The Chemical Company

BASF DocID 2013/1110704

STUDY TITLE

Report

BAS 750 F

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
Administration via the diet

TEST GUIDELINE(S)

OECD 407
OPPTS 870.3050
Commission Regulation (EC) No 440/2008

AUTHOR(S)

Dr. R. Stark (Study Director)
Dr. V. Strauss
Dr. H. Marxfeld
Dr. M. Becker
Prof. Dr. B. van Ravenzwaay

STUDY COMPLETION DATE

18 Dec 2014

TEST FACILITY

BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen, Germany

TEST FACILITY PROJECT IDENTIFICATION

Project No. 31C0741/11C201

SPONSOR IDENTIFICATION NUMBER

AP study ID.: 435003

SPONSOR

BASF SE
67056 Ludwigshafen, Germany

PART I OF III (REPORT SECTION AND SUMMARY TABLES)

The following statement is for US EPA submissions only:

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

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

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

Typed Name of Signer:

Typed Name of Company: BASF Corporation, Agricultural Products
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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: 18 Dec 2014

Typed name of Study Director: Dr. med. vet. R. Stark

Typed name of Laboratory: BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen
Germany

To be filled for USA EPA submission only:

Sponsor: ..... Date: .....

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

Typed Name of Submitter:

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The following statement is for US EPA submissions only:

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:

SIGNATURE PAGE

Study Director: 18 Dec 2014
Dr. med. vet. R. Stark

Clinical Pathology: 18 Dec 2014
Dr. med. vet. V. Strauss

Pathology: 18 Dec 2014
H. Marxfeld, Ph.D.

Analytical Chemistry: 18. Dec. 2014
for Dr. rer. nat. M. Becker
Dr. E. Fabian

Management: 18. Dec. 2014
Prof. Dr. rer. nat. B. van Ravenzwaay

CONTRIBUTORS TO THE STUDY/ SUPERVISORY LABORATORY PERSONNEL

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Clinical Pathology/Hematology:	I. Weber
Pathology:	P. Koch
Histopathology:	M. Jahnke
Central Food Mixing Laboratory:	K. Hummel

STATEMENT OF THE QUALITY ASSURANCE UNIT

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

The final report reflects the raw data.

Phase of study	Date of inspection (mm-dd-yyyy)	Reported to Study Director and to Test Facility Management (mm-dd-yyyy)
Study Plan:	01-14-2013	01-14-2013
Conduct of study:	01-18-2013	01-18-2013
	02-04-2013	02-04-2013
	02-19-2013	02-19-2013
Report:	07-10-2013	07-10-2013
	12-15-2014	12-15-2014

Ludwigshafen, 18 Dec 2014

W. Leiskau

W. Leiskau

GLP CERTIFICATE (FROM THE COMPETENT AUTHORITY)

RheinlandPfalz
LANDESAMT FÜR UMWELT, WASSERWIRTSCHAFT UND GEWERBEAUFSICHT

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-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

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

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

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

Based on the inspection report it can be con- firmed, 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 - Stellvertretung Präsident -
(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 adress of the GLP Monitoring Authority)

MESSEN BEWERTEN BERATEN

CONTENTS OF PART I (REPORT SECTION AND SUMMARY TABLES)

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

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

Part C:
PATHOLOGY (MEAN VALUES AND SUMMARY TABLES)

CONTENTS OF PART II (TABLES SECTION; INDIVIDUAL VALUES)

CONTENTS OF PART III (SUPPLEMENT)

THIS REPORT CONSISTS OF PART I, II AND III.

1. SUMMARY

1.1. METHODS

BAS 750 F was administered via the diet to groups of 5 male and 5 female C57BL/6 J Rj mice at concentrations of 0 (test group 0), 30 (test group 1), 100 (test group 2), 300 (test group 3) and 1000 ppm (test group 4) over a period of 4 weeks.

1.2. OBSERVATIONS

Food consumption, water consumption and body weight were determined weekly. The animals were examined for signs of toxicity or mortality at least once a day. Detailed clinical examinations in an open field were conducted prior to the start of the administration period and weekly thereafter. Clinicochemical and hematological examinations were performed towards the end of the administration period. After the administration period all mice were sacrificed and assessed by gross pathology, followed by histopathological examinations.

