | 294.3 **                     |
|        | S.d.                 | 27.2                  | 33.9                    | 19.3                    | 26.5                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -2.2                    | -7.2                    | -16.2                        |
| day 49 | Mean                 | 359.0 n               | 355.8                   | 336.5                   | 302.0 **                     |
|        | S.d.                 | 28.1                  | 38.2                    | 19.5                    | 31.8                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -0.9                    | -6.3                    | -15.9                        |
| day 56 | Mean                 | 375.1 n               | 367.8                   | 345.8                   | 306.2 **                     |
|        | S.d.                 | 28.1                  | 40.3                    | 19.4                    | 32.3                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -1.9                    | -7.9                    | -18.4                        |

Statistic Profile = Dunnett test (two-sided), \* p<=0.05, \*\* p<=0.01, X = Group excluded from statistics  
n=DUNNETT

IA- 8  
21-Nov-2013 14:11  
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### Summary Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

|        |                      | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|--------|----------------------|-----------------------|-------------------------|-------------------------|------------------------------|
| day 63 | Mean                 | 389.4 n               | 377.8                   | 354.6                   | 312.4 **                     |
|        | S.d.                 | 31.6                  | 40.1                    | 19.7                    | 36.4                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -3.0                    | -8.9                    | -19.8                        |
| day 70 | Mean                 | 396.6 n               | 387.5                   | 362.3                   | 317.8 **                     |
|        | S.d.                 | 31.6                  | 45.4                    | 22.8                    | 36.6                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -2.3                    | -8.6                    | -19.9                        |
| day 77 | Mean                 | 406.4 n               | 390.6                   | 369.1                   | 326.6 **                     |
|        | S.d.                 | 31.0                  | 43.9                    | 22.5                    | 40.5                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -3.9                    | -9.2                    | -19.6                        |
| day 84 | Mean                 | 413.4 n               | 396.8                   | 373.8                   | 332.7 **                     |
|        | S.d.                 | 32.3                  | 45.4                    | 19.5                    | 42.2                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -4.0                    | -9.6                    | -19.5                        |
| day 91 | Mean                 | 417.1 n               | 400.7                   | 377.3                   | 334.7 **                     |
|        | S.d.                 | 31.8                  | 46.4                    | 21.7                    | 41.6                         |
|        | N                    | 10                    | 10                      | 10                      | 10                           |
|        | Deviation Vs Control |                       | -3.9                    | -9.5                    | -19.8                        |

Statistic Profile = Dunnett test (two-sided), \* p<=0.05, \*\* p <=0.01, X = Group excluded from statistics  
n=DUNNETT

IA- 9  
21-Nov-2013 14:11  
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### Summary Body Weights BW / Body Weights [g]

Sex: Female - Phase: In-life

|        |                      | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|--------|----------------------|-----------------------|-------------------------|-------------------------|--------------------------|
| day 0  | Mean                 | 126.1 n               | 127.0                   | 126.0                   | 126.7                    |
|        | S.d.                 | 6.9                   | 6.9                     | 7.5                     | 7.8                      |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | 0.8                     | -0.1                    | 0.5                      |
| day 7  | Mean                 | 143.7 n               | 147.0                   | 144.0                   | 142.7                    |
|        | S.d.                 | 8.6                   | 8.2                     | 7.3                     | 7.9                      |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | 2.3                     | 0.3                     | -0.7                     |
| day 14 | Mean                 | 162.9 n               | 163.1                   | 162.4                   | 162.9                    |
|        | S.d.                 | 11.3                  | 10.2                    | 7.8                     | 8.8                      |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | 0.1                     | -0.3                    | 0.0                      |
| day 21 | Mean                 | 180.1 n               | 177.2                   | 173.7                   | 176.9                    |
|        | S.d.                 | 14.5                  | 9.5                     | 9.3                     | 9.4                      |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | -1.6                    | -3.5                    | -1.8                     |
| day 28 | Mean                 | 191.0 n               | 188.3                   | 187.6                   | 189.4                    |
|        | S.d.                 | 14.5                  | 10.7                    | 11.6                    | 11.6                     |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | -1.4                    | -1.8                    | -0.8                     |
| day 35 | Mean                 | 201.1 n               | 199.0                   | 196.4                   | 197.4                    |
|        | S.d.                 | 19.0                  | 11.8                    | 10.2                    | 11.9                     |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | -1.1                    | -2.3                    | -1.9                     |
| day 42 | Mean                 | 208.4 n               | 204.7                   | 202.8                   | 205.2                    |
|        | S.d.                 | 19.1                  | 13.8                    | 12.2                    | 12.0                     |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | -1.8                    | -2.6                    | -1.5                     |
| day 49 | Mean                 | 216.8 n               | 209.3                   | 207.2                   | 208.7                    |
|        | S.d.                 | 19.6                  | 13.2                    | 14.2                    | 13.6                     |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | -3.4                    | -4.5                    | -3.7                     |
| day 56 | Mean                 | 219.3 n               | 214.8                   | 212.5                   | 213.5                    |
|        | S.d.                 | 18.9                  | 13.1                    | 15.5                    | 13.8                     |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | -2.1                    | -3.1                    | -2.6                     |

Statistic Profile = Dunnett test (two-sided), \* p<=0.05, \*\* p<=0.01, X = Group excluded from statistics  
n=DUNNETT

IA- 10  
21-Nov-2013 14:11  
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### Summary Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

|        |                      | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|--------|----------------------|-----------------------|-------------------------|-------------------------|--------------------------|
| day 63 | Mean                 | 227.2 n               | 222.2                   | 216.1                   | 217.4                    |
|        | S.d.                 | 20.8                  | 13.7                    | 12.6                    | 14.4                     |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | -2.2                    | -4.9                    | -4.3                     |
| day 70 | Mean                 | 230.2 n               | 223.8                   | 220.6                   | 218.9                    |
|        | S.d.                 | 21.0                  | 16.2                    | 14.2                    | 15.0                     |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | -2.8                    | -4.2                    | -4.9                     |
| day 77 | Mean                 | 235.5 n               | 228.3                   | 222.1                   | 220.8                    |
|        | S.d.                 | 22.2                  | 14.2                    | 16.4                    | 16.6                     |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | -3.1                    | -5.7                    | -6.3                     |
| day 84 | Mean                 | 236.1 n               | 230.1                   | 224.9                   | 222.9                    |
|        | S.d.                 | 20.4                  | 13.9                    | 15.8                    | 15.9                     |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | -2.5                    | -4.7                    | -5.6                     |
| day 91 | Mean                 | 237.3 n               | 231.7                   | 225.0                   | 222.5                    |
|        | S.d.                 | 23.4                  | 14.2                    | 14.9                    | 15.3                     |
|        | N                    | 10                    | 10                      | 10                      | 10                       |
|        | Deviation Vs Control |                       | -2.3                    | -5.2                    | -6.2                     |

Statistic Profile = Dunnett test (two-sided), \* p<=0.05, \*\* p<=0.01, X = Group excluded from statistics  
n=DUNNETT

IA- 11  
21-Nov-2013 14:14  
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### Summary Changes Body Weights -BW / Body Weights [g]

Sex: Male - Phase: In-life

|           |                      | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|-----------|----------------------|-----------------------|-------------------------|-------------------------|------------------------------|
| d 0 -> 7  | Mean                 | 44.8 n                | 42.8                    | 39.9                    | 31.7 **                      |
|           | S.d.                 | 3.9                   | 6.3                     | 7.1                     | 5.0                          |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -4.5                    | -11.0                   | -29.4                        |
| d 0 -> 14 | Mean                 | 88.3 n                | 85.7                    | 82.5                    | 66.3 **                      |
|           | S.d.                 | 7.1                   | 12.1                    | 9.4                     | 10.7                         |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -2.9                    | -6.6                    | -24.9                        |
| d 0 -> 21 | Mean                 | 124.9 n               | 119.6                   | 116.0                   | 95.4 **                      |
|           | S.d.                 | 11.6                  | 18.7                    | 9.5                     | 14.2                         |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -4.2                    | -7.1                    | -23.6                        |
| d 0 -> 28 | Mean                 | 153.3 n               | 147.1                   | 140.0                   | 109.4 **                     |
|           | S.d.                 | 15.2                  | 24.0                    | 14.0                    | 16.3                         |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -4.1                    | -8.7                    | -28.6                        |
| d 0 -> 35 | Mean                 | 174.6 n               | 171.5                   | 154.1                   | 123.9 **                     |
|           | S.d.                 | 19.3                  | 27.8                    | 17.0                    | 19.6                         |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -1.8                    | -11.8                   | -29.1                        |
| d 0 -> 42 | Mean                 | 193.0 n               | 186.7                   | 167.9                   | 136.1 **                     |
|           | S.d.                 | 22.8                  | 31.6                    | 18.6                    | 23.6                         |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -3.3                    | -13.0                   | -29.5                        |
| d 0 -> 49 | Mean                 | 200.6 n               | 198.7                   | 178.4                   | 143.8 **                     |
|           | S.d.                 | 24.4                  | 36.1                    | 17.7                    | 28.8                         |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -0.9                    | -11.1                   | -28.3                        |
| d 0 -> 56 | Mean                 | 216.7 n               | 210.7                   | 187.2                   | 148.0 **                     |
|           | S.d.                 | 23.9                  | 38.1                    | 18.9                    | 29.1                         |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -2.7                    | -13.6                   | -31.7                        |
| d 0 -> 63 | Mean                 | 231.0 n               | 220.7                   | 196.5 *                 | 154.1 **                     |
|           | S.d.                 | 27.5                  | 38.1                    | 19.8                    | 32.6                         |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -4.5                    | -14.9                   | -33.3                        |

Statistic Profile = Dunnett test (two-sided), \* p<=0.05, \*\* p<=0.01, X = Group excluded from statistics  
d = day, n=DUNNETT

IA- 12  
21-Nov-2013 14:14  
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Study 50C0066/05S019

### Summary Changes Body Weights - BW / Body Weights [g]

Sex: Male - Phase: In-life

|           |                      | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|-----------|----------------------|-----------------------|-------------------------|-------------------------|------------------------------|
| d 0 -> 70 | Mean                 | 238.2 n               | 230.4                   | 204.2                   | 159.5 **                     |
|           | S.d.                 | 27.5                  | 43.0                    | 23.4                    | 33.0                         |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -3.3                    | -14.3                   | -33.0                        |
| d 0 -> 77 | Mean                 | 247.9 n               | 233.5                   | 211.0 *                 | 168.3 **                     |
|           | S.d.                 | 27.1                  | 41.8                    | 23.3                    | 36.9                         |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -5.8                    | -14.9                   | -32.1                        |
| d 0 -> 84 | Mean                 | 255.0 n               | 239.7                   | 215.7 *                 | 174.5 **                     |
|           | S.d.                 | 28.5                  | 43.5                    | 21.0                    | 38.5                         |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -6.0                    | -15.4                   | -31.6                        |
| d 0 -> 91 | Mean                 | 258.7 n               | 243.6                   | 219.2 *                 | 176.4 **                     |
|           | S.d.                 | 28.1                  | 44.2                    | 22.5                    | 37.9                         |
|           | N                    | 10                    | 10                      | 10                      | 10                           |
|           | Deviation Vs Control |                       | -5.8                    | -15.3                   | -31.8                        |

Statistic Profile = Dunnett test (two-sided), \* p<=0.05, \*\* p<=0.01, X = Group excluded from statistics  
n=DUNNETT; d = day

IA- 13  
21-Nov-2013 14:14  
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Study 50C0066/05S019

### Summary Changes Body Weights -BW / Body Weights [g]

Sex: Female - Phase: In-life

|           |                      | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|-----------|----------------------|-----------------------|-------------------------|-------------------------|--------------------------|
| d 0 -> 7  | Mean                 | 17.6 n                | 20.0                    | 18.1                    | 16.0                     |
|           | S.d.                 | 6.2                   | 3.6                     | 2.6                     | 4.0                      |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | 13.8                    | 2.9                     | -8.8                     |
| d 0 -> 14 | Mean                 | 36.8 n                | 36.1                    | 36.5                    | 36.2                     |
|           | S.d.                 | 9.4                   | 5.9                     | 5.6                     | 5.4                      |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | -2.0                    | -0.9                    | -1.7                     |
| d 0 -> 21 | Mean                 | 54.0 n                | 50.1                    | 47.8                    | 50.2                     |
|           | S.d.                 | 11.3                  | 5.9                     | 6.1                     | 6.2                      |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | -7.2                    | -11.4                   | -7.0                     |
| d 0 -> 28 | Mean                 | 64.9 n                | 61.2                    | 61.6                    | 62.7                     |
|           | S.d.                 | 10.8                  | 5.5                     | 5.6                     | 8.2                      |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | -5.6                    | -5.0                    | -3.3                     |
| d 0 -> 35 | Mean                 | 75.0 n                | 71.9                    | 70.5                    | 70.7                     |
|           | S.d.                 | 16.1                  | 7.8                     | 5.0                     | 7.9                      |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | -4.1                    | -6.1                    | -5.8                     |
| d 0 -> 42 | Mean                 | 82.3 n                | 77.7                    | 76.9                    | 78.5                     |
|           | S.d.                 | 17.5                  | 12.3                    | 8.0                     | 9.2                      |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | -5.6                    | -6.5                    | -4.5                     |
| d 0 -> 49 | Mean                 | 90.7 n                | 82.3                    | 81.2                    | 82.0                     |
|           | S.d.                 | 16.9                  | 9.9                     | 10.6                    | 10.1                     |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | -9.3                    | -10.5                   | -9.6                     |
| d 0 -> 56 | Mean                 | 93.2 n                | 87.8                    | 86.6                    | 86.9                     |
|           | S.d.                 | 15.4                  | 8.7                     | 10.6                    | 10.6                     |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | -5.9                    | -7.1                    | -6.8                     |
| d 0 -> 63 | Mean                 | 101.1 n               | 95.2                    | 90.1                    | 90.7                     |
|           | S.d.                 | 18.4                  | 10.2                    | 9.3                     | 12.7                     |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | -5.9                    | -10.8                   | -10.3                    |

Statistic Profile = Dunnett test (two-sided), \* p<=0.05, \*\* p <=0.01, X = Group excluded from statistics  
d = day, n=DUNNETT

IA- 14  
21-Nov-2013 14:14  
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Study 50C0066/05S019

### Summary Changes Body Weights - BW / Body Weights [g]

Sex: Female - Phase: In-life

|           |                      | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|-----------|----------------------|-----------------------|-------------------------|-------------------------|--------------------------|
| d 0 -> 70 | Mean                 | 104.1 n               | 96.7                    | 94.7                    | 92.2                     |
|           | S.d.                 | 19.5                  | 12.6                    | 10.1                    | 13.6                     |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | -7.1                    | -9.1                    | -11.5                    |
| d 0 -> 77 | Mean                 | 109.4 n               | 101.3                   | 96.1                    | 94.1                     |
|           | S.d.                 | 20.1                  | 11.1                    | 12.1                    | 14.2                     |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | -7.4                    | -12.1                   | -14.0                    |
| d 0 -> 84 | Mean                 | 110.0 n               | 103.1                   | 99.0                    | 96.2                     |
|           | S.d.                 | 17.4                  | 9.7                     | 11.1                    | 14.0                     |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | -6.3                    | -10.0                   | -12.5                    |
| d 0 -> 91 | Mean                 | 111.2 n               | 104.6                   | 99.0                    | 95.9                     |
|           | S.d.                 | 21.1                  | 9.9                     | 11.0                    | 13.2                     |
|           | N                    | 10                    | 10                      | 10                      | 10                       |
|           | Deviation Vs Control |                       | -5.9                    | -10.9                   | -13.8                    |

Statistic Profile = Dunnett test (two-sided), \* p<=0.05, \*\* p <=0.01, X = Group excluded from statistics  
n=DUNNETT; d = day



Table IA - 15

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

male animals

Mean values week 12

| HOME CAGE OBSERVATION  | Rank | test group 0<br>N=10 | test group 1<br>N=10 | test group 2<br>N=10 | test group 3<br>N=10 |
|--|------|----------------------|----------------------|----------------------|----------------------|
| <b>posture</b>   |      |                      |                      |                      |                      |
| - animal is sitting or laying                                  | 0    | 5                    | 4                    | 8                    | 4                    |
| - animal is standing or moving                                 | 1    | 5                    | 6                    | 2                    | 6                    |
| - squatting posture  | 2    | 0                    | 0                    | 0                    | 0                    |
| - abdominal position   | 3    | 0                    | 0                    | 0                    | 0                    |
| - abdominal position with splayed limbs                        | 4    | 0                    | 0                    | 0                    | 0                    |
| - lateral position   | 5    | 0                    | 0                    | 0                    | 0                    |
| - oblique head posture   | 6    | 0                    | 0                    | 0                    | 0                    |
| - opisthotonus   | 7    | 0                    | 0                    | 0                    | 0                    |
| <b>tremors</b>   |      |                      |                      |                      |                      |
| - no tremors   | 0    | 10                   | 10                   | 10                   | 10                   |
| - slight tremors   | 1    | 0                    | 0                    | 0                    | 0                    |
| - moderate tremors   | 2    | 0                    | 0                    | 0                    | 0                    |
| - severe tremors   | 3    | 0                    | 0                    | 0                    | 0                    |
| <b>convulsions</b>   |      |                      |                      |                      |                      |
| - no convulsions   | 0    | 10                   | 10                   | 10                   | 10                   |
| - slight convulsions   | 1    | 0                    | 0                    | 0                    | 0                    |
| - moderate convulsions   | 2    | 0                    | 0                    | 0                    | 0                    |
| - severe convulsions   | 3    | 0                    | 0                    | 0                    | 0                    |
| <b>abnormal movements</b>                                      |      |                      |                      |                      |                      |
| - no abnormalities   | 0    | 10                   | 10                   | 10                   | 8                    |
| - manege movements   | 1    | 0                    | 0                    | 0                    | 2                    |
| - head shaking   | 2    | 0                    | 0                    | 0                    | 0                    |
| - excessive cleaning   | 3    | 0                    | 0                    | 0                    | 0                    |
| - frequent chewing   | 4    | 0                    | 0                    | 0                    | 0                    |
| <b>impairment of gait</b>                                      |      |                      |                      |                      |                      |
| - animal is not walking during observation                     | 0    | 9                    | 6                    | 9                    | 9                    |
| - no impairment of gait  | 1    | 1                    | 4                    | 1                    | 1                    |
| - stiff gait   | 2    | 0                    | 0                    | 0                    | 0                    |
| - slight impairment of coordination, unsteady gait             | 3    | 0                    | 0                    | 0                    | 0                    |
| - moderate impairment of coordination, shuffling gait          | 4    | 0                    | 0                    | 0                    | 0                    |
| - severe impairment of coordination, dragging of the hindlimbs | 5    | 0                    | 0                    | 0                    | 0                    |
| - severe impairment of coordination, with splayed limbs        | 6    | 0                    | 0                    | 0                    | 0                    |
| - animal is unable to walk (abdominal or lateral position)     | 7    | 0                    | 0                    | 0                    | 0                    |
| <b>other findings</b>  | 0    | 10                   | 10                   | 10                   | 10                   |

Table IA - 16

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

male animals

Mean values week 12

|   | Rank | test group 0<br>N=10 | test group 1<br>N=10 | test group 2<br>N=10 | test group 3<br>N=10 |
|---|------|----------------------|----------------------|----------------------|----------------------|
| <b>OPEN FIELD OBSERVATIONS</b>  |      |                      |                      |                      |                      |
| <b>behavior when removed from cage</b>                                    |      |                      |                      |                      |                      |
| - animal is tense, but it shows no resistance against handling            | 0    | 10                   | 10                   | 10                   | 10                   |
| - animal shows a slight resistance against the handling                   | 1    | 0                    | 0                    | 0                    | 0                    |
| - animal shows no resistance against the handling but appears indifferent | 2    | 0                    | 0                    | 0                    | 0                    |
| - animal is difficult to handle, it shows aggressiveness                  | 3    | 0                    | 0                    | 0                    | 0                    |
| - animal is very difficult to handle, it shows severe aggressiveness      | 4    | 0                    | 0                    | 0                    | 0                    |
| <b>fur</b>  |      |                      |                      |                      |                      |
| - nothing abnormal detected   | 0    | 10                   | 10                   | 10                   | 10                   |
| - discolored fur  | 1    | 0                    | 0                    | 0                    | 0                    |
| - urine staining of anogenital region                                     | 2    | 0                    | 0                    | 0                    | 0                    |
| - piloerection  | 3    | 0                    | 0                    | 0                    | 0                    |
| - alopecia  | 4    | 0                    | 0                    | 0                    | 0                    |
| - reduced care on fur   | 5    | 0                    | 0                    | 0                    | 0                    |
| <b>skin</b>   |      |                      |                      |                      |                      |
| - nothing abnormal detected   | 0    | 10                   | 10                   | 10                   | 10                   |
| - discolored skin   | 1    | 0                    | 0                    | 0                    | 0                    |
| - reddening   | 2    | 0                    | 0                    | 0                    | 0                    |
| - paleness  | 3    | 0                    | 0                    | 0                    | 0                    |
| - dehydration (exsiccosis)  | 4    | 0                    | 0                    | 0                    | 0                    |
| - hypothermia (skin is cold during handling)                              | 5    | 0                    | 0                    | 0                    | 0                    |
| - lesion(s)   | 6    | 0                    | 0                    | 0                    | 0                    |
| - crust(s)  | 7    | 0                    | 0                    | 0                    | 0                    |
| <b>salivation</b>   |      |                      |                      |                      |                      |
| - no salivation   | 0    | 10                   | 10                   | 10                   | 10                   |
| - slight salivation (area around the mouth is moist)                      | 1    | 0                    | 0                    | 0                    | 0                    |
| - moderate salivation (wet mouth)   | 2    | 0                    | 0                    | 0                    | 0                    |
| - severe salivation (mouth very wet, wet paws)                            | 3    | 0                    | 0                    | 0                    | 0                    |
| <b>nose discharge</b>   |      |                      |                      |                      |                      |
| - no discharge, dry nose  | 0    | 10                   | 10                   | 10                   | 10                   |
| - clear discharge   | 1    | 0                    | 0                    | 0                    | 0                    |
| - reddish discharge   | 2    | 0                    | 0                    | 0                    | 0                    |

Table IA - 17

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

male animals

Mean values week 12

| OPEN FIELD OBSERVATIONS                                      |      | test group 0<br>N=10 | test group 1<br>N=10 | test group 2<br>N=10 | test group 3<br>N=10 |
|--|------|----------------------|----------------------|----------------------|----------------------|
|  | Rank |                      |                      |                      |                      |
| <b>lacrimation</b>   |      |                      |                      |                      |                      |
| - no lacrimation   | 0    | 10                   | 10                   | 10                   | 10                   |
| - slight lacrimation   | 1    | 0                    | 0                    | 0                    | 0                    |
| - moderate lacrimation                                       | 2    | 0                    | 0                    | 0                    | 0                    |
| - severe lacrimation   | 3    | 0                    | 0                    | 0                    | 0                    |
| <b>eyes/pupil size</b>                                       |      |                      |                      |                      |                      |
| - nothing abnormal detected, pupils contracted at room light | 0    | 10                   | 10                   | 10                   | 10                   |
| - chromodacryorrhea  | 1    | 0                    | 0                    | 0                    | 0                    |
| - exophthalmos   | 2    | 0                    | 0                    | 0                    | 0                    |
| - pupils dilated   | 3    | 0                    | 0                    | 0                    | 0                    |
| - abnormal shape of pupils                                   | 4    | 0                    | 0                    | 0                    | 0                    |
| - oblique eye posture  | 5    | 0                    | 0                    | 0                    | 0                    |
| - opacity  | 6    | 0                    | 0                    | 0                    | 0                    |
| - cataract   | 7    | 0                    | 0                    | 0                    | 0                    |
| <b>posture</b>   |      |                      |                      |                      |                      |
| - animal is sitting or laying                                | 0    | 0                    | 0                    | 0                    | 0                    |
| - animal is standing or moving                               | 1    | 10                   | 10                   | 10                   | 10                   |
| - squatting posture  | 2    | 0                    | 0                    | 0                    | 0                    |
| - abdominal position   | 3    | 0                    | 0                    | 0                    | 0                    |
| - abdominal position with splayed limbs                      | 4    | 0                    | 0                    | 0                    | 0                    |
| - lateral position   | 5    | 0                    | 0                    | 0                    | 0                    |
| - oblique head posture                                       | 6    | 0                    | 0                    | 0                    | 0                    |
| - opisthotonus   | 7    | 0                    | 0                    | 0                    | 0                    |
| <b>palpebral closure</b>                                     |      |                      |                      |                      |                      |
| - nothing abnormal detected                                  | 0    | 10                   | 10                   | 10                   | 10                   |
| - eyelid(s) slight closure                                   | 1    | 0                    | 0                    | 0                    | 0                    |
| - eyelid(s) half closure                                     | 2    | 0                    | 0                    | 0                    | 0                    |
| - eyelid(s) permanent closure                                | 3    | 0                    | 0                    | 0                    | 0                    |

Table IA - 18

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

male animals

Mean values week 12

| OPEN FIELD OBSERVATIONS  | Rank | test group |           |           |           |
|--|------|------------|-----------|-----------|-----------|
|  |      | 0<br>N=10  | 1<br>N=10 | 2<br>N=10 | 3<br>N=10 |
| <b>respiration</b>   |      |            |           |           |           |
| - nothing abnormal detected                                    | 0    | 10         | 10        | 10        | 10        |
| - respiration labored  | 1    | 0          | 0         | 0         | 0         |
| - gasping/respiratory sounds                                   | 2    | 0          | 0         | 0         | 0         |
| - respiration accelerated                                      | 3    | 0          | 0         | 0         | 0         |
| - respiration irregular  | 4    | 0          | 0         | 0         | 0         |
| <b>tremors</b>   |      |            |           |           |           |
| - no tremors   | 0    | 10         | 10        | 10        | 10        |
| - slight tremors   | 1    | 0          | 0         | 0         | 0         |
| - moderate tremors   | 2    | 0          | 0         | 0         | 0         |
| - severe tremors   | 3    | 0          | 0         | 0         | 0         |
| <b>convulsions</b>   |      |            |           |           |           |
| - no convulsions   | 0    | 10         | 10        | 10        | 10        |
| - slight convulsions   | 1    | 0          | 0         | 0         | 0         |
| - moderate convulsions   | 2    | 0          | 0         | 0         | 0         |
| - severe convulsions   | 3    | 0          | 0         | 0         | 0         |
| <b>abnormal movements/stereotypics</b>                         |      |            |           |           |           |
| - no abnormalities   | 0    | 10         | 10        | 10        | 10        |
| - manege movements   | 1    | 0          | 0         | 0         | 0         |
| - head shaking   | 2    | 0          | 0         | 0         | 0         |
| - excessive cleaning   | 3    | 0          | 0         | 0         | 0         |
| - frequent chewing   | 4    | 0          | 0         | 0         | 0         |
| <b>impairment of gait</b>                                      |      |            |           |           |           |
| - animal is not walking during observation                     | 0    | 0          | 0         | 0         | 0         |
| - no impairment of gait  | 1    | 10         | 10        | 10        | 10        |
| - stiff gait   | 2    | 0          | 0         | 0         | 0         |
| - slight impairment of coordination, unsteady gait             | 3    | 0          | 0         | 0         | 0         |
| - moderate impairment of coordination, shuffling gait          | 4    | 0          | 0         | 0         | 0         |
| - severe impairment of coordination, dragging of the hindlimbs | 5    | 0          | 0         | 0         | 0         |
| - severe impairment of coordination, with splayed limbs        | 6    | 0          | 0         | 0         | 0         |
| - animal is unable to walk (abdominal or lateral position)     | 7    | 0          | 0         | 0         | 0         |

Table IA - 19

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

male animals

Mean values week 12

## OPEN FIELD OBSERVATIONS

test group 0 N=10 test group 1 N=10 test group 2 N=10 test group 3 N=10

Rank

## 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)

Table IA - 20

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

male animals

Mean values week 12

| SENSORIMOTOR TESTS/REFLEXES  |      | test group 0<br>N=10 | test group 1<br>N=10 | test group 2<br>N=10 | test group 3<br>N=10 |
|--|------|----------------------|----------------------|----------------------|----------------------|
|  | Rank |                      |                      |                      |                      |
| <b>approach response</b>   |      |                      |                      |                      |                      |
| - no reaction  | 0    | 4                    | 5                    | 4                    | 7                    |
| - approaching to object  | 1    | 6                    | 5                    | 6                    | 3                    |
| - escape reaction  | 2    | 0                    | 0                    | 0                    | 0                    |
| - aggressive reaction and attacking of object                                      | 3    | 0                    | 0                    | 0                    | 0                    |
| <b>touch response</b>  |      |                      |                      |                      |                      |
| - no reaction  | 0    | 7                    | 9                    | 7                    | 10                   |
| - orientation to the stimulus  | 1    | 3                    | 1                    | 3                    | 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                    |
| <b>vision</b>  |      |                      |                      |                      |                      |
| - nothing abnormal detected (grasping with forelimbs)                              | 0    | 10                   | 10                   | 10                   | 10                   |
| - no grasping  | 1    | 0                    | 0                    | 0                    | 0                    |
| <b>pupillary reflex</b>  |      |                      |                      |                      |                      |
| - 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                    |
| <b>pinna reflex</b>  |      |                      |                      |                      |                      |
| - immediate response to the stimulus   | 0    | 10                   | 10                   | 10                   | 10                   |
| - no response to the stimulus  | 1    | 0                    | 0                    | 0                    | 0                    |
| <b>audition</b>  |      |                      |                      |                      |                      |
| - 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                    |
| <b>coordination of movements</b>   |      |                      |                      |                      |                      |
| - 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 - 21

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

male animals

Mean values week 12

|   | Rank | test group 0<br>N=10 | test group 1<br>N=10 | test group 2<br>N=10 | test group 3<br>N=10 |
|---|------|----------------------|----------------------|----------------------|----------------------|
| <b>SENSORIMOTOR TESTS/REFLEXES</b>  |      |                      |                      |                      |                      |
| <b>behavior during handling</b>   |      |                      |                      |                      |                      |
| - normal behavior, easy to handle, animal is tense, but it shows no resistance    | 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                    |
| <b>vocalization</b>   |      |                      |                      |                      |                      |
| - 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                    |
| <b>pain perception</b>  |      |                      |                      |                      |                      |
| - 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                    |
| <b>other findings</b>   | 6    | 10                   | 10                   | 10                   | 10                   |

Table IA - 22

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

female animals

Mean values week 12

| HOME CAGE OBSERVATION  | Rank | test group 0<br>N=10 | test group 1<br>N=10 | test group 2<br>N=10 | test group 3<br>N=10 |
|--|------|----------------------|----------------------|----------------------|----------------------|
| <b>posture</b>   |      |                      |                      |                      |                      |
| - animal is sitting or laying                                  | 0    | 3                    | 3                    | 2                    | 2                    |
| - animal is standing or moving                                 | 1    | 7                    | 7                    | 8                    | 8                    |
| - squatting posture  | 2    | 0                    | 0                    | 0                    | 0                    |
| - abdominal position   | 3    | 0                    | 0                    | 0                    | 0                    |
| - abdominal position with splayed limbs                        | 4    | 0                    | 0                    | 0                    | 0                    |
| - lateral position   | 5    | 0                    | 0                    | 0                    | 0                    |
| - oblique head posture   | 6    | 0                    | 0                    | 0                    | 0                    |
| - opisthotonus   | 7    | 0                    | 0                    | 0                    | 0                    |
| <b>tremors</b>   |      |                      |                      |                      |                      |
| - no tremors   | 0    | 10                   | 10                   | 10                   | 10                   |
| - slight tremors   | 1    | 0                    | 0                    | 0                    | 0                    |
| - moderate tremors   | 2    | 0                    | 0                    | 0                    | 0                    |
| - severe tremors   | 3    | 0                    | 0                    | 0                    | 0                    |
| <b>convulsions</b>   |      |                      |                      |                      |                      |
| - no convulsions   | 0    | 10                   | 10                   | 10                   | 10                   |
| - slight convulsions   | 1    | 0                    | 0                    | 0                    | 0                    |
| - moderate convulsions   | 2    | 0                    | 0                    | 0                    | 0                    |
| - severe convulsions   | 3    | 0                    | 0                    | 0                    | 0                    |
| <b>abnormal movements</b>                                      |      |                      |                      |                      |                      |
| - no abnormalities   | 0    | 10                   | 10                   | 10                   | 10                   |
| - manege movements   | 1    | 0                    | 0                    | 0                    | 0                    |
| - head shaking   | 2    | 0                    | 0                    | 0                    | 0                    |
| - excessive cleaning   | 3    | 0                    | 0                    | 0                    | 0                    |
| - frequent chewing   | 4    | 0                    | 0                    | 0                    | 0                    |
| <b>impairment of gait</b>                                      |      |                      |                      |                      |                      |
| - animal is not walking during observation                     | 0    | 7                    | 7                    | 7                    | 7                    |
| - no impairment of gait  | 1    | 3                    | 3                    | 3                    | 3                    |
| - stiff gait   | 2    | 0                    | 0                    | 0                    | 0                    |
| - slight impairment of coordination, unsteady gait             | 3    | 0                    | 0                    | 0                    | 0                    |
| - moderate impairment of coordination, shuffling gait          | 4    | 0                    | 0                    | 0                    | 0                    |
| - severe impairment of coordination, dragging of the hindlimbs | 5    | 0                    | 0                    | 0                    | 0                    |
| - severe impairment of coordination, with splayed limbs        | 6    | 0                    | 0                    | 0                    | 0                    |
| - animal is unable to walk (abdominal or lateral position)     | 7    | 0                    | 0                    | 0                    | 0                    |
| <b>other findings</b>  | 0    | 10                   | 10                   | 10                   | 10                   |