1.3. RESULTS

1.3.1. Analytics

The various analyses confirmed

- the stability of the test-substance preparations with 50 ppm for a period of 35 days and with 30 ppm of 32 days at room temperature,
- the homogeneous 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 4: 1000 ppm
(128.2 mg/kg bw/d in males and 145.2 mg/kg bw/d in females)

Clinical Examinations:
- Decreased body weight (-13.1% in males and -6.2% in females on study day 28) and body weight change (-103% in males and -65.2% in females) in both sexes
- Decreased food consumption in male and female animals over the entire study period up to -41.9% on study day 7 in males and up to -45.0% on study day 14 in female animals

Clinical Pathology:
- Increased alanine aminotransferase (ALT) activities in males
- Decreased cholesterol levels in males
- Decreased glucose and albumin levels in females

Pathology
- Hepatocellular hypertrophy in all male and female animals accompanied by necrosis in 4/5 male and 3/5 female animals and an increase in absolute and relative weights above the historical control range
- Increase in absolute and relative thymus weights above historical controls in female animals

Test group 3: 300 ppm
(47.9 mg/kg bw/d in males and 61 mg/kg bw/d in females)

Clinical Examinations:
- No test substance-related, adverse effects

Clinical Pathology:
- No test substance-related, adverse effects

Pathology
- Hepatocellular hypertrophy in all female animals accompanied by an increase in absolute and relative weights

Test group 2: 100 ppm
(15.5 mg/kg bw/d in males and 18.5 mg/kg bw/d in females)

Clinical Examinations:
- No test substance-related, adverse effects

Clinical Pathology:
- No test substance-related, adverse effects

Pathology
- No test substance-related, adverse effects

Test group 1: 30 ppm
(4.8 mg/kg bw/d in males and 5.8 mg/kg bw/d in females)

Clinical Examinations:
- No test substance-related, adverse effects

Clinical Pathology:
- No test substance-related, adverse effects

Pathology
- No test substance-related, adverse effects

1.4. CONCLUSION

The administration of BAS 750 F via the diet to male and female C57BL/6 J Rj mice for 4 weeks caused test substance-related adverse signs of systemic toxicity at concentrations of 1000 ppm (128 mg/kg bw/d) in male and at 300 ppm in female (61 mg/kg bw/d) C57BL/6 J Rj mice.

In conclusion, concerning clinical findings and clinical pathology parameters, the no observed adverse effect level (NOAEL) for this test compound in mice is 300 ppm in male (48 mg/kg bw/d) and 100 ppm in female (19 mg/kg bw/d) C57BL/6 J Rj mice.

2. INTRODUCTION

2.1. OBJECTIVES

The aim of the study was to assess the toxicological profile of the test substance including the target organs and the “no observed adverse effect level” (NOAEL) after 4 weeks administration via the diet.

2.2. SELECTION OF DOSES

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

1000 ppm	as high dose
300 ppm	as intermediate doses
100 ppm	
30 ppm	as low dose

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

2.3. TEST GUIDELINES

- OECD Guidelines for Testing of Chemicals; Method No. 407: Repeated Dose 28-day Oral Toxicity Study in Rodents; adopted 03 Oct 2008.

- U.S. EPA Health Effects Test Guidelines. OPPTS 870.3050; Jul 2000

- 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: Methods for the determination of toxicity and other health effects:
  B.7. Repeated Dose (28 Days) Toxicity (Oral); Official Journal of the European Union, No. L 142.

2.4. STUDY DATES

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

Dates	Phase of study/ Examination	Study day
14 Jan 2013	Study initiation date: signature of study director	-7
15 Jan 2013	Experimental starting date: arrival of the mice and start of the acclimatization period	-6
18 Jan 2013	Randomization of the mice	-3
21 Jan 2013	Start of the administration period	0
18 Feb 2013	Last weighing	28
19 Feb 2013	Blood sampling and necropsy[a)]	29
Feb – May 2013	Organ fixation, processing and evaluation	
07 Jun 2013	Experimental completion date; draft report to QAU	

a) = Fasting period (withdrawal of food) of about 16 to 20 hours before necropsy

2.5. RETENTION OF RECORDS

GLP-relevant records and materials are stored at BASF SE for at least the period of time specified in the GLP principles. Details concerning responsibilities or locations of archiving can be seen from the respective SOPs and from the raw data.

2.6. ANIMAL WELFARE

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

3. MATERIAL AND METHODS

3.1. TEST ITEM

The analyses of the test item (= test substance) were carried out at the Crop Protection - Ecology and Environmental Analytics of BASF SE, Speyerer Straße 2, 67117 Limburgerhof, Germany.

Name of test substance:	BAS 750 F
Test substance No.:	11/0741-6
Batch No.:	COD-001662
Purity:	95.5 % (tolerance ± 1.0%; Study No. 429913_4)
Homogeneity:	given (Study No. 429913_4)
Stability:	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

Date of production:	07 Aug 2012
Expiration Date:	31 Aug 2013
Synonym:	Reg.No. 5834378
Physical state/ color:	solid/beige
Storage conditions:	ambient (room temperature)

3.2. TEST SYSTEM

3.2.1. Species and strain

Species:	mouse
Strain:	C57BL/6 J Rj
Supplier:	Raison sociale : JANVIER S.A.S Route des Chenês Secs – C.S. 4105 Le Genest-St-Isle F-53941 ST Berthevin Cedex
Sex:	males and females
Age when supplied:	42 - 44 days
Age at the beginning of the administration period:	48 - 50 days
Reason for the selection:	The mouse 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.
Animal identification:	ear tattoo (animal number)

3.3. HOUSING AND DIET

The mice were housed together (5 animals per cage) in polycarbonate cages type M III with mesh wire tops, supplied by BECKER & Co., Castrop-Rauxel. Dust-free wooden bedding was used in this study (the present supplier is documented in the raw data). PLEXX mouse tunnel (red, transparent) and nest building material Nestlets NES 3600 (PLEXX b.v.; Elst, Netherlands) were added for enrichment. The mice 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 h-18.00 h, 12 hours dark from 18.00 h-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 disinfector ("AUTEX", fully automatic, formalin-ammonia-based terminal disinfector). 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

Males

Test group	Concentration (ppm)	No. of mice	Animal No.	Cage No.
0	0	5	1 - 5	1
1	30	5	6 - 10	2
2	100	5	11 - 15	3
3	300	5	16 - 20	4
4	1000	5	21 - 25	5

Females

Test group	Concentration (ppm)	No. of mice	Animal No.	Cage No.
0	0	5	26 - 30	6
1	30	5	31 - 35	7
2	100	5	36 - 40	8
3	300	5	41 - 45	9
4	1000	5	46 - 50	10

3.5. TEST SUBSTANCE PREPARATIONS AND PREPARATION FREQUENCY

For each concentration, the test substance BAS 750 F was weighted out and mixed with a small amount of food. Then corresponding amounts of food, depending on test group, were added to this premix in order to obtain the desired concentrations. Mixing was carried out for about 10 minutes in a laboratory mixer. Details of the mixers used are retained with the raw data.

3.6. ANALYSES

3.6.1. Analyses of the test-substance preparations

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

The stability of the test substance in the diet of 50 ppm at room temperature for a period of 35 days was demonstrated before the start of the administration period (BASF Project No. 01Y0741/11Y094), see PART III, Supplement) and of 30 ppm in the diet over a period of up to 32 days at room temperature was demonstrated during the study period (BASF Project No. 01Y0741/11Y115, see PART III, Supplement).

Homogeneity control analyses of test-substance preparations were verified in the highest and lowest concentration. The samples were used as a concentration control at the same time. Additionally concentration control analyses were verified in all concentrations at the beginning of the study.

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

Starting on day of arrival, the mice were accustomed to the environmental conditions of the study. During the adaptation period the animals received ground diet and drinking water ad libitum.
Prior to the first detailed clinical observation, the mice 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.
At the start of the administration period (day 0) the mice were 48-50 days old.
The test substance was administered daily for 28 days. Control animals received only the vehicle. All remaining 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 clinically abnormal signs. Abnormalities and changes were documented for each animal.