Table IA - 23

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

female animals

Mean values week 12

|   | Rank | test group 0<br>N=10 | test group 1<br>N=10 | test group 2<br>N=10 | test group 3<br>N=10 |
|---|------|----------------------|----------------------|----------------------|----------------------|
| <b>OPEN FIELD OBSERVATIONS</b>  |      |                      |                      |                      |                      |
| <b>behavior when removed from cage</b>                                    |      |                      |                      |                      |                      |
| - animal is tense, but it shows no resistance against handling            | 0    | 10                   | 10                   | 10                   | 10                   |
| - animal shows a slight resistance against the handling                   | 1    | 0                    | 0                    | 0                    | 0                    |
| - animal shows no resistance against the handling but appears indifferent | 2    | 0                    | 0                    | 0                    | 0                    |
| - animal is difficult to handle, it shows aggressiveness                  | 3    | 0                    | 0                    | 0                    | 0                    |
| - animal is very difficult to handle, it shows severe aggressiveness      | 4    | 0                    | 0                    | 0                    | 0                    |
| <b>fur</b>  |      |                      |                      |                      |                      |
| - nothing abnormal detected   | 0    | 10                   | 10                   | 10                   | 10                   |
| - discolored fur  | 1    | 0                    | 0                    | 0                    | 0                    |
| - urine staining of anogenital region                                     | 2    | 0                    | 0                    | 0                    | 0                    |
| - piloerection  | 3    | 0                    | 0                    | 0                    | 0                    |
| - alopecia  | 4    | 0                    | 0                    | 0                    | 0                    |
| - reduced care on fur   | 5    | 0                    | 0                    | 0                    | 0                    |
| <b>skin</b>   |      |                      |                      |                      |                      |
| - nothing abnormal detected   | 0    | 10                   | 10                   | 10                   | 10                   |
| - discolored skin   | 1    | 0                    | 0                    | 0                    | 0                    |
| - reddening   | 2    | 0                    | 0                    | 0                    | 0                    |
| - paleness  | 3    | 0                    | 0                    | 0                    | 0                    |
| - dehydration (exsiccosis)  | 4    | 0                    | 0                    | 0                    | 0                    |
| - hypothermia (skin is cold during handling)                              | 5    | 0                    | 0                    | 0                    | 0                    |
| - lesion(s)   | 6    | 0                    | 0                    | 0                    | 0                    |
| - crust(s)  | 7    | 0                    | 0                    | 0                    | 0                    |
| <b>salivation</b>   |      |                      |                      |                      |                      |
| - no salivation   | 0    | 10                   | 10                   | 10                   | 10                   |
| - slight salivation (area around the mouth is moist)                      | 1    | 0                    | 0                    | 0                    | 0                    |
| - moderate salivation (wet mouth)   | 2    | 0                    | 0                    | 0                    | 0                    |
| - severe salivation (mouth very wet, wet paws)                            | 3    | 0                    | 0                    | 0                    | 0                    |
| <b>nose discharge</b>   |      |                      |                      |                      |                      |
| - no discharge, dry nose  | 0    | 10                   | 10                   | 10                   | 10                   |
| - clear discharge   | 1    | 0                    | 0                    | 0                    | 0                    |
| - reddish discharge   | 2    | 0                    | 0                    | 0                    | 0                    |

Table IA - 24

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

female animals

Mean values week 12

|  | Rank | test group 0<br>N=10 | test group 1<br>N=10 | test group 2<br>N=10 | test group 3<br>N=10 |
|--|------|----------------------|----------------------|----------------------|----------------------|
| <b>OPEN FIELD OBSERVATIONS</b>                               |      |                      |                      |                      |                      |
| <b>lacrimation</b>   |      |                      |                      |                      |                      |
| - no lacrimation   | 0    | 10                   | 10                   | 10                   | 10                   |
| - slight lacrimation   | 1    | 0                    | 0                    | 0                    | 0                    |
| - moderate lacrimation                                       | 2    | 0                    | 0                    | 0                    | 0                    |
| - severe lacrimation   | 3    | 0                    | 0                    | 0                    | 0                    |
| <b>eyes/pupil size</b>                                       |      |                      |                      |                      |                      |
| - nothing abnormal detected, pupils contracted at room light | 0    | 10                   | 10                   | 10                   | 10                   |
| - chromodacryorrhea  | 1    | 0                    | 0                    | 0                    | 0                    |
| - exophthalmos   | 2    | 0                    | 0                    | 0                    | 0                    |
| - pupils dilated   | 3    | 0                    | 0                    | 0                    | 0                    |
| - abnormal shape of pupils                                   | 4    | 0                    | 0                    | 0                    | 0                    |
| - oblique eye posture  | 5    | 0                    | 0                    | 0                    | 0                    |
| - opacity  | 6    | 0                    | 0                    | 0                    | 0                    |
| - cataract   | 7    | 0                    | 0                    | 0                    | 0                    |
| <b>posture</b>   |      |                      |                      |                      |                      |
| - animal is sitting or laying                                | 0    | 0                    | 0                    | 0                    | 0                    |
| - animal is standing or moving                               | 1    | 10                   | 10                   | 10                   | 10                   |
| - squatting posture  | 2    | 0                    | 0                    | 0                    | 0                    |
| - abdominal position   | 3    | 0                    | 0                    | 0                    | 0                    |
| - abdominal position with splayed limbs                      | 4    | 0                    | 0                    | 0                    | 0                    |
| - lateral position   | 5    | 0                    | 0                    | 0                    | 0                    |
| - oblique head posture                                       | 6    | 0                    | 0                    | 0                    | 0                    |
| - opisthotonus   | 7    | 0                    | 0                    | 0                    | 0                    |
| <b>palpebral closure</b>                                     |      |                      |                      |                      |                      |
| - nothing abnormal detected                                  | 0    | 10                   | 10                   | 10                   | 10                   |
| - eyelid(s) slight closure                                   | 1    | 0                    | 0                    | 0                    | 0                    |
| - eyelid(s) half closure                                     | 2    | 0                    | 0                    | 0                    | 0                    |
| - eyelid(s) permanent closure                                | 3    | 0                    | 0                    | 0                    | 0                    |

Table IA - 25

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

female animals

Mean values week 12

| OPEN FIELD OBSERVATIONS  | Rank | test group |           |           |           |
|--|------|------------|-----------|-----------|-----------|
|  |      | 0<br>N=10  | 1<br>N=10 | 2<br>N=10 | 3<br>N=10 |
| <b>respiration</b>   |      |            |           |           |           |
| - nothing abnormal detected                                    | 0    | 10         | 10        | 10        | 10        |
| - respiration labored  | 1    | 0          | 0         | 0         | 0         |
| - gasping/respiratory sounds                                   | 2    | 0          | 0         | 0         | 0         |
| - respiration accelerated                                      | 3    | 0          | 0         | 0         | 0         |
| - respiration irregular  | 4    | 0          | 0         | 0         | 0         |
| <b>tremors</b>   |      |            |           |           |           |
| - no tremors   | 0    | 10         | 10        | 10        | 10        |
| - slight tremors   | 1    | 0          | 0         | 0         | 0         |
| - moderate tremors   | 2    | 0          | 0         | 0         | 0         |
| - severe tremors   | 3    | 0          | 0         | 0         | 0         |
| <b>convulsions</b>   |      |            |           |           |           |
| - no convulsions   | 0    | 10         | 10        | 10        | 10        |
| - slight convulsions   | 1    | 0          | 0         | 0         | 0         |
| - moderate convulsions   | 2    | 0          | 0         | 0         | 0         |
| - severe convulsions   | 3    | 0          | 0         | 0         | 0         |
| <b>abnormal movements/stereotypics</b>                         |      |            |           |           |           |
| - no abnormalities   | 0    | 10         | 10        | 10        | 10        |
| - manege movements   | 1    | 0          | 0         | 0         | 0         |
| - head shaking   | 2    | 0          | 0         | 0         | 0         |
| - excessive cleaning   | 3    | 0          | 0         | 0         | 0         |
| - frequent chewing   | 4    | 0          | 0         | 0         | 0         |
| <b>impairment of gait</b>                                      |      |            |           |           |           |
| - animal is not walking during observation                     | 0    | 0          | 0         | 0         | 0         |
| - no impairment of gait  | 1    | 10         | 10        | 10        | 10        |
| - stiff gait   | 2    | 0          | 0         | 0         | 0         |
| - slight impairment of coordination, unsteady gait             | 3    | 0          | 0         | 0         | 0         |
| - moderate impairment of coordination, shuffling gait          | 4    | 0          | 0         | 0         | 0         |
| - severe impairment of coordination, dragging of the hindlimbs | 5    | 0          | 0         | 0         | 0         |
| - severe impairment of coordination, with splayed limbs        | 6    | 0          | 0         | 0         | 0         |
| - animal is unable to walk (abdominal or lateral position)     | 7    | 0          | 0         | 0         | 0         |

Table IA - 26

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

female animals

Mean values week 12

| OPEN FIELD OBSERVATIONS  | Rank | test group |           |           |           |
|--|------|------------|-----------|-----------|-----------|
|  |      | 0<br>N=10  | 1<br>N=10 | 2<br>N=10 | 3<br>N=10 |
| <b>activity/arousal level</b>                                      |      |            |           |           |           |
| - normal exploration of the area                                   | 0    | 10         | 10        | 10        | 10        |
| - reduced exploration of the area                                  | 1    | 0          | 0         | 0         | 0         |
| - 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         |
| <b>feces</b>   |      |            |           |           |           |
| - no defecation during observation period                          | 0    | 10         | 10        | 10        | 10        |
| - feces without abnormalities                                      | 1    | 0          | 0         | 0         | 0         |
| - 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         |
| <b>urine</b>   |      |            |           |           |           |
| - no urination during observation period                           | 0    | 10         | 9         | 4         | 9         |
| - urine without abnormalities (some wet areas on the filter paper) | 1    | 0          | 1         | 6         | 1         |
| - discoloration of urine   | 2    | 0          | 0         | 0         | 0         |
| - polyuria (great wet areas on the filter paper)                   | 3    | 0          | 0         | 0         | 0         |

Table IA - 27

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

female animals

Mean values week 12

|  | Rank | test group 0<br>N=10 | test group 1<br>N=10 | test group 2<br>N=10 | test group 3<br>N=10 |
|--|------|----------------------|----------------------|----------------------|----------------------|
| <b>SENSORIMOTOR TESTS/REFLEXES</b>   |      |                      |                      |                      |                      |
| <b>approach response</b>   |      |                      |                      |                      |                      |
| - no reaction  | 0    | 5                    | 8                    | 6                    | 8                    |
| - approaching to object  | 1    | 5                    | 2                    | 4                    | 2                    |
| - escape reaction  | 2    | 0                    | 0                    | 0                    | 0                    |
| - aggressive reaction and attacking of object                                      | 3    | 0                    | 0                    | 0                    | 0                    |
| <b>touch response</b>  |      |                      |                      |                      |                      |
| - no reaction  | 0    | 9                    | 7                    | 7                    | 10                   |
| - orientation to the stimulus  | 1    | 1                    | 3                    | 3                    | 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                    |
| <b>vision</b>  |      |                      |                      |                      |                      |
| - nothing abnormal detected (grasping with forelimbs)                              | 0    | 10                   | 10                   | 10                   | 10                   |
| - no grasping  | 1    | 0                    | 0                    | 0                    | 0                    |
| <b>pupillary reflex</b>  |      |                      |                      |                      |                      |
| - 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                    |
| <b>pinna reflex</b>  |      |                      |                      |                      |                      |
| - immediate response to the stimulus   | 0    | 10                   | 10                   | 10                   | 10                   |
| - no response to the stimulus  | 1    | 0                    | 0                    | 0                    | 0                    |
| <b>audition</b>  |      |                      |                      |                      |                      |
| - 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                    |
| <b>coordination of movements</b>   |      |                      |                      |                      |                      |
| - 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 - 28

## FUNCTIONAL OBSERVATIONAL BATTERY

Project No. 50C0066/05S019

female animals

Mean values week 12

|   | Rank | test group 0<br>N=10 | test group 1<br>N=10 | test group 2<br>N=10 | test group 3<br>N=10 |
|---|------|----------------------|----------------------|----------------------|----------------------|
| <b>SENSORIMOTOR TESTS/REFLEXES</b>  |      |                      |                      |                      |                      |
| <b>behavior during handling</b>   |      |                      |                      |                      |                      |
| - normal behavior, easy to handle, animal is tense, but it shows no resistance    | 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                    |
| <b>vocalization</b>   |      |                      |                      |                      |                      |
| - 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                    |
| <b>pain perception</b>  |      |                      |                      |                      |                      |
| - 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                    |
| <b>other findings</b>   | 6    | 10                   | 10                   | 10                   | 10                   |

IA- 29  
21-Nov-2013 14:26  
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Study 50C0066/05S019

# Summary Functional Observation Battery

Sex: **Male** - Phase: **In-life**

|                             |      | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|-----------------------------|------|-----------------------|-------------------------|-------------------------|------------------------------|
| Feces<br>[N]<br>week 12     | Mean | 0 k                   | 0                       | 0                       | 0                            |
|                             | S.d. | 0                     | 0                       | 1                       | 0                            |
|                             | N    | 10                    | 10                      | 10                      | 10                           |
| Deviation Vs Control        |      |                       |                         |                         |                              |
| Rearing<br>[N]<br>week 12   | Mean | 6 k                   | 4                       | 6                       | 6                            |
|                             | S.d. | 3                     | 2                       | 4                       | 2                            |
|                             | N    | 10                    | 10                      | 10                      | 10                           |
| Deviation Vs Control        |      |                       |                         |                         |                              |
| GS F<br>[Newton]<br>week 12 | Mean | 16.2 v                | 15.6                    | 15.4                    | 13.1 **                      |
|                             | S.d. | 2.2                   | 2.0                     | 1.7                     | 1.6                          |
|                             | N    | 10                    | 10                      | 10                      | 10                           |
| Deviation Vs Control        |      |                       |                         |                         |                              |
| GS H<br>[Newton]<br>week 12 | Mean | 10.5 k                | 10.3                    | 10.0                    | 9.7                          |
|                             | S.d. | 1.6                   | 1.4                     | 1.4                     | 1.2                          |
|                             | N    | 10                    | 10                      | 10                      | 10                           |
| Deviation Vs Control        |      |                       |                         |                         |                              |
| FST<br>[cm]<br>week 12      | Mean | 12.7 k                | 12.9                    | 13.8                    | 11.7                         |
|                             | S.d. | 1.4                   | 2.4                     | 1.7                     | 2.3                          |
|                             | N    | 10                    | 10                      | 10                      | 10                           |
| Deviation Vs Control        |      |                       |                         |                         |                              |
|                             |      |                       | 1.1                     | 8.0                     | -7.9                         |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), \* p<=0.05, \*\* p <=0.01, X = Group excluded from statistics  
k=KRUSKAL-WALLIS; v=WILCOX

IA- 30  
21-Nov-2013 14:26  
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Study 50C0066/05S019

# Summary Functional Observation Battery

Sex: Female - Phase: In-life

|                             |      | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|-----------------------------|------|-----------------------|-------------------------|-------------------------|--------------------------|
| Feces<br>[N]<br>week 12     | Mean | 0 k                   | 0                       | 0                       | 0                        |
|                             | S.d. | 0                     | 0                       | 0                       | 0                        |
|                             | N    | 10                    | 10                      | 10                      | 10                       |
| Deviation Vs Control        |      |                       |                         |                         |                          |
| Rearing<br>[N]<br>week 12   | Mean | 11 k                  | 11                      | 11                      | 10                       |
|                             | S.d. | 3                     | 6                       | 5                       | 5                        |
|                             | N    | 10                    | 10                      | 10                      | 10                       |
| Deviation Vs Control        |      |                       |                         |                         |                          |
| GS F<br>[Newton]<br>week 12 | Mean | 11.6 k                | 12.1                    | 12.0                    | 12.0                     |
|                             | S.d. | 2.2                   | 1.4                     | 2.0                     | 1.8                      |
|                             | N    | 10                    | 10                      | 10                      | 10                       |
| Deviation Vs Control        |      |                       |                         |                         |                          |
| GS H<br>[Newton]<br>week 12 | Mean | 8.8 k                 | 7.4                     | 7.9                     | 8.0                      |
|                             | S.d. | 1.4                   | 1.1                     | 0.9                     | 1.2                      |
|                             | N    | 10                    | 10                      | 10                      | 10                       |
| Deviation Vs Control        |      |                       |                         |                         |                          |
| FST<br>[cm]<br>week 12      | Mean | 10.1 k                | 10.6                    | 11.0                    | 10.7                     |
|                             | S.d. | 1.4                   | 1.3                     | 1.7                     | 1.3                      |
|                             | N    | 10                    | 10                      | 10                      | 10                       |
| Deviation Vs Control        |      |                       |                         |                         |                          |
|                             |      |                       | 4.8                     | 9.0                     | 6.1                      |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), \* p<=0.05, \*\* p <=0.01, X = Group excluded from statistics  
k=KRUSKAL-WALLIS



Table IA-31

PRINT DATE 19NOV13

MOTOR ACTIVITY WEEK 12

BASF  
Project Number 50C0066/05S019

GROUP MEANS

M A L E S

0 / M

|    | 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.   |
| M  | 826.8     | 542.0     | 406.2     | 269.2     | 183.8     | 82.4      | 79.9      | 56.1      |
| SD | 308.4     | 101.6     | 190.6     | 121.6     | 106.1     | 136.8     | 103.5     | 84.5      |
| N  | 10        | 10        | 10        | 10        | 10        | 10        | 10        | 10        |

1 / M

|    |       |       |       |       |      |      |      |      |
|----|-------|-------|-------|-------|------|------|------|------|
| M  | 889.0 | 546.6 | 282.1 | 197.7 | 98.0 | 57.9 | 14.9 | 27.6 |
| SD | 251.2 | 147.7 | 107.5 | 138.9 | 80.1 | 48.1 | 16.2 | 32.1 |
| N  | 10    | 10    | 10    | 10    | 10   | 10   | 10   | 10   |

2 / M

|    |       |       |       |       |       |      |      |      |
|----|-------|-------|-------|-------|-------|------|------|------|
| M  | 881.7 | 513.5 | 346.4 | 211.9 | 154.6 | 77.0 | 55.1 | 28.9 |
| SD | 223.7 | 96.0  | 101.8 | 84.5  | 112.0 | 87.6 | 62.3 | 52.5 |
| N  | 10    | 10    | 10    | 10    | 10    | 10   | 10   | 10   |

3 / M

|    |       |       |       |       |      |      |      |      |
|----|-------|-------|-------|-------|------|------|------|------|
| M  | 868.4 | 499.6 | 347.9 | 189.9 | 75.7 | 54.8 | 23.0 | 41.6 |
| SD | 353.7 | 116.8 | 88.8  | 119.9 | 88.8 | 64.1 | 27.8 | 48.8 |
| N  | 10    | 10    | 10    | 10    | 10   | 10   | 10   | 10   |

Kruskal-Wallis + Wilcoxon-tests (two-sided): \* p<=0.05; \*\* p<=0.01 (Statistical unit = Animal)

Table IA-32

PRINT DATE 19NOV13

BASF  
Project Number 50C0066/05S019  
GROUP MEANS  
MOTOR ACTIVITY WEEK 12

M A L E S

0 / M

|    | Interv. 9 | Interv. 10 | Interv. 11 | Interv. 12 | Interv. 1-12 |
|----|-----------|------------|------------|------------|--------------|
|    | Beam      | Beam       | Beam       | Beam       | Sum          |
|    | Interr.   | Interr.    | Interr.    | Interr.    | Interr.      |
| M  | 47.2      | 25.4       | 10.8       | 3.7        | 2533.5       |
| SD | 89.3      | 29.5       | 9.6        | 5.5        | 778.6        |
| N  | 10        | 10         | 10         | 10         | 10           |

1 / M

|    |      |      |      |      |        |
|----|------|------|------|------|--------|
| M  | 17.4 | 29.4 | 14.2 | 8.9  | 2183.7 |
| SD | 23.6 | 54.5 | 22.7 | 13.2 | 191.6  |
| N  | 10   | 10   | 10   | 10   | 10     |

2 / M

|    |      |       |      |         |        |
|----|------|-------|------|---------|--------|
| M  | 56.6 | 52.7  | 20.8 | 31.4 ** | 2430.6 |
| SD | 94.6 | 104.2 | 48.7 | 32.2    | 735.7  |
| N  | 10   | 10    | 10   | 10      | 10     |

3 / M

|    |      |      |      |        |        |
|----|------|------|------|--------|--------|
| M  | 26.4 | 18.4 | 14.1 | 32.2 * | 2192.0 |
| SD | 29.4 | 17.3 | 11.8 | 54.3   | 513.6  |
| N  | 10   | 10   | 10   | 10     | 10     |

-----  
Kruskal-Wallis + Wilcoxon-tests (two-sided): \* p<=0.05; \*\* p<=0.01 (Statistical unit = Animal)

Table IA-33

PRINT DATE 19NOV13

MOTOR ACTIVITY WEEK 12

BASF  
Project Number 50C0066/05S019

GROUP MEANS

F E M A L E S

0 / F

|    | 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.   |
| M  | 1350.9    | 865.1     | 517.9     | 216.2     | 175.8     | 182.3     | 104.9     | 101.9     |
| SD | 458.5     | 291.8     | 207.9     | 143.3     | 239.7     | 313.5     | 144.4     | 152.8     |
| N  | 10        | 10        | 10        | 10        | 10        | 10        | 10        | 10        |

1 / F

|    |        |       |       |       |       |      |      |      |
|----|--------|-------|-------|-------|-------|------|------|------|
| M  | 1046.8 | 633.2 | 349.6 | 221.4 | 176.0 | 62.2 | 38.5 | 27.5 |
| SD | 221.5  | 111.9 | 142.4 | 149.4 | 153.0 | 55.8 | 61.8 | 29.5 |
| N  | 10     | 10    | 10    | 10    | 10    | 10   | 10   | 10   |

2 / F

|    |          |       |       |       |       |      |      |      |
|----|----------|-------|-------|-------|-------|------|------|------|
| M  | 849.6 ** | 588.7 | 391.7 | 252.3 | 174.2 | 74.1 | 43.3 | 49.8 |
| SD | 246.2    | 244.9 | 169.4 | 106.6 | 143.3 | 84.7 | 81.3 | 61.8 |
| N  | 10       | 10    | 10    | 10    | 10    | 10   | 10   | 10   |

3 / F

|    |          |       |       |       |       |       |      |       |
|----|----------|-------|-------|-------|-------|-------|------|-------|
| M  | 896.8 ** | 645.6 | 371.9 | 274.2 | 251.3 | 160.7 | 66.1 | 74.4  |
| SD | 190.9    | 243.6 | 167.7 | 148.6 | 163.2 | 150.9 | 91.7 | 104.0 |
| N  | 10       | 10    | 10    | 10    | 10    | 10    | 10   | 10    |

Kruskal-Wallis + Wilcoxon-tests (two-sided): \* p&lt;=0.05; \*\* p&lt;=0.01 (Statistical unit = Animal)

Table IA-34

PRINT DATE 19NOV13

BASF  
Project Number 50C0066/05S019  
GROUP MEANS  
MOTOR ACTIVITY WEEK 12

| 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. |
| 0 / F         | M  | 140.2     |         | 102.7      |         | 56.7       |         | 45.7       |         | 3860.3       |         |
|               | SD | 124.1     |         | 124.6      |         | 102.2      |         | 80.3       |         | 1640.7       |         |
|               | N  | 10        |         | 10         |         | 10         |         | 10         |         | 10           |         |
| 1 / F         | M  | 43.7      |         | 156.6      |         | 65.9       |         | 51.9       |         | 2873.3       |         |
|               | SD | 59.6      |         | 159.8      |         | 97.1       |         | 72.0       |         | 477.1        |         |
|               | N  | 10        |         | 10         |         | 10         |         | 10         |         | 10           |         |
| 2 / F         | M  | 38.9      |         | 128.2      |         | 137.8      |         | 124.5      |         | 2853.1       |         |
|               | SD | 48.8      |         | 138.1      |         | 177.7      |         | 121.7      |         | 853.1        |         |
|               | N  | 10        |         | 10         |         | 10         |         | 10         |         | 10           |         |
| 3 / F         | M  | 113.3     |         | 146.8      |         | 106.1      |         | 131.3      |         | 3238.5       |         |
|               | SD | 96.9      |         | 137.9      |         | 117.0      |         | 164.2      |         | 1199.8       |         |
|               | N  | 10        |         | 10         |         | 10         |         | 10         |         | 10           |         |

Kruskal-Wallis + Wilcoxon-tests (two-sided): \* p<=0.05; \*\* p<=0.01 (Statistical unit = Animal)

Table IA - 35

## OPHTHALMOLOGICAL FINDINGS

Project No. 50C0066/05S019

male animals

Mean values

|   | day -1       |              |              |              | day 91       |              |
|---|--------------|--------------|--------------|--------------|--------------|--------------|
|   | test group 0 | test group 1 | test group 2 | test group 3 | test group 0 | test group 3 |
| Number of animals examined                | 10           | 10           | 10           | 10           | 10           | 10           |
| Animals without ophthalmological findings | 0            | 0            | 0            | 0            | 0            | 0            |
| corneal stipplings                        | 10           | 10           | 10           | 10           | 10           | 10           |
| remainders of the pupillary membrane      | 4            | 3            | 3            | 7            | 1            | 2            |

Table IA - 36

## OPHTHALMOLOGICAL FINDINGS

Project No. 50C0066/05S019

female animals

Mean values

|   | day -1       |              |              |              | day 91       |              |
|---|--------------|--------------|--------------|--------------|--------------|--------------|
|   | test group 0 | test group 1 | test group 2 | test group 3 | test group 0 | test group 3 |
| Number of animals examined                | 10           | 10           | 10           | 10           | 10           | 10           |
| Animals without ophthalmological findings | 0            | 1            | 0            | 0            | 0            | 0            |
| corneal stipplings                        | 10           | 9            | 9            | 10           | 10           | 10           |
| remainders of the pupillary membrane      | 4            | 5            | 5            | 4            | 0            | 0            |

Study

50C0066/05S019

IB 1

16-Jan-2014 13:41

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## Red blood cell + coagulation parameters

Sex: Male - Phase: In-life

|                            |        | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|----------------------------|--------|-----------------------|-------------------------|-------------------------|------------------------------|
| RBC<br>[tera/L]<br>day 92  | Mean   | 8.71 v                | 8.83                    | 8.46                    | 8.08 **                      |
|                            | S.d.   | 0.35                  | 0.32                    | 0.26                    | 0.39                         |
|                            | N      | 10                    | 10                      | 10                      | 10                           |
|                            | Median | 8.75                  | 8.75                    | 8.41                    | 8.07                         |
| HGB<br>[mmol/L]<br>day 92  | Mean   | 9.0 v                 | 9.0                     | 8.8                     | 8.6 **                       |
|                            | S.d.   | 0.2                   | 0.4                     | 0.3                     | 0.2                          |
|                            | N      | 10                    | 10                      | 10                      | 10                           |
|                            | Median | 9.0                   | 9.0                     | 8.7                     | 8.7                          |
| HCT<br>[L/L]<br>day 92     | Mean   | 0.427 k               | 0.426                   | 0.420                   | 0.412                        |
|                            | S.d.   | 0.014                 | 0.022                   | 0.018                   | 0.014                        |
|                            | N      | 10                    | 10                      | 10                      | 10                           |
|                            | Median | 0.432                 | 0.429                   | 0.419                   | 0.412                        |
| MCV<br>[fL]<br>day 92      | Mean   | 49.1 v                | 48.2                    | 49.6                    | 51.0 **                      |
|                            | S.d.   | 1.0                   | 1.6                     | 1.5                     | 1.6                          |
|                            | N      | 10                    | 10                      | 10                      | 10                           |
|                            | Median | 49.4                  | 48.0                    | 49.6                    | 51.0                         |
| MCH<br>[fmol]<br>day 92    | Mean   | 1.03 k                | 1.02                    | 1.04                    | 1.07                         |
|                            | S.d.   | 0.02                  | 0.03                    | 0.03                    | 0.04                         |
|                            | N      | 10                    | 10                      | 10                      | 10                           |
|                            | Median | 1.03                  | 1.02                    | 1.04                    | 1.07                         |
| MCHC<br>[mmol/L]<br>day 92 | Mean   | 21.05 k               | 21.17                   | 20.97                   | 20.95                        |
|                            | S.d.   | 0.29                  | 0.46                    | 0.41                    | 0.37                         |
|                            | N      | 10                    | 10                      | 10                      | 10                           |
|                            | Median | 21.02                 | 21.09                   | 20.92                   | 20.92                        |
| RET<br>[%]<br>day 92       | Mean   | 1.5 v                 | 1.2                     | 1.6                     | 1.9 *                        |
|                            | S.d.   | 0.1                   | 0.5                     | 0.2                     | 0.4                          |
|                            | N      | 10                    | 10                      | 10                      | 10                           |
|                            | Median | 1.5                   | 1.3                     | 1.6                     | 1.9                          |
| PLT<br>[giga/L]<br>day 92  | Mean   | 744 k                 | 812                     | 727                     | 698                          |
|                            | S.d.   | 57                    | 159                     | 77                      | 47                           |
|                            | N      | 10                    | 10                      | 10                      | 10                           |
|                            | Median | 756                   | 786                     | 746                     | 696                          |
| HQT<br>[sec]<br>day 92     | Mean   | 38.2 k                | 39.2                    | 39.5                    | 40.5                         |
|                            | S.d.   | 2.2                   | 2.8                     | 2.7                     | 1.8                          |
|                            | N      | 10                    | 10                      | 10                      | 10                           |
|                            | Median | 38.0                  | 39.3                    | 39.3                    | 40.8                         |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), \* p<=0.05, \*\* p <=0.01, X = Group excluded from statistics  
v=KRUSKAL-WALLIS-WILCOX; k=KRUSKAL-WALLIS

Study

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IB 2

16-Jan-2014 13:46

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## Red blood cell + coagulation parameters

Sex: Female - Phase: In-life

|                            |        | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|----------------------------|--------|-----------------------|-------------------------|-------------------------|--------------------------|
| RBC<br>[tera/L]<br>day 93  | Mean   | 7.89 v                | 7.82                    | 7.76                    | 7.45 **                  |
|                            | S.d.   | 0.31                  | 0.20                    | 0.36                    | 0.25                     |
|                            | N      | 10                    | 10                      | 10                      | 10                       |
|                            | Median | 7.89                  | 7.84                    | 7.93                    | 7.54                     |
| HGB<br>[mmol/L]<br>day 93  | Mean   | 8.8 v                 | 8.6                     | 8.5                     | 8.0 **                   |
|                            | S.d.   | 0.3                   | 0.2                     | 0.3                     | 0.3                      |
|                            | N      | 10                    | 10                      | 10                      | 10                       |
|                            | Median | 8.8                   | 8.6                     | 8.6                     | 8.0                      |
| HCT<br>[L/L]<br>day 93     | Mean   | 0.408 v               | 0.406                   | 0.402                   | 0.380 **                 |
|                            | S.d.   | 0.012                 | 0.011                   | 0.015                   | 0.013                    |
|                            | N      | 10                    | 10                      | 10                      | 10                       |
|                            | Median | 0.407                 | 0.407                   | 0.407                   | 0.378                    |
| MCV<br>[fL]<br>day 93      | Mean   | 51.8 k                | 52.0                    | 51.8                    | 51.0                     |
|                            | S.d.   | 1.4                   | 2.0                     | 1.1                     | 1.8                      |
|                            | N      | 10                    | 10                      | 10                      | 10                       |
|                            | Median | 52.0                  | 51.5                    | 51.6                    | 50.9                     |
| MCH<br>[fmol]<br>day 93    | Mean   | 1.12 k                | 1.11                    | 1.10                    | 1.07                     |
|                            | S.d.   | 0.04                  | 0.04                    | 0.04                    | 0.05                     |
|                            | N      | 10                    | 10                      | 10                      | 10                       |
|                            | Median | 1.12                  | 1.09                    | 1.10                    | 1.06                     |
| MCHC<br>[mmol/L]<br>day 93 | Mean   | 21.62 v               | 21.28                   | 21.24 *                 | 21.07 **                 |
|                            | S.d.   | 0.29                  | 0.40                    | 0.42                    | 0.43                     |
|                            | N      | 10                    | 10                      | 10                      | 10                       |
|                            | Median | 21.68                 | 21.22                   | 21.19                   | 20.99                    |
| RET<br>[%]<br>day 93       | Mean   | 1.8 k                 | 2.0                     | 2.2                     | 2.3                      |
|                            | S.d.   | 0.5                   | 0.5                     | 0.6                     | 0.5                      |
|                            | N      | 10                    | 10                      | 10                      | 10                       |
|                            | Median | 1.7                   | 2.0                     | 2.4                     | 2.3                      |
| PLT<br>[giga/L]<br>day 93  | Mean   | 778 k                 | 727                     | 769                     | 731                      |
|                            | S.d.   | 91                    | 93                      | 68                      | 28                       |
|                            | N      | 10                    | 10                      | 10                      | 10                       |
|                            | Median | 786                   | 747                     | 774                     | 725                      |
| HQT<br>[sec]<br>day 93     | Mean   | 35.5 v                | 35.2                    | 36.8                    | 38.2 **                  |
|                            | S.d.   | 2.2                   | 1.3                     | 1.5                     | 1.2                      |
|                            | N      | 10                    | 10                      | 10                      | 10                       |
|                            | Median | 35.9                  | 35.0                    | 36.6                    | 38.4                     |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), \* p<=0.05, \*\* p <=0.01, X = Group excluded from statistics  
v=KRUSKAL-WALLIS-WILCOX; k=KRUSKAL-WALLIS



Study

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IB 3

16-Jan-2014 14:04

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### White blood cell parameters