3.8.3. Detailed clinical observations

Detailed clinical observations (DCO) were performed in all animals prior to the administration period and thereafter at weekly intervals. The findings were ranked according to the degree of severity, if applicable. The animals were transferred to a standard arena (50 × 37.5 cm with sides of 25 cm high). The following parameters were examined:

1. Abnormal behavior during “handling”
2. Fur
3. Skin
4. Posture
5. Salivation
6. Respiration
7. Activity/ arousal level

8. Tremors
9. Convulsions
10. Abnormal movements
11. Impairment of gait
12. Lacrimation
13. Palpebral closure
14. Exophthalmus
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 over a period of 1 day and calculated as mean food consumption in g per mouse and day.

3.8.5. Water consumption

Drinking water consumption was determined on study days 7, 14, 21 and 28 and calculated as mean water consumption in grams per mouse and day.

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 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 day 0 was calculated as body weight change.

3.8.7. Intake of test substance

The mean daily intake of test substance (group means) was calculated based upon individual values for body weight and mean food consumption per cage.

$$\frac{FC_x \times C}{BW_x} = \text{test substance intake for study day x}$$

BW_x = body weight on study day x [g]
FC_x = mean daily food consumption on study day x [g]
C = concentration in the diet on study day x [mg/kg]

3.8.8. 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 tables:

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 $p \leq 0.05$ ** for $p \leq 0.01$	DUNNETT, C.W. (1955): A multiple comparison procedure for comparing several treatments with a control. JASA, Vol. 50, 1096-1121 DUNNETT, C.W. (1964). New tables for multiple comparisons with a control. Biometrics, Vol. 20, 482-491

3.9. CLINICAL PATHOLOGY

In the morning blood was taken from the retro-bulbar venous plexus (for hematology) or after decapitation (for clinical chemistry) 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.

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 5 animals per test group and sex.

3.9.1. Hematology

The following parameters were determined in blood with EDTA-K_3 as anticoagulant using a particle counter (Advia 120 model; Bayer, Fernwald, Germany):
Parameters and methods:

Parameter	Unit	Method	References
Leukocyte count (WBC)	giga/L	cytochemistry coupled with flow cytometry	Operator's Guide for Advia 120 System
Erythrocyte count (RBC)	tera/L	flow cytometric laserlight scattering	
Hemoglobin (HGB)	mmol/L	cyanmethemoglobin method; according to ICSH	
Hematocrit (HCT)	L/L	calculation: MCV x erythrocytes	
Mean corpuscular volume (MCV)	fL	RBC/PLT method; mean of RBC volume distribution curve (histogram)	
Mean corpuscular hemoglobin (MCH)	fmol	calculation: $\frac{\text{hemoglobin}}{\text{erythrocytes}}$	
Mean corpuscular hemoglobin concentration (MCHC)	mmol/L	calculation: $\frac{\text{hemoglobin}}{\text{hematocrit}}$	
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, 6th Edition, Brown AB, Lea & Febiger, Philadelphia, 1993, page 101).