Sex: Male - Phase: In-life

|                              |        | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|------------------------------|--------|-----------------------|-------------------------|-------------------------|------------------------------|
| WBC<br>[giga/L]<br>day 92    | Mean   | 5.51 v                | 5.11                    | 4.59 *                  | 4.28 **                      |
|                              | S.d.   | 0.95                  | 1.16                    | 0.58                    | 0.90                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 5.64                  | 5.24                    | 4.49                    | 4.37                         |
| NEUTA<br>[giga/L]<br>day 92  | Mean   | 0.94 k                | 0.92                    | 1.06                    | 1.11                         |
|                              | S.d.   | 0.22                  | 0.41                    | 0.30                    | 0.30                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 0.84                  | 0.80                    | 0.98                    | 1.07                         |
| LYMPHA<br>[giga/L]<br>day 92 | Mean   | 4.30 v                | 3.93                    | 3.29 **                 | 2.98 **                      |
|                              | S.d.   | 0.77                  | 0.92                    | 0.55                    | 0.63                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 4.43                  | 4.21                    | 3.15                    | 3.15                         |
| MONOA<br>[giga/L]<br>day 92  | Mean   | 0.12 k                | 0.12                    | 0.11                    | 0.08                         |
|                              | S.d.   | 0.05                  | 0.09                    | 0.10                    | 0.03                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 0.11                  | 0.09                    | 0.08                    | 0.07                         |
| EOSA<br>[giga/L]<br>day 92   | Mean   | 0.11 k                | 0.10                    | 0.10                    | 0.08                         |
|                              | S.d.   | 0.03                  | 0.04                    | 0.02                    | 0.03                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 0.11                  | 0.09                    | 0.10                    | 0.08                         |
| BASOA<br>[giga/L]<br>day 92  | Mean   | 0.02 k                | 0.01                    | 0.01                    | 0.01                         |
|                              | S.d.   | 0.01                  | 0.01                    | 0.01                    | 0.01                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 0.02                  | 0.01                    | 0.01                    | 0.01                         |
| LUCA<br>[giga/L]<br>day 92   | Mean   | 0.03 v                | 0.02                    | 0.01 **                 | 0.02 *                       |
|                              | S.d.   | 0.01                  | 0.01                    | 0.01                    | 0.01                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 0.03                  | 0.02                    | 0.01                    | 0.01                         |
| NEUT<br>[%]<br>day 92        | Mean   | 17.2 v                | 18.2                    | 23.1 **                 | 26.0 **                      |
|                              | S.d.   | 3.1                   | 5.6                     | 5.6                     | 4.1                          |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 18.5                  | 17.7                    | 22.9                    | 25.3                         |
| LYMPH<br>[%]<br>day 92       | Mean   | 77.9 v                | 77.0                    | 71.8 **                 | 69.6 **                      |
|                              | S.d.   | 3.2                   | 6.8                     | 7.0                     | 4.2                          |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 77.4                  | 78.3                    | 72.3                    | 70.1                         |
| MONO<br>[%]<br>day 92        | Mean   | 2.1 k                 | 2.2                     | 2.5                     | 1.8                          |
|                              | S.d.   | 0.8                   | 1.2                     | 2.0                     | 0.5                          |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 1.9                   | 1.9                     | 1.8                     | 1.6                          |
| EOS<br>[%]<br>day 92         | Mean   | 2.0 k                 | 2.0                     | 2.1                     | 1.9                          |
|                              | S.d.   | 0.5                   | 0.5                     | 0.4                     | 0.5                          |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 1.9                   | 1.9                     | 2.2                     | 1.8                          |
| BASO<br>[%]<br>day 92        | Mean   | 0.3 k                 | 0.2                     | 0.3                     | 0.2                          |
|                              | S.d.   | 0.1                   | 0.1                     | 0.1                     | 0.1                          |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 0.3                   | 0.3                     | 0.2                     | 0.2                          |
| LUC<br>[%]<br>day 92         | Mean   | 0.4 k                 | 0.3                     | 0.3                     | 0.4                          |
|                              | S.d.   | 0.2                   | 0.1                     | 0.2                     | 0.2                          |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 0.3                   | 0.3                     | 0.3                     | 0.3                          |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), \*  $p \leq 0.05$ , \*\*  $p \leq 0.01$ , X = Group excluded from statistics  
v=KRUSKAL-WALLIS-WILCOX; k=KRUSKAL-WALLIS

Study

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IB 4

16-Jan-2014 13:48

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### White blood cell parameters

Sex: Female - Phase: In-life

|                              |        | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|------------------------------|--------|-----------------------|-------------------------|-------------------------|--------------------------|
| WBC<br>[giga/L]<br>day 93    | Mean   | 4.09 k                | 4.35                    | 3.85                    | 3.56                     |
|                              | S.d.   | 0.82                  | 0.81                    | 0.97                    | 0.48                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 3.78                  | 4.29                    | 3.85                    | 3.69                     |
| NEUTA<br>[giga/L]<br>day 93  | Mean   | 0.57 k                | 0.65                    | 0.55                    | 0.51                     |
|                              | S.d.   | 0.10                  | 0.23                    | 0.11                    | 0.14                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 0.59                  | 0.57                    | 0.58                    | 0.45                     |
| LYMPHA<br>[giga/L]<br>day 93 | Mean   | 3.31 k                | 3.50                    | 3.14                    | 2.90                     |
|                              | S.d.   | 0.75                  | 0.87                    | 0.93                    | 0.40                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 3.17                  | 3.49                    | 3.09                    | 2.91                     |
| MONOA<br>[giga/L]<br>day 93  | Mean   | 0.08 k                | 0.09                    | 0.07                    | 0.08                     |
|                              | S.d.   | 0.02                  | 0.03                    | 0.02                    | 0.02                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 0.07                  | 0.08                    | 0.07                    | 0.07                     |
| EOSA<br>[giga/L]<br>day 93   | Mean   | 0.09 v                | 0.08                    | 0.07                    | 0.05**                   |
|                              | S.d.   | 0.03                  | 0.02                    | 0.03                    | 0.02                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 0.08                  | 0.08                    | 0.06                    | 0.05                     |
| BASOA<br>[giga/L]<br>day 93  | Mean   | 0.02 k                | 0.01                    | 0.01                    | 0.01                     |
|                              | S.d.   | 0.01                  | 0.01                    | 0.00                    | 0.01                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 0.01                  | 0.01                    | 0.01                    | 0.01                     |
| LUCA<br>[giga/L]<br>day 93   | Mean   | 0.02 k                | 0.02                    | 0.02                    | 0.01                     |
|                              | S.d.   | 0.01                  | 0.01                    | 0.01                    | 0.01                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 0.02                  | 0.01                    | 0.01                    | 0.01                     |
| NEUT<br>[%]<br>day 93        | Mean   | 14.1 k                | 15.8                    | 15.1                    | 14.3                     |
|                              | S.d.   | 2.8                   | 7.2                     | 4.5                     | 3.2                      |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 14.3                  | 12.8                    | 14.4                    | 14.2                     |
| LYMPH<br>[%]<br>day 93       | Mean   | 80.8 k                | 79.7                    | 80.8                    | 81.5                     |
|                              | S.d.   | 3.4                   | 7.9                     | 4.6                     | 3.9                      |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 80.1                  | 83.0                    | 81.5                    | 82.1                     |
| MONO<br>[%]<br>day 93        | Mean   | 2.0 k                 | 2.0                     | 1.8                     | 2.1                      |
|                              | S.d.   | 0.2                   | 0.6                     | 0.5                     | 0.5                      |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 1.9                   | 1.9                     | 1.8                     | 1.9                      |
| EOS<br>[%]<br>day 93         | Mean   | 2.2 k                 | 1.9                     | 1.7                     | 1.5                      |
|                              | S.d.   | 0.7                   | 0.6                     | 0.4                     | 0.4                      |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 2.2                   | 1.8                     | 1.8                     | 1.4                      |
| BASO<br>[%]<br>day 93        | Mean   | 0.4 v                 | 0.3                     | 0.3                     | 0.2**                    |
|                              | S.d.   | 0.1                   | 0.1                     | 0.1                     | 0.1                      |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 0.4                   | 0.3                     | 0.2                     | 0.2                      |
| LUC<br>[%]<br>day 93         | Mean   | 0.5 k                 | 0.3                     | 0.4                     | 0.4                      |
|                              | S.d.   | 0.2                   | 0.2                     | 0.1                     | 0.2                      |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 0.5                   | 0.3                     | 0.4                     | 0.3                      |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), \* p<=0.05, \*\* p <=0.01, X = Group excluded from statistics  
k=KRUSKAL-WALLIS; v=KRUSKAL-WALLIS-WILCOX

Study 50C0066/05S019

IB 5

16-Jan-2014 14:12

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## Enzymes

Sex: Male - Phase: In-life

|                             |        | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|-----------------------------|--------|-----------------------|-------------------------|-------------------------|------------------------------|
| ALT<br>[µkat/L]<br>day 92   | Mean   | 0.68 v                | 0.80                    | 0.91 **                 | 0.92                         |
|                             | S.d.   | 0.12                  | 0.47                    | 0.16                    | 0.46                         |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 0.62                  | 0.65                    | 0.90                    | 0.82                         |
| AST<br>[µkat/L]<br>day 92   | Mean   | 1.63 k                | 1.42                    | 1.77                    | 1.81                         |
|                             | S.d.   | 0.68                  | 0.16                    | 0.57                    | 0.73                         |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 1.47                  | 1.42                    | 1.71                    | 1.64                         |
| ALP<br>[µkat/L]<br>day 92   | Mean   | 1.25 k                | 1.43                    | 1.40                    | 1.41                         |
|                             | S.d.   | 0.21                  | 0.24                    | 0.27                    | 0.32                         |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 1.19                  | 1.40                    | 1.29                    | 1.48                         |
| GGT_C<br>[nkat/L]<br>day 92 | Mean   | 0 k                   | 0                       | 0                       | 0                            |
|                             | S.d.   | 0                     | 0                       | 0                       | 0                            |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 0                     | 0                       | 0                       | 0                            |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), \* p<=0.05, \*\* p <=0.01, X = Group excluded from statistics  
v=KRUSKAL-WALLIS-WILCOX; k=KRUSKAL-WALLIS

Study 50C0066/05S019

IB 6

16-Jan-2014 14:13

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## Enzymes

Sex: Female - Phase: In-life

|                             |        | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|-----------------------------|--------|-----------------------|-------------------------|-------------------------|--------------------------|
| ALT<br>[µkat/L]<br>day 93   | Mean   | 0.58 k                | 0.63                    | 0.58                    | 0.79                     |
|                             | S.d.   | 0.13                  | 0.16                    | 0.10                    | 0.23                     |
|                             | N      | 10                    | 10                      | 10                      | 10                       |
|                             | Median | 0.58                  | 0.62                    | 0.59                    | 0.70                     |
| AST<br>[µkat/L]<br>day 93   | Mean   | 1.38 k                | 1.54                    | 1.36                    | 1.19                     |
|                             | S.d.   | 0.32                  | 0.41                    | 0.29                    | 0.24                     |
|                             | N      | 10                    | 10                      | 10                      | 10                       |
|                             | Median | 1.38                  | 1.36                    | 1.40                    | 1.11                     |
| ALP<br>[µkat/L]<br>day 93   | Mean   | 0.66 v                | 0.55                    | 0.69                    | 1.01 *                   |
|                             | S.d.   | 0.19                  | 0.09                    | 0.25                    | 0.37                     |
|                             | N      | 10                    | 10                      | 10                      | 10                       |
|                             | Median | 0.66                  | 0.55                    | 0.63                    | 0.93                     |
| GGT_C<br>[nkat/L]<br>day 93 | Mean   | 0 v                   | 0                       | 0                       | 3                        |
|                             | S.d.   | 0                     | 0                       | 0                       | 6                        |
|                             | N      | 10                    | 10                      | 10                      | 10                       |
|                             | Median | 0                     | 0                       | 0                       | 0                        |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), \* p<=0.05, \*\* p<=0.01, X = Group excluded from statistics  
k=KRUSKAL-WALLIS; v=KRUSKAL-WALLIS-WILCOX

## Substrates

Sex: Male - Phase: In-life

|                              |        | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|------------------------------|--------|-----------------------|-------------------------|-------------------------|------------------------------|
| UREA<br>[mmol/L]<br>day 92   | Mean   | 5.09 v                | 4.82                    | 4.47 **                 | 5.30                         |
|                              | S.d.   | 0.54                  | 0.41                    | 0.53                    | 0.62                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 4.98                  | 4.76                    | 4.42                    | 5.38                         |
| CREA<br>[µmol/L]<br>day 92   | Mean   | 30.3 v                | 28.2 *                  | 30.8                    | 34.2 *                       |
|                              | S.d.   | 2.2                   | 1.4                     | 2.7                     | 3.7                          |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 31.4                  | 28.6                    | 31.3                    | 34.0                         |
| GLUC<br>[mmol/L]<br>day 92   | Mean   | 6.37 v                | 6.10                    | 5.48 *                  | 5.16 **                      |
|                              | S.d.   | 0.68                  | 0.94                    | 0.64                    | 0.65                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 6.25                  | 6.26                    | 5.25                    | 5.29                         |
| TBIL_C<br>[µmol/L]<br>day 92 | Mean   | 1.62 v                | 1.57                    | 1.49                    | 1.26 **                      |
|                              | S.d.   | 0.20                  | 0.15                    | 0.34                    | 0.37                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 1.67                  | 1.53                    | 1.57                    | 1.21                         |
| TPROT<br>[g/L]<br>day 92     | Mean   | 63.38 k               | 64.68                   | 63.68                   | 62.64                        |
|                              | S.d.   | 1.81                  | 2.50                    | 1.66                    | 2.30                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 63.00                 | 65.25                   | 63.53                   | 62.34                        |
| ALB<br>[g/L]<br>day 92       | Mean   | 38.64 k               | 38.89                   | 38.85                   | 38.23                        |
|                              | S.d.   | 0.56                  | 1.04                    | 1.21                    | 0.89                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 38.66                 | 38.89                   | 38.65                   | 38.21                        |
| GLOB<br>[g/L]<br>day 92      | Mean   | 24.74 k               | 25.79                   | 24.83                   | 24.41                        |
|                              | S.d.   | 1.33                  | 1.87                    | 1.01                    | 1.61                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 24.39                 | 26.30                   | 24.75                   | 24.02                        |
| CHOL<br>[mmol/L]<br>day 92   | Mean   | 1.85 v                | 1.65                    | 1.23 **                 | 1.03 **                      |
|                              | S.d.   | 0.29                  | 0.36                    | 0.29                    | 0.17                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 1.92                  | 1.68                    | 1.23                    | 0.92                         |
| TRIG<br>[mmol/L]<br>day 92   | Mean   | 0.97 v                | 1.53 **                 | 1.48 **                 | 2.32 **                      |
|                              | S.d.   | 0.39                  | 0.37                    | 0.31                    | 0.64                         |
|                              | N      | 10                    | 10                      | 10                      | 10                           |
|                              | Median | 0.91                  | 1.60                    | 1.43                    | 2.28                         |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), \* p<=0.05, \*\* p <=0.01, X = Group excluded from statistics  
v=KRUSKAL-WALLIS-WILCOX; k=KRUSKAL-WALLIS

# Substrates

Sex: Female - Phase: In-life

|                              |        | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|------------------------------|--------|-----------------------|-------------------------|-------------------------|--------------------------|
| UREA<br>[mmol/L]<br>day 93   | Mean   | 6.22 k                | 6.29                    | 5.73                    | 5.42                     |
|                              | S.d.   | 0.98                  | 0.70                    | 0.58                    | 0.54                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 6.01                  | 6.62                    | 5.63                    | 5.62                     |
| CREA<br>[μmol/L]<br>day 93   | Mean   | 36.6 k                | 35.9                    | 34.2                    | 32.1                     |
|                              | S.d.   | 5.9                   | 2.9                     | 3.8                     | 4.0                      |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 36.5                  | 35.4                    | 34.5                    | 31.1                     |
| GLUC<br>[mmol/L]<br>day 93   | Mean   | 5.17 v                | 5.04                    | 5.48                    | 5.66 *                   |
|                              | S.d.   | 0.42                  | 0.44                    | 0.28                    | 0.39                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 5.12                  | 5.06                    | 5.46                    | 5.66                     |
| TBIL_C<br>[μmol/L]<br>day 93 | Mean   | 2.52 k                | 2.18                    | 2.02                    | 2.32                     |
|                              | S.d.   | 0.45                  | 0.56                    | 0.39                    | 0.41                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 2.31                  | 2.01                    | 1.96                    | 2.36                     |
| TPROT<br>[g/L]<br>day 93     | Mean   | 68.13 k               | 69.00                   | 68.95                   | 70.12                    |
|                              | S.d.   | 3.25                  | 2.37                    | 2.64                    | 3.78                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 68.00                 | 69.65                   | 68.04                   | 68.27                    |
| ALB<br>[g/L]<br>day 93       | Mean   | 42.63 k               | 42.86                   | 41.86                   | 43.28                    |
|                              | S.d.   | 1.43                  | 1.28                    | 1.67                    | 2.28                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 42.64                 | 43.30                   | 41.58                   | 42.97                    |
| GLOB<br>[g/L]<br>day 93      | Mean   | 25.50 k               | 26.14                   | 27.09                   | 26.84                    |
|                              | S.d.   | 2.08                  | 1.57                    | 1.70                    | 1.80                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 25.51                 | 26.39                   | 26.99                   | 26.29                    |
| CHOL<br>[mmol/L]<br>day 93   | Mean   | 1.62 k                | 1.56                    | 1.30                    | 1.33                     |
|                              | S.d.   | 0.44                  | 0.26                    | 0.29                    | 0.32                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 1.60                  | 1.55                    | 1.21                    | 1.31                     |
| TRIG<br>[mmol/L]<br>day 93   | Mean   | 0.72 k                | 0.81                    | 0.79                    | 0.99                     |
|                              | S.d.   | 0.31                  | 0.23                    | 0.27                    | 0.29                     |
|                              | N      | 10                    | 10                      | 10                      | 10                       |
|                              | Median | 0.68                  | 0.77                    | 0.78                    | 0.90                     |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), \* p<=0.05, \*\* p <=0.01, X = Group excluded from statistics  
k=KRUSKAL-WALLIS; v=KRUSKAL-WALLIS-WILCOX