3.9.2. Clinical chemistry

An automatic analyzer (Hitachi 917; 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 (ALT) (L-alanine: 2-oxoglutarate aminotransferase; EC 2.6.1.2.)	µkat/L	kinetic UV test, 340 nm; 37°C	Recommendations of the German Society for Clinical Chemistry: "Standardization of methods for determining enzyme activities in biological liquids". J. Clin. Chem. Clin. Biochem. 8, 658-660 (1970); J. Clin. Chem. Clin. Biochem. 9, 464-465 (1971); J. Clin. Chem. Clin. Biochem. 10, 182-192 (1972) Roche working instructions
Aspartate aminotransferase (AST) (L-aspartate: 2-oxoglutarate aminotransferase; EC 2.6.1.1.)	µkat/L	kinetic UV test, 340 nm; 37°C	
Alkaline phosphatase (ALP) (orthophosphoric acid monoester phosphohydrolase; EC 3.1.3.1.)	µkat/L	kinetic color test, 415 nm, 37°C	
γ-Glutamyltransferase (GGT) (γ -glutamyl) peptide: aminoacid-γ-glutamyl-transferase; EC 2.3.2.2.)	nkat/L	kinetic color test, 415 nm, 37°C	Szasz, G. et al., J. Clin. Chem. Clin. Biochem. 12, 228 (1974) 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. 20, 155 (1967); Roche working instructions
Urea (UREA)	mmol/L	enzymatic determination with the urease/ glutamate dehydro-genase method	Neumann, U. and Ziegenhorn, J.: XVI, Nordiska kongressen for klinisk kemi och klinisk fysiologi 1977, Oulu, Finland; Roche working instructions
Creatinine (CREA)	µmol/L	kinetic Jaffé method without deproteinization	Bartels, H. et al., Clin. Chim. Acta 37, 193 (1972); Roche working instructions
Glucose (GLUC)	mmol/L	hexokinase/glucose-6-phosphate dehydrogenase method	Schmidt, F.H., Klin. Wschr. 39, 1244-1247 (1961); Roche working instructions
Total bilirubin (TBIL)	µmol/L	DPD method	Wahlefeld, A.W. et al., Scand. J. Clin. Lab. Invest. 29, Suppl. 126 (1972) Abstract 11.12; Roche working instructions
Total protein (TPROT)	g/L	biuret method	Weichselbaum, T.E., Amer. J. Clin. Path. 10, 40 (1946); Roche working instructions
Albumin (ALB)	g/L	bromocresol green method	Doumas et al., Clin. Chim. Acta 31, 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. 19, 838 (1981); Roche working instructions
Bile acids (TBA)	µmol/L	enzymatic colorimetric determination with 3α-hydroxy-steroid dehydrogenase and NAD	Agape, V. et al., Minerva Dietol Gastroenterol, 35, 159 – 164 (1989); Randox working instruction

3.9.3. 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 **bidirectional** changes: Non-parametric one-way analysis using KRUSKAL-WALLIS test. If the resulting p-value was equal or less than 0.05, a pairwise comparison of each dose group with the control group was performed using WILCOXON-test (two-sided) for the hypothesis of equal medians For parameters with **unidirectional** changes: Pairwise comparison of each dose group with the control group using the WILCOXON-test (one-sided) for the hypothesis of equal medians	* for $p \leq 0.05$ ** for $p \leq 0.01$	SIEGEL, S. (1956): Non-parametric statistics for the behavioural sciences. McGraw-Hill New York

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. 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. Gallbladder
17. Harderian glands
18. Heart
19. Ileum
20. Jejunum (with Peyer’s patches)
21. Kidneys
22. Larynx
23. Liver
24. Lung
25. Lymph nodes (mesenteric and axillary lymph nodes)
26. Mammary gland (male and female)
27. Nose (nasal cavity)
28. Ovaries
29. Oviducts
30. Pancreas
31. Parathyroid glands
32. Pharynx
33. Pituitary gland
34. Prostate
35. Rectum
36. Salivary glands (mandibular and sublingual glands)
37. Sciatic nerve
38. Seminal vesicles
39. Skeletal muscle
40. Skin
41. Spinal cord (cervical, thoracic and lumbar cord)
42. Spleen
43. Sternum with marrow
44. Stomach (forestomach and glandular stomach)
45. Testes (modified Davidson’s solution)
46. Thymus
47. Thyroid glands
48. Trachea
49. Urinary bladder
50. Uterus
51. 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	4
1. All gross lesions	A2	A2	A2	A2	A2
2. Adrenal glands	A1				A1
3. Kidneys	A1				A1
4. Liver	A1	A1	A1	A1	A1
5. Spleen	A1				A1
6. Thyroid glands	A1				A1

A = Hematoxylin and Eosin (H&E) stain
1 = all animals/test group
2 = all animals affected/test group

The immunorelevant organs and tissues were evaluated according to the following parameters:

Spleen:
- Changes of the cellularity of PALS, lymphoid follicles, marginal zone, red pulp
- Altered cellular composition of follicles
- Altered number of germinal centers

Whenever the histopathologic evaluation of the immunorelevant organs and tissues did not reveal a morphologic alteration of these items and/or whenever no other pathologic finding was noted, these organs were diagnosed as "no abnormalities detected".

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) including livers of all animals. Results presented in this report reflect the consensus opinion of the study pathologist and the peer review pathologist.

3.11. STATISTICS OF PATHOLOGY

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

Parameter	Statistical test	Markers in the tables	References
Weight parameters	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 ≤ 0.05 ** for p ≤