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50C0066/05S019

IB 9

16-Jan-2014 14:16

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**Electrolytes + minerals**

Sex: **Male** - Phase: **In-life**

|                           |        | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|---------------------------|--------|-----------------------|-------------------------|-------------------------|------------------------------|
| NA<br>[mmol/L]<br>day 92  | Mean   | 143.2 k               | 142.7                   | 143.2                   | 142.4                        |
|                           | S.d.   | 0.9                   | 0.7                     | 1.2                     | 0.7                          |
|                           | N      | 10                    | 10                      | 10                      | 10                           |
|                           | Median | 143.3                 | 142.7                   | 143.3                   | 142.4                        |
| K<br>[mmol/L]<br>day 92   | Mean   | 4.84 k                | 4.78                    | 4.84                    | 4.68                         |
|                           | S.d.   | 0.22                  | 0.29                    | 0.29                    | 0.31                         |
|                           | N      | 10                    | 10                      | 10                      | 10                           |
|                           | Median | 4.86                  | 4.81                    | 4.86                    | 4.75                         |
| CL<br>[mmol/L]<br>day 92  | Mean   | 101.5 v               | 100.5 **                | 100.8                   | 99.6 **                      |
|                           | S.d.   | 0.5                   | 0.7                     | 1.1                     | 1.3                          |
|                           | N      | 10                    | 10                      | 10                      | 10                           |
|                           | Median | 101.5                 | 100.5                   | 100.8                   | 99.6                         |
| INP<br>[mmol/L]<br>day 92 | Mean   | 1.65 v                | 1.56                    | 1.77                    | 1.88 **                      |
|                           | S.d.   | 0.14                  | 0.17                    | 0.22                    | 0.24                         |
|                           | N      | 10                    | 10                      | 10                      | 10                           |
|                           | Median | 1.65                  | 1.58                    | 1.75                    | 1.81                         |
| CA<br>[mmol/L]<br>day 92  | Mean   | 2.54 k                | 2.59                    | 2.57                    | 2.60                         |
|                           | S.d.   | 0.06                  | 0.06                    | 0.06                    | 0.04                         |
|                           | N      | 10                    | 10                      | 10                      | 10                           |
|                           | Median | 2.54                  | 2.59                    | 2.58                    | 2.59                         |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), \*  $p \leq 0.05$ , \*\*  $p \leq 0.01$ , X = Group excluded from statistics  
k=KRUSKAL-WALLIS; v=KRUSKAL-WALLIS-WILCOX

Study 50C0066/05S019

IB 10  
16-Jan-2014 14:16  
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**Electrolytes + minerals**

Sex: **Female** - Phase: **In-life**

|                           |        | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|---------------------------|--------|-----------------------|-------------------------|-------------------------|--------------------------|
| NA<br>[mmol/L]<br>day 93  | Mean   | 140.7 k               | 140.7                   | 140.4                   | 140.0                    |
|                           | S.d.   | 1.0                   | 1.5                     | 1.4                     | 1.8                      |
|                           | N      | 10                    | 10                      | 10                      | 10                       |
|                           | Median | 140.6                 | 140.2                   | 140.1                   | 139.6                    |
| K<br>[mmol/L]<br>day 93   | Mean   | 4.35 k                | 4.43                    | 4.32                    | 4.46                     |
|                           | S.d.   | 0.33                  | 0.23                    | 0.27                    | 0.26                     |
|                           | N      | 10                    | 10                      | 10                      | 10                       |
|                           | Median | 4.41                  | 4.46                    | 4.26                    | 4.46                     |
| CL<br>[mmol/L]<br>day 93  | Mean   | 99.2 v                | 100.1                   | 98.8                    | 97.3 **                  |
|                           | S.d.   | 0.8                   | 1.9                     | 1.3                     | 1.5                      |
|                           | N      | 10                    | 10                      | 10                      | 10                       |
|                           | Median | 99.2                  | 100.1                   | 98.8                    | 97.1                     |
| INP<br>[mmol/L]<br>day 93 | Mean   | 1.52 k                | 1.48                    | 1.42                    | 1.66                     |
|                           | S.d.   | 0.16                  | 0.20                    | 0.25                    | 0.30                     |
|                           | N      | 10                    | 10                      | 10                      | 10                       |
|                           | Median | 1.48                  | 1.47                    | 1.46                    | 1.60                     |
| CA<br>[mmol/L]<br>day 93  | Mean   | 2.62 k                | 2.62                    | 2.60                    | 2.66                     |
|                           | S.d.   | 0.09                  | 0.05                    | 0.06                    | 0.06                     |
|                           | N      | 10                    | 10                      | 10                      | 10                       |
|                           | Median | 2.62                  | 2.64                    | 2.62                    | 2.66                     |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), \* p<=0.05, \*\* p<=0.01, X = Group excluded from statistics  
k=KRUSKAL-WALLIS; v=KRUSKAL-WALLIS-WILCOX



Study

50C0066/05S019

IB 11

16-Jan-2014 14:17

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## Urinalyses

Sex: Male - Phase: In-life

|                             |        | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|-----------------------------|--------|-----------------------|-------------------------|-------------------------|------------------------------|
| PH_C<br>[---]<br>day 85     | Mean   | 6.8 v                 | 6.2 **                  | 5.7 **                  | 6.2 **                       |
|                             | S.d.   | 0.2                   | 0.5                     | 0.7                     | 0.7                          |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 7.0                   | 6.5                     | 5.5                     | 6.5                          |
| PRO_C<br>[---]<br>day 85    | Mean   | 1 x+                  | 1                       | 1                       | 1                            |
|                             | S.d.   | 0                     | 0                       | 0                       | 0                            |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 1                     | 1                       | 1                       | 1                            |
| GLU_C<br>[---]<br>day 85    | Mean   | 0 x+                  | 0                       | 0                       | 0                            |
|                             | S.d.   | 0                     | 0                       | 0                       | 0                            |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 0                     | 0                       | 0                       | 0                            |
| KET_C<br>[---]<br>day 85    | Mean   | 1 x+                  | 1                       | 1                       | 1                            |
|                             | S.d.   | 0                     | 0                       | 0                       | 0                            |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 1                     | 1                       | 1                       | 1                            |
| UBG_C<br>[---]<br>day 85    | Mean   | 1 x+                  | 1                       | 1                       | 1                            |
|                             | S.d.   | 0                     | 0                       | 0                       | 0                            |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 1                     | 1                       | 1                       | 1                            |
| BIL_C<br>[---]<br>day 85    | Mean   | 1 x+                  | 1                       | 1                       | 1                            |
|                             | S.d.   | 0                     | 0                       | 0                       | 0                            |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 1                     | 1                       | 1                       | 1                            |
| BLOOD_C<br>[---]<br>day 85  | Mean   | 1 x+                  | 1                       | 1                       | 1                            |
|                             | S.d.   | 0                     | 1                       | 0                       | 0                            |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 1                     | 1                       | 1                       | 1                            |
| VOL<br>[ml]<br>day 85       | Mean   | 5.3 k                 | 4.3                     | 4.3                     | 5.8                          |
|                             | S.d.   | 1.0                   | 1.7                     | 1.7                     | 2.8                          |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 5.5                   | 3.8                     | 3.8                     | 4.8                          |
| SP.GR._C<br>[g/L]<br>day 85 | Mean   | 1,042 k               | 1,057                   | 1,059                   | 1,051                        |
|                             | S.d.   | 8                     | 19                      | 21                      | 16                           |
|                             | N      | 10                    | 10                      | 10                      | 10                           |
|                             | Median | 1,043                 | 1,055                   | 1,057                   | 1,048                        |

Statistic Profile = Kruskal-Wallis + Wilcoxon test (two-sided), Wilcoxon test (one-sided+), \* p<=0.05, \*\* p <=0.01, X = Group excluded from statistics

v=KRUSKAL-WALLIS-WILCOX; x=WILCOX; k=KRUSKAL-WALLIS

Study 50C0066/05S019

IB 12

16-Jan-2014 14:18

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# Urinalyses

Sex: Male - Phase: In-life

|                               |        | 0 / M<br>0 mg/kg bw/d | 1 / M<br>100 mg/kg bw/d | 2 / M<br>300 mg/kg bw/d | 3 / M<br>1000/600 mg/kg bw/d |
|-------------------------------|--------|-----------------------|-------------------------|-------------------------|------------------------------|
| CRYST_C<br>[---]<br>day 85    | Mean   | 2 x+                  | 2                       | 2                       | 2                            |
|                               | S.d.   | 1                     | 1                       | 0                       | 0                            |
|                               | N      | 10                    | 10                      | 10                      | 10                           |
|                               | Median | 2                     | 2                       | 2                       | 2                            |
| RENAL_EC_C<br>[---]<br>day 85 | Mean   | 1 x+                  | 1                       | 1                       | 1                            |
|                               | S.d.   | 0                     | 0                       | 0                       | 0                            |
|                               | N      | 10                    | 10                      | 10                      | 10                           |
|                               | Median | 1                     | 1                       | 1                       | 1                            |
| TRANS_EC_C<br>[---]<br>day 85 | Mean   | 1 x+                  | 1                       | 1                       | 1                            |
|                               | S.d.   | 0                     | 0                       | 1                       | 0                            |
|                               | N      | 10                    | 10                      | 10                      | 10                           |
|                               | Median | 1                     | 1                       | 1                       | 1                            |
| SQUAM_EC_C<br>[---]<br>day 85 | Mean   | 1 x+                  | 1                       | 1                       | 1                            |
|                               | S.d.   | 0                     | 0                       | 0                       | 0                            |
|                               | N      | 10                    | 10                      | 10                      | 10                           |
|                               | Median | 1                     | 1                       | 1                       | 1                            |
| CASTS_C<br>[---]<br>day 85    | Mean   | 0 x+                  | 0                       | 1                       | 0                            |
|                               | S.d.   | 0                     | 0                       | 1                       | 0                            |
|                               | N      | 10                    | 10                      | 10                      | 10                           |
|                               | Median | 0                     | 0                       | 1                       | 0                            |
| ERY_C<br>[---]<br>day 85      | Mean   | 1 x+                  | 1                       | 1                       | 1                            |
|                               | S.d.   | 0                     | 0                       | 0                       | 0                            |
|                               | N      | 10                    | 10                      | 10                      | 10                           |
|                               | Median | 1                     | 1                       | 1                       | 1                            |
| LEUCO_C<br>[---]<br>day 85    | Mean   | 1 x+                  | 1                       | 1                       | 1                            |
|                               | S.d.   | 0                     | 0                       | 0                       | 0                            |
|                               | N      | 10                    | 10                      | 10                      | 10                           |
|                               | Median | 1                     | 1                       | 1                       | 1                            |

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

Study

50C0066/05S019

IB 13

16-Jan-2014 14:18

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# Urinalyses

Sex: Female - Phase: In-life

|          |        | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|----------|--------|-----------------------|-------------------------|-------------------------|--------------------------|
| PH_C     | Mean   | 6.0 k                 | 5.7                     | 6.0                     | 6.2                      |
| [---]    | S.d.   | 0.6                   | 0.7                     | 0.7                     | 0.7                      |
| day 85   | N      | 10                    | 10                      | 10                      | 10                       |
|          | Median | 6.0                   | 5.5                     | 6.2                     | 6.5                      |
| PRO_C    | Mean   | 1 x+                  | 1                       | 1                       | 1                        |
| [---]    | S.d.   | 0                     | 0                       | 0                       | 0                        |
| day 85   | N      | 10                    | 10                      | 10                      | 10                       |
|          | Median | 1                     | 1                       | 1                       | 1                        |
| GLU_C    | Mean   | 0 x+                  | 0                       | 0                       | 0                        |
| [---]    | S.d.   | 0                     | 0                       | 0                       | 0                        |
| day 85   | N      | 10                    | 10                      | 10                      | 10                       |
|          | Median | 0                     | 0                       | 0                       | 0                        |
| KET_C    | Mean   | 1 x+                  | 1                       | 1                       | 1                        |
| [---]    | S.d.   | 0                     | 0                       | 0                       | 0                        |
| day 85   | N      | 10                    | 10                      | 10                      | 10                       |
|          | Median | 1                     | 1                       | 1                       | 1                        |
| UBG_C    | Mean   | 1 x+                  | 1                       | 1                       | 1                        |
| [---]    | S.d.   | 0                     | 0                       | 0                       | 0                        |
| day 85   | N      | 10                    | 10                      | 10                      | 10                       |
|          | Median | 1                     | 1                       | 1                       | 1                        |
| BIL_C    | Mean   | 1 x+                  | 1                       | 1                       | 1                        |
| [---]    | S.d.   | 0                     | 0                       | 0                       | 0                        |
| day 85   | N      | 10                    | 10                      | 10                      | 10                       |
|          | Median | 1                     | 1                       | 1                       | 1                        |
| BLOOD_C  | Mean   | 1 x+                  | 1                       | 1                       | 1                        |
| [---]    | S.d.   | 0                     | 0                       | 0                       | 0                        |
| day 85   | N      | 10                    | 10                      | 10                      | 10                       |
|          | Median | 1                     | 1                       | 1                       | 1                        |
| VOL      | Mean   | 2.6 v                 | 2.6                     | 3.0                     | 4.8 **                   |
| [ml]     | S.d.   | 1.5                   | 1.0                     | 1.0                     | 1.6                      |
| day 85   | N      | 10                    | 10                      | 10                      | 10                       |
|          | Median | 2.4                   | 2.5                     | 3.0                     | 4.9                      |
| SP.GR._C | Mean   | 1,065 k               | 1,056                   | 1,060                   | 1,048                    |
| [g/L]    | S.d.   | 28                    | 18                      | 32                      | 10                       |
| day 85   | N      | 10                    | 10                      | 10                      | 10                       |
|          | Median | 1,056                 | 1,047                   | 1,050                   | 1,044                    |

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; x=WILCOX; v=KRUSKAL-WALLIS-WILCOX

Study 50C0066/05S019

IB 14

16-Jan-2014 14:18

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## Urinalyses

Sex: Female - Phase: In-life

|                               |        | 0 / F<br>0 mg/kg bw/d | 1 / F<br>100 mg/kg bw/d | 2 / F<br>300 mg/kg bw/d | 3 / F<br>1000 mg/kg bw/d |
|-------------------------------|--------|-----------------------|-------------------------|-------------------------|--------------------------|
| CRYST_C<br>[---]<br>day 85    | Mean   | 2 x+                  | 2                       | 2                       | 2                        |
|                               | S.d.   | 0                     | 0                       | 0                       | 0                        |
|                               | N      | 10                    | 10                      | 10                      | 10                       |
|                               | Median | 2                     | 2                       | 2                       | 2                        |
| RENAL_EC_C<br>[---]<br>day 85 | Mean   | 1 x+                  | 1                       | 1                       | 1                        |
|                               | S.d.   | 0                     | 0                       | 0                       | 0                        |
|                               | N      | 10                    | 10                      | 10                      | 10                       |
|                               | Median | 1                     | 1                       | 1                       | 1                        |
| TRANS_EC_C<br>[---]<br>day 85 | Mean   | 1 x+                  | 1                       | 1                       | 1                        |
|                               | S.d.   | 0                     | 0                       | 0                       | 0                        |
|                               | N      | 10                    | 10                      | 10                      | 10                       |
|                               | Median | 1                     | 1                       | 1                       | 1                        |
| SQUAM_EC_C<br>[---]<br>day 85 | Mean   | 1 x+                  | 1                       | 1                       | 1                        |
|                               | S.d.   | 0                     | 0                       | 0                       | 0                        |
|                               | N      | 10                    | 10                      | 10                      | 10                       |
|                               | Median | 1                     | 1                       | 1                       | 1                        |
| CASTS_C<br>[---]<br>day 85    | Mean   | 0 x+                  | 0                       | 0                       | 0                        |
|                               | S.d.   | 0                     | 0                       | 0                       | 0                        |
|                               | N      | 10                    | 10                      | 10                      | 10                       |
|                               | Median | 0                     | 0                       | 0                       | 0                        |
| ERY_C<br>[---]<br>day 85      | Mean   | 1 x+                  | 1                       | 1                       | 1                        |
|                               | S.d.   | 0                     | 0                       | 0                       | 0                        |
|                               | N      | 10                    | 10                      | 10                      | 10                       |
|                               | Median | 1                     | 1                       | 1                       | 1                        |
| LEUCO_C<br>[---]<br>day 85    | Mean   | 1 x+                  | 1                       | 1                       | 1                        |
|                               | S.d.   | 0                     | 0                       | 0                       | 0                        |
|                               | N      | 10                    | 10                      | 10                      | 10                       |
|                               | Median | 1                     | 1                       | 1                       | 1                        |

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

BASF PATHOLOGY REPORT IC 1/15  
50C0066/05S019  
Repeated-dose 90-day oral toxicity study in Wistar rats  
Administration by gavage 11.Apr.2014 HAMA

## ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

| Sacrifice            |       | F1 |        |         |         |    |           |
|----------------------|-------|----|--------|---------|---------|----|-----------|
| Sex                  |       | M  |        |         |         |    |           |
| Group                |       | 0  |        | 1       |         | 2  |           |
|                      |       |    |        |         |         |    |           |
| Terminal body weight | g     | M  | 394.02 | 376.95  | 356.6   | ** | 311.89 ** |
|                      | % dev |    | 100    | 96      | 91      |    | 79        |
|                      | SD    |    | 30.946 | 43.639  | 18.245  |    | 38.163    |
|                      | n     |    | 10     | 10      | 10      |    | 10        |
| Adrenal glands       | mg    | M  | 64.5   | 59.1    | 63.7    |    | 90.1 **   |
|                      | % dev |    | 100    | 92      | 99      |    | 140       |
|                      | SD    |    | 6.671  | 9.158   | 6.8     |    | 14.364    |
|                      | n     |    | 10     | 10      | 10      |    | 10        |
| Brain                | g     | M  | 2.212  | 2.098** | 2.074** |    | 2.084**   |
|                      | % dev |    | 100    | 95      | 94      |    | 94        |
|                      | SD    |    | 0.059  | 0.029   | 0.073   |    | 0.071     |
|                      | n     |    | 10     | 10      | 10      |    | 10        |
| Epididymides         | g     | M  | 1.209  | 1.16    | 1.126   |    | 1.072**   |
|                      | % dev |    | 100    | 96      | 93      |    | 89        |
|                      | SD    |    | 0.102  | 0.096   | 0.088   |    | 0.082     |
|                      | n     |    | 10     | 10      | 10      |    | 10        |
| Heart                | g     | M  | 1.115  | 1.039   | 1.026*  |    | 0.958**   |
|                      | % dev |    | 100    | 93      | 92      |    | 86        |
|                      | SD    |    | 0.088  | 0.093   | 0.073   |    | 0.091     |
|                      | n     |    | 10     | 10      | 10      |    | 10        |
| Kidneys              | g     | M  | 2.507  | 2.646   | 2.762   |    | 2.485     |
|                      | % dev |    | 100    | 106     | 110     |    | 99        |
|                      | SD    |    | 0.265  | 0.388   | 0.238   |    | 0.419     |
|                      | n     |    | 10     | 10      | 10      |    | 10        |
| Liver                | g     | M  | 8.936  | 8.402   | 8.415   |    | 8.347     |
|                      | % dev |    | 100    | 94      | 94      |    | 93        |
|                      | SD    |    | 0.718  | 1.152   | 0.727   |    | 1.173     |
|                      | n     |    | 10     | 10      | 10      |    | 10        |
| Spleen               | g     | M  | 0.628  | 0.585   | 0.535** |    | 0.595     |
|                      | % dev |    | 100    | 93      | 85      |    | 95        |
|                      | SD    |    | 0.073  | 0.096   | 0.066   |    | 0.118     |
|                      | n     |    | 10     | 10      | 10      |    | 10        |
| Testes               | g     | M  | 3.914  | 3.862   | 3.636*  |    | 3.592*    |
|                      | % dev |    | 100    | 99      | 93      |    | 92        |
|                      | SD    |    | 0.325  | 0.305   | 0.202   |    | 0.226     |
|                      | n     |    | 10     | 10      | 10      |    | 10        |

\*: P <= 0.05, \*\*: P <= 0.01  
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PATHOLOGY REPORT

IC 2/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats

11.Apr.2014 HAMA

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## ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

| Sacrifice      |    |       | F1    |       |        |          |
|----------------|----|-------|-------|-------|--------|----------|
| Sex            |    |       | M     |       |        |          |
| Group          |    |       | 0     | 1     | 2      | 3        |
| .....          |    |       |       |       |        |          |
| Thymus         | mg | M     | 327.5 | 269.4 | 271.3  | 226.1 ** |
|                |    | % dev | 100   | 82    | 83     | 69       |
|                |    | SD    | 79.59 | 72.11 | 66.416 | 54.834   |
|                |    | n     | 10    | 10    | 10     | 10       |
| .....          |    |       |       |       |        |          |
| Thyroid glands | mg | M     | 25.3  | 21.6  | 23.7   | 23.2     |
|                |    | % dev | 100   | 85    | 94     | 92       |
|                |    | SD    | 3.164 | 4.169 | 4.165  | 3.938    |
|                |    | n     | 10    | 10    | 10     | 10       |
| .....          |    |       |       |       |        |          |

\*: P &lt;= 0.05, \*\*: P &lt;= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

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PATHOLOGY REPORT

IC 3/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats

11.Apr.2014 HAMA

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## ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

| Sacrifice            |    |       | F1     |        |        |          |
|----------------------|----|-------|--------|--------|--------|----------|
| Sex                  |    |       | F      |        |        |          |
| Group                |    |       | 0      | 1      | 2      | 3        |
| .....                |    |       |        |        |        |          |
| Terminal body weight | g  | M     | 221.72 | 214.72 | 207.95 | 205.6    |
|                      |    | % dev | 100    | 97     | 94     | 93       |
|                      |    | SD    | 20.389 | 13.154 | 15.256 | 12.413   |
|                      |    | n     | 10     | 10     | 10     | 10       |
| .....                |    |       |        |        |        |          |
| Adrenal glands       | mg | M     | 65.6   | 64.5   | 74.6   | 80.4 **  |
|                      |    | % dev | 100    | 98     | 114    | 123      |
|                      |    | SD    | 7.397  | 8.759  | 13.818 | 10.648   |
|                      |    | n     | 10     | 10     | 10     | 10       |
| .....                |    |       |        |        |        |          |
| Brain                | g  | M     | 2.007  | 1.992  | 1.99   | 1.913*   |
|                      |    | % dev | 100    | 99     | 99     | 95       |
|                      |    | SD    | 0.084  | 0.089  | 0.054  | 0.069    |
|                      |    | n     | 10     | 10     | 10     | 10       |
| .....                |    |       |        |        |        |          |
| Heart                | g  | M     | 0.752  | 0.739  | 0.755  | 0.763    |
|                      |    | % dev | 100    | 98     | 100    | 101      |
|                      |    | SD    | 0.034  | 0.081  | 0.058  | 0.065    |
|                      |    | n     | 10     | 10     | 10     | 10       |
| .....                |    |       |        |        |        |          |
| Kidneys              | g  | M     | 1.5    | 1.489  | 1.584  | 1.644*   |
|                      |    | % dev | 100    | 99     | 106    | 110      |
|                      |    | SD    | 0.134  | 0.104  | 0.117  | 0.135    |
|                      |    | n     | 10     | 10     | 10     | 10       |
| .....                |    |       |        |        |        |          |
| Liver                | g  | M     | 5.106  | 5.39   | 5.688  | 7.043**  |
|                      |    | % dev | 100    | 106    | 111    | 138      |
|                      |    | SD    | 0.718  | 0.763  | 0.514  | 0.52     |
|                      |    | n     | 10     | 10     | 10     | 10       |
| .....                |    |       |        |        |        |          |
| Ovaries              | mg | M     | 104.7  | 104.0  | 106.9  | 126.9    |
|                      |    | % dev | 100    | 99     | 102    | 121      |
|                      |    | SD    | 20.205 | 11.963 | 19.284 | 30.33    |
|                      |    | n     | 10     | 10     | 10     | 10       |
| .....                |    |       |        |        |        |          |
| Spleen               | g  | M     | 0.44   | 0.447  | 0.465  | 0.454    |
|                      |    | % dev | 100    | 102    | 106    | 103      |
|                      |    | SD    | 0.054  | 0.032  | 0.045  | 0.062    |
|                      |    | n     | 10     | 10     | 10     | 10       |
| .....                |    |       |        |        |        |          |
| Thymus               | mg | M     | 303.2  | 292.4  | 245.3  | 222.7 ** |
|                      |    | % dev | 100    | 96     | 81     | 73       |
|                      |    | SD    | 67.82  | 59.191 | 47.287 | 38.43    |
|                      |    | n     | 10     | 10     | 10     | 10       |

\*: P &lt;= 0.05, \*\*: P &lt;= 0.01

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PATHOLOGY REPORT

IC 4/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats

11.Apr.2014 HAMA

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## ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

| Sacrifice      |    |       | F1    |       |       |       |
|----------------|----|-------|-------|-------|-------|-------|
| Sex            |    |       | F     |       |       |       |
| Group          |    |       | 0     | 1     | 2     | 3     |
| .....          |    |       |       |       |       |       |
| Thyroid glands | mg | M     | 17.4  | 15.5  | 17.2  | 19.6  |
|                |    | % dev | 100   | 89    | 99    | 113   |
|                |    | SD    | 2.459 | 2.838 | 3.327 | 2.633 |
|                |    | n     | 10    | 10    | 10    | 10    |
| .....          |    |       |       |       |       |       |
| Uterus         | g  | M     | 0.724 | 0.864 | 1.284 | 0.648 |
|                |    | % dev | 100   | 119   | 177   | 90    |
|                |    | SD    | 0.263 | 0.396 | 0.795 | 0.145 |
|                |    | n     | 10    | 10    | 10    | 10    |
| .....          |    |       |       |       |       |       |

\*: P &lt;= 0.05, \*\*: P &lt;= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided



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PATHOLOGY REPORT

IC 5/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats

11.Apr.2014 HAMA

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## RELATIVE WEIGHTS - MEAN VALUES (MALE)

| Sacrifice            |       |   | F1    |        |         |         |
|----------------------|-------|---|-------|--------|---------|---------|
| Sex                  |       |   | M     |        |         |         |
| Group                |       |   | 0     | 1      | 2       | 3       |
| .....                |       |   |       |        |         |         |
| Terminal body weight | %     | M | 100.0 | 100.0  | 100.0   | 100.0   |
|                      | % dev |   | 100   | 100    | 100     | 100     |
|                      | n     |   | 10    | 10     | 10      | 10      |
| .....                |       |   |       |        |         |         |
| Adrenal glands       | %     | M | 0.016 | 0.016  | 0.018   | 0.029** |
|                      | % dev |   | 100   | 96     | 109     | 177     |
|                      | SD    |   | 0.002 | 0.002  | 0.002   | 0.005   |
|                      | n     |   | 10    | 10     | 10      | 10      |
| .....                |       |   |       |        |         |         |
| Brain                | %     | M | 0.565 | 0.564  | 0.583   | 0.675** |
|                      | % dev |   | 100   | 100    | 103     | 120     |
|                      | SD    |   | 0.05  | 0.069  | 0.032   | 0.069   |
|                      | n     |   | 10    | 10     | 10      | 10      |
| .....                |       |   |       |        |         |         |
| Epididymides         | %     | M | 0.308 | 0.31   | 0.316   | 0.346** |
|                      | % dev |   | 100   | 101    | 103     | 112     |
|                      | SD    |   | 0.029 | 0.033  | 0.027   | 0.027   |
|                      | n     |   | 10    | 10     | 10      | 10      |
| .....                |       |   |       |        |         |         |
| Heart                | %     | M | 0.284 | 0.277  | 0.288   | 0.309*  |
|                      | % dev |   | 100   | 98     | 101     | 109     |
|                      | SD    |   | 0.021 | 0.017  | 0.016   | 0.026   |
|                      | n     |   | 10    | 10     | 10      | 10      |
| .....                |       |   |       |        |         |         |
| Kidneys              | %     | M | 0.636 | 0.702* | 0.775** | 0.795** |
|                      | % dev |   | 100   | 110    | 122     | 125     |
|                      | SD    |   | 0.05  | 0.065  | 0.053   | 0.081   |
|                      | n     |   | 10    | 10     | 10      | 10      |
| .....                |       |   |       |        |         |         |
| Liver                | %     | M | 2.269 | 2.226  | 2.359   | 2.676** |
|                      | % dev |   | 100   | 98     | 104     | 118     |
|                      | SD    |   | 0.09  | 0.111  | 0.165   | 0.201   |
|                      | n     |   | 10    | 10     | 10      | 10      |
| .....                |       |   |       |        |         |         |
| Spleen               | %     | M | 0.16  | 0.156  | 0.15    | 0.19 ** |
|                      | % dev |   | 100   | 97     | 94      | 119     |
|                      | SD    |   | 0.018 | 0.022  | 0.019   | 0.018   |
|                      | n     |   | 10    | 10     | 10      | 10      |
| .....                |       |   |       |        |         |         |
| Testes               | %     | M | 0.999 | 1.035  | 1.021   | 1.162** |
|                      | % dev |   | 100   | 104    | 102     | 116     |
|                      | SD    |   | 0.126 | 0.123  | 0.063   | 0.115   |
|                      | n     |   | 10    | 10     | 10      | 10      |
| .....                |       |   |       |        |         |         |

\*: P &lt;= 0.05, \*\*: P &lt;= 0.01

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PATHOLOGY REPORT

IC 6/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats

11.Apr.2014 HAMA

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## RELATIVE WEIGHTS - MEAN VALUES (MALE)

| Sacrifice      |   |     | F1    |       |       |        |
|----------------|---|-----|-------|-------|-------|--------|
| Sex            |   |     | M     |       |       |        |
| Group          |   |     | 0     | 1     | 2     | 3      |
| .....          |   |     |       |       |       |        |
| Thymus         | % | M   | 0.084 | 0.071 | 0.076 | 0.073  |
|                | % | dev | 100   | 85    | 91    | 88     |
|                |   | SD  | 0.021 | 0.013 | 0.018 | 0.02   |
|                |   | n   | 10    | 10    | 10    | 10     |
| .....          |   |     |       |       |       |        |
| Thyroid glands | % | M   | 0.006 | 0.006 | 0.007 | 0.007* |
|                | % | dev | 100   | 89    | 104   | 116    |
|                |   | SD  | 0.001 | 0.001 | 0.001 | 0.001  |
|                |   | n   | 10    | 10    | 10    | 10     |
| .....          |   |     |       |       |       |        |

\*: P &lt;= 0.05, \*\*: P &lt;= 0.01

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BASF PATHOLOGY REPORT IC 7/15  
50C0066/05S019  
Repeated-dose 90-day oral toxicity study in Wistar rats  
Administration by gavage 11.Apr.2014 HAMA

## RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

| Sacrifice            |   |     | F1    |       |         |         |  |
|----------------------|---|-----|-------|-------|---------|---------|--|
| Sex                  |   |     | F     |       |         |         |  |
| Group                |   |     | 0     | 1     | 2       | 3       |  |
| Terminal body weight | % | M   | 100.0 | 100.0 | 100.0   | 100.0   |  |
|                      | % | dev | 100   | 100   | 100     | 100     |  |
|                      |   | n   | 10    | 10    | 10      | 10      |  |
| Adrenal glands       | % | M   | 0.03  | 0.03  | 0.036*  | 0.039** |  |
|                      | % | dev | 100   | 101   | 121     | 131     |  |
|                      |   | SD  | 0.004 | 0.004 | 0.007   | 0.004   |  |
|                      |   | n   | 10    | 10    | 10      | 10      |  |
| Brain                | % | M   | 0.91  | 0.931 | 0.962   | 0.932   |  |
|                      | % | dev | 100   | 102   | 106     | 102     |  |
|                      |   | SD  | 0.069 | 0.07  | 0.078   | 0.042   |  |
|                      |   | n   | 10    | 10    | 10      | 10      |  |
| Heart                | % | M   | 0.341 | 0.344 | 0.364   | 0.371*  |  |
|                      | % | dev | 100   | 101   | 107     | 109     |  |
|                      |   | SD  | 0.021 | 0.035 | 0.033   | 0.028   |  |
|                      |   | n   | 10    | 10    | 10      | 10      |  |
| Kidneys              | % | M   | 0.679 | 0.695 | 0.765*  | 0.799** |  |
|                      | % | dev | 100   | 102   | 113     | 118     |  |
|                      |   | SD  | 0.054 | 0.047 | 0.074   | 0.03    |  |
|                      |   | n   | 10    | 10    | 10      | 10      |  |
| Liver                | % | M   | 2.297 | 2.502 | 2.75 ** | 3.433** |  |
|                      | % | dev | 100   | 109   | 120     | 149     |  |
|                      |   | SD  | 0.182 | 0.24  | 0.331   | 0.28    |  |
|                      |   | n   | 10    | 10    | 10      | 10      |  |
| Ovaries              | % | M   | 0.047 | 0.048 | 0.052   | 0.061*  |  |
|                      | % | dev | 100   | 102   | 109     | 130     |  |
|                      |   | SD  | 0.008 | 0.005 | 0.01    | 0.012   |  |
|                      |   | n   | 10    | 10    | 10      | 10      |  |
| Spleen               | % | M   | 0.198 | 0.209 | 0.224** | 0.22 *  |  |
|                      | % | dev | 100   | 105   | 113     | 111     |  |
|                      |   | SD  | 0.015 | 0.018 | 0.025   | 0.023   |  |
|                      |   | n   | 10    | 10    | 10      | 10      |  |
| Thymus               | % | M   | 0.136 | 0.136 | 0.118   | 0.108*  |  |
|                      | % | dev | 100   | 100   | 87      | 79      |  |
|                      |   | SD  | 0.025 | 0.026 | 0.023   | 0.018   |  |
|                      |   | n   | 10    | 10    | 10      | 10      |  |

\*: P <= 0.05, \*\*: P <= 0.01  
Kruskal-Wallis H and Wilcoxon test, two sided

BASF

PATHOLOGY REPORT

IC 8/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats

11.Apr.2014 HAMA

Administration by gavage

## RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

| Sacrifice      |   |     | F1    |       |       |         |
|----------------|---|-----|-------|-------|-------|---------|
| Sex            |   |     | F     |       |       |         |
| Group          |   |     | 0     | 1     | 2     | 3       |
| .....          |   |     |       |       |       |         |
| Thyroid glands | % | M   | 0.008 | 0.007 | 0.008 | 0.01 ** |
|                | % | dev | 100   | 92    | 105   | 121     |
|                |   | SD  | 0.001 | 0.001 | 0.002 | 0.001   |
|                |   | n   | 10    | 10    | 10    | 10      |
| .....          |   |     |       |       |       |         |
| Uterus         | % | M   | 0.332 | 0.41  | 0.615 | 0.315   |
|                | % | dev | 100   | 124   | 185   | 95      |
|                |   | SD  | 0.135 | 0.205 | 0.36  | 0.069   |
|                |   | n   | 10    | 10    | 10    | 10      |
| .....          |   |     |       |       |       |         |

\*: P &lt;= 0.05, \*\*: P &lt;= 0.01

Kruskal-Wallis H and Wilcoxon test, two sided

BASF

PATHOLOGY REPORT

IC 9/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats  
Administration by gavage

11.Apr.2014 HAMA

## INCIDENCE OF GROSS LESIONS

| Sacrifice                 | F1 |    |    |    |    |    |    |    |
|---------------------------|----|----|----|----|----|----|----|----|
| Sex                       | M  |    |    |    | F  |    |    |    |
| Group                     | 0  | 1  | 2  | 3  | 0  | 1  | 2  | 3  |
| Animals in selected group | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| No abnormalities          | 9  | 9  | 8  | .  | 10 | 9  | 7  | 2  |
| Axillary lymph nodes      | .  | .  | .  | .  | .  | .  | .  | .  |
| Enlarged                  | .  | 1  | .  | .  | .  | .  | .  | .  |
| Cecum                     | .  | .  | .  | .  | .  | .  | .  | .  |
| Dilation                  | .  | .  | .  | 10 | .  | .  | .  | .  |
| Forestomach               | .  | .  | .  | .  | .  | .  | .  | .  |
| Focus                     | .  | .  | .  | .  | .  | 1  | .  | .  |
| Glandular stomach         | .  | .  | .  | .  | .  | .  | .  | .  |
| Erosion/ulcer             | .  | .  | .  | .  | .  | .  | 1  | .  |
| Heart                     | .  | .  | .  | .  | .  | .  | .  | .  |
| Deposition                | .  | .  | 1  | .  | .  | .  | .  | .  |
| Kidneys                   | .  | .  | .  | .  | .  | .  | .  | .  |
| Pelvic dilation           | 1  | .  | 1  | .  | .  | .  | .  | .  |
| Liver                     | .  | .  | .  | .  | .  | .  | .  | .  |
| Enlarged                  | .  | .  | .  | .  | .  | .  | .  | 8  |
| Pericard                  | .  | .  | .  | .  | .  | .  | .  | .  |
| Inflammation              | .  | .  | 1  | .  | .  | .  | .  | .  |
| Skin                      | .  | .  | .  | .  | .  | .  | .  | .  |
| Abscess                   | .  | 1  | .  | .  | .  | .  | .  | .  |
| Uterus                    | .  | .  | .  | .  | .  | .  | .  | .  |
| Dilation                  | .  | .  | .  | .  | .  | .  | 3  | .  |

BASF

PATHOLOGY REPORT

IC 10/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats  
Administration by gavage

11.Apr.2014 HAMA

## INCIDENCE OF ALL MICROSCOPIC FINDINGS

| Sacrifice                    |       | F1 |    |    |    | F  |    |    |    |
|------------------------------|-------|----|----|----|----|----|----|----|----|
| Sex                          |       | M  |    |    |    | F  |    |    |    |
| Group                        |       | 0  | 1  | 2  | 3  | 0  | 1  | 2  | 3  |
| Animals in selected group    |       | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Adrenal cortex               | exam. | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Hypertrophy/hyperplasia cort |       | .  | .  | .  | 8  | .  | .  | .  | .  |
| Adrenal medulla              | exam. | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Aorta                        | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Axillary lymph nodes         | exam. | 10 | 1  | .  | 10 | 10 | .  | .  | 10 |
| Plasmocytosis                |       | .  | 1  | .  | .  | .  | .  | .  | .  |
| Bone marrow (femur)          | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Brain                        | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Cecum                        | exam. | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Dilation                     |       | .  | .  | .  | 10 | .  | .  | 1  | 10 |
| Parasite(s) in lumen         |       | .  | .  | .  | 1  | .  | .  | .  | .  |
| Apoptosis, increased         |       | .  | 3  | 4  | 7  | .  | 1  | 4  | 7  |
| Cervical cord                | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Cervix                       | exam. | .  | .  | .  | .  | 10 | 10 | 10 | 10 |
| Coagulating glands           | exam. | 10 | .  | .  | 10 | .  | .  | .  | .  |
| Colon                        | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Parasite(s) in lumen         |       | 2  | .  | .  | 1  | .  | .  | .  | 1  |
| Duodenum                     | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Epididymides                 | exam. | 10 | .  | .  | 10 | .  | .  | .  | .  |
| Esophagus                    | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Eyes with opt. nerve         | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Forestomach                  | exam. | 10 | .  | .  | 10 | 10 | 1  | .  | 10 |
| Cyst, squamous               |       | .  | .  | .  | .  | .  | 1  | .  | .  |
| Glandular stomach            | exam. | 10 | .  | .  | 10 | 10 | .  | 1  | 10 |
| Erosion/ ulcer               |       | .  | .  | .  | .  | .  | .  | 1  | .  |
| Heart                        | exam. | 10 | .  | 1  | 10 | 10 | .  | .  | 10 |
| Inflammation, pericard       |       | .  | .  | 1  | .  | .  | .  | .  | .  |
| Necrosis/fibrosis            |       | 1  | .  | .  | .  | .  | .  | .  | .  |

BASF

PATHOLOGY REPORT

IC 11/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats  
Administration by gavage

11.Apr.2014 HAMA

## INCIDENCE OF ALL MICROSCOPIC FINDINGS

| Sacrifice                     |       | F1 |    |    |    |    |    |    |    |
|-------------------------------|-------|----|----|----|----|----|----|----|----|
| Sex                           |       | M  |    |    |    | F  |    |    |    |
| Group                         |       | 0  | 1  | 2  | 3  | 0  | 1  | 2  | 3  |
| Animals in selected group     |       | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| .....                         |       |    |    |    |    |    |    |    |    |
| Ileum                         | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Jejunum                       | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Kidneys                       | exam. | 10 | 10 | 10 | 10 | 10 | .  | .  | 10 |
| Mineralization, medulla, (m)f |       | .  | 7  | 9  | 6  | 5  | .  | .  | 3  |
| Tubules, basophilic, (m)f     |       | 8  | 8  | 9  | 8  | 2  | .  | .  | 3  |
| Nuclear crowding              |       | 1  | .  | 4  | .  | .  | .  | .  | .  |
| Cast, hyaline                 |       | 2  | 2  | 4  | .  | .  | .  | .  | .  |
| Hyperplasia, transit., (m)f   |       | 1  | .  | 1  | .  | .  | .  | .  | .  |
| Cyst(s)                       |       | .  | .  | 1  | .  | .  | .  | .  | 2  |
| Dilation, renal pelvis        |       | 1  | 1  | 2  | .  | .  | .  | .  | .  |
| Scar(s), cortical             |       | 1  | .  | .  | .  | .  | .  | .  | .  |
| Proliferation, interst. cell  |       | .  | .  | 1  | .  | .  | .  | .  | .  |
| Liver                         | exam. | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Infiltration, lymphoid, (m)f  |       | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Hypertrophy, centrilobular    |       | .  | .  | .  | .  | .  | 2  | 5  | 10 |
| Hyperplasia, bile duct, dif   |       | .  | .  | .  | .  | .  | .  | .  | 2  |
| Peri-/vasculitis              |       | 3  | .  | .  | .  | .  | .  | .  | .  |
| Focus of cellular alteration  |       | .  | 1  | .  | 2  | 1  | 1  | 1  | 6  |
| - Eosinophilic                |       | .  | .  | .  | 1  | .  | 1  | .  | 6  |
| - Basophilic (NOS)            |       | .  | .  | .  | .  | .  | .  | .  | 1  |
| - Basophilic diffuse          |       | .  | .  | .  | .  | .  | .  | .  | 2  |
| - Basophilic tigroid          |       | .  | 1  | .  | 2  | 1  | .  | 1  | .  |
| Lumbar cord                   | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Lungs                         | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Inflammation, (multi)focal    |       | 3  | .  | .  | 1  | .  | .  | .  | 1  |
| Histiocytosis, alv., (m)f     |       | 2  | .  | .  | 1  | 2  | .  | .  | .  |
| Mammary gland                 | exam. | 10 | 8  | 10 | 10 | 10 | .  | .  | 10 |
| Atrophy, (multi)focal         |       | .  | .  | 7  | 10 | .  | .  | .  | .  |
| Mandibular glands             | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Mesenteric lymph n.           | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Ovaries                       | exam. | .  | .  | .  | .  | 10 | .  | .  | 10 |
| Pancreas                      | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Ectopic spleen                |       | 1  | .  | .  | .  | .  | .  | .  | .  |
| Parathyroid glands            | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |

BASF

PATHOLOGY REPORT

IC 12/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats  
Administration by gavage

11.Apr.2014 HAMA

## INCIDENCE OF ALL MICROSCOPIC FINDINGS

| Sacrifice                     |       | F1 |    |    |    |    |    |    |    |
|-------------------------------|-------|----|----|----|----|----|----|----|----|
| Sex                           |       | M  |    |    |    | F  |    |    |    |
| Group                         |       | 0  | 1  | 2  | 3  | 0  | 1  | 2  | 3  |
| Animals in selected group     |       | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Pericard                      | exam. | .  | .  | 1  | .  | .  | .  | .  | .  |
| Inflammation, granulomatous   |       | .  | .  | 1  | .  | .  | .  | .  | .  |
| Peyers patch                  | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Pituitary gland               | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Prostate                      | exam. | 10 | .  | .  | 10 | .  | .  | .  | .  |
| Inflammation, chronic         |       | 3  | .  | .  | .  | .  | .  | .  | .  |
| Rectum                        | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Parasite(s) in lumen          |       | 2  | .  | .  | 2  | .  | .  | .  | 1  |
| Sciatic nerve                 | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Seminal vesicle               | exam. | 10 | .  | .  | 10 | .  | .  | .  | .  |
| Skin                          | exam. | 10 | 1  | .  | 10 | 10 | .  | .  | 10 |
| Abscess                       |       | .  | 1  | .  | .  | .  | .  | .  | .  |
| Spleen                        | exam. | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Hematopoiesis, extramedullar  |       | .  | .  | .  | 8  | 2  | 1  | 4  | 10 |
| Sublingual glands             | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Testes                        | exam. | 10 | .  | .  | 10 | .  | .  | .  | .  |
| Thoracic cord                 | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Thymus                        | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Hyperplasia, tub/cords, (m) f |       | 1  | .  | .  | 3  | 2  | .  | .  | 2  |
| Thyroid glands                | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Trachea                       | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Urinary bladder               | exam. | 10 | .  | .  | 10 | 10 | .  | .  | 10 |
| Uterus                        | exam. | .  | .  | .  | .  | 10 | 10 | 10 | 10 |
| Metaplasia, squamous, (m) f   |       | .  | .  | .  | .  | .  | 2  | 2  | 5  |
| Hyperplasia, glandular, (m) f |       | .  | .  | .  | .  | .  | .  | .  | 1  |
| Dilation of horn(s)           |       | .  | .  | .  | .  | .  | .  | 3  | .  |
| Vagina                        | exam. | .  | .  | .  | .  | 10 | 10 | 10 | 10 |



BASF

PATHOLOGY REPORT

IC 13/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats  
Administration by gavage

11.Apr.2014 HAMA

## INCIDENCE AND GRADING OF MICROSCOPIC FINDINGS IN TARGET ORGANS

| Sacrifice                     |       | F1 |    |    |    |    |    |    |    |
|-------------------------------|-------|----|----|----|----|----|----|----|----|
| Sex                           |       | M  |    |    |    | F  |    |    |    |
| Group                         |       | 0  | 1  | 2  | 3  | 0  | 1  | 2  | 3  |
| Animals in selected group     |       | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| .....                         |       |    |    |    |    |    |    |    |    |
| Adrenal cortex                | exam. | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Hypertrophy/hyperplasia cort  |       | .  | .  | .  | 8  | .  | .  | .  | .  |
| . P.                          |       | .  | .  | .  | 8  | .  | .  | .  | .  |
| Cecum                         | exam. | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Dilation                      |       | .  | .  | .  | 10 | .  | .  | 1  | 10 |
| . P.                          |       | .  | .  | .  | 10 | .  | .  | 1  | 10 |
| Apoptosis, increased          |       | .  | 3  | 4  | 7  | .  | 1  | 4  | 7  |
| . 1.                          |       | .  | 3  | 4  | 7  | .  | 1  | 4  | 7  |
| Kidneys                       | exam. | 10 | 10 | 10 | 10 | 10 | .  | .  | 10 |
| Mineralization, medulla, (m)f |       | .  | 7  | 9  | 6  | 5  | .  | .  | 3  |
| . 1.                          |       | .  | 4  | 6  | 6  | 3  | .  | .  | 2  |
| . 2.                          |       | .  | 3  | 2  | .  | 2  | .  | .  | 1  |
| . 3.                          |       | .  | .  | 1  | .  | .  | .  | .  | .  |
| Liver                         | exam. | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Hypertrophy, centrilobular    |       | .  | .  | .  | .  | .  | 2  | 5  | 10 |
| . 1.                          |       | .  | .  | .  | .  | .  | 1  | 1  | .  |
| . 2.                          |       | .  | .  | .  | .  | .  | 1  | 3  | .  |
| . 3.                          |       | .  | .  | .  | .  | .  | .  | 1  | 10 |
| Focus of cellular alteration  |       | .  | 1  | .  | 2  | 1  | 1  | 1  | 6  |
| . P.                          |       | .  | 1  | .  | 2  | 1  | 1  | 1  | 6  |
| - Eosinophilic                |       | .  | .  | .  | 1  | .  | 1  | .  | 6  |
| . P.                          |       | .  | .  | .  | 1  | .  | 1  | .  | 6  |
| - Basophilic (NOS)            |       | .  | .  | .  | .  | .  | .  | .  | 1  |
| . P.                          |       | .  | .  | .  | .  | .  | .  | .  | 1  |
| - Basophilic diffuse          |       | .  | .  | .  | .  | .  | .  | .  | 2  |
| . P.                          |       | .  | .  | .  | .  | .  | .  | .  | 2  |
| - Basophilic tigroid          |       | .  | 1  | .  | 2  | 1  | .  | 1  | .  |
| . P.                          |       | .  | 1  | .  | 2  | 1  | .  | 1  | .  |
| Mammary gland                 | exam. | 10 | 8  | 10 | 10 | 10 | .  | .  | 10 |
| Atrophy, (multi)focal         |       | .  | .  | 7  | 10 | .  | .  | .  | .  |
| . 1.                          |       | .  | .  | 7  | .  | .  | .  | .  | .  |
| . 2.                          |       | .  | .  | .  | 4  | .  | .  | .  | .  |
| . 3.                          |       | .  | .  | .  | 2  | .  | .  | .  | .  |
| . 4.                          |       | .  | .  | .  | 3  | .  | .  | .  | .  |
| . 5.                          |       | .  | .  | .  | 1  | .  | .  | .  | .  |
| Spleen                        | exam. | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Hematopoiesis, extramedullar  |       | .  | .  | .  | 8  | 2  | 1  | 4  | 10 |
| . 1.                          |       | .  | .  | .  | 5  | 2  | 1  | 4  | 3  |
| . 2.                          |       | .  | .  | .  | 3  | .  | .  | .  | 7  |

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PATHOLOGY REPORT

IC 14/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats  
Administration by gavage

11.Apr.2014 HAMA

INCIDENCE AND GRADING OF MICROSCOPIC FINDINGS IN TARGET  
ORGANS

| Sacrifice                     |       | F1 |    |    |    |    |    |    |    |
|-------------------------------|-------|----|----|----|----|----|----|----|----|
| Sex                           |       | M  |    |    |    | F  |    |    |    |
| Group                         |       | 0  | 1  | 2  | 3  | 0  | 1  | 2  | 3  |
| Animals in selected group     |       | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Uterus                        | exam. | .  | .  | .  | .  | 10 | 10 | 10 | 10 |
| Metaplasia, squamous, (m) f   |       | .  | .  | .  | .  | .  | 2  | 2  | 5  |
|                               | . 1.  | .  | .  | .  | .  | .  | 2  | 2  | 4  |
|                               | . 2.  | .  | .  | .  | .  | .  | .  | .  | 1  |
| Hyperplasia, glandular, (m) f |       | .  | .  | .  | .  | .  | .  | .  | 1  |
|                               | . P.  | .  | .  | .  | .  | .  | .  | .  | 1  |

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PATHOLOGY REPORT

IC 15/15

50C0066/05S019

Repeated-dose 90-day oral toxicity study in Wistar rats  
Administration by gavage

11.Apr.2014 HAMA

LIVER GSTP

| Sacrifice                   |  | F1 |    |    |    |    |    |    |    |
|-----------------------------|--|----|----|----|----|----|----|----|----|
| Sex                         |  | M  |    |    |    | F  |    |    |    |
| Group                       |  | 0  | 1  | 2  | 3  | 0  | 1  | 2  | 3  |
| Animals in selected group   |  | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Liver                       |  | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| GSTP + cells, centrilobular |  | .  | .  | .  | .  | 1  | 2  | 4  | 9  |
| . 1.                        |  | .  | .  | .  | .  | .  | .  | 2  | 4  |
| . 2.                        |  | .  | .  | .  | .  | .  | .  | 1  | .  |
| . 3.                        |  | .  | .  | .  | .  | 1  | 1  | 1  | 5  |
| . 4.                        |  | .  | .  | .  | .  | .  | 1  | .  | .  |
| GSTP+ focus, (m)f           |  | 1  | 2  | 1  | 2  | 1  | 1  | 1  | 6  |
| . P.                        |  | 1  | 2  | 1  | 2  | 1  | 1  | 1  | 6  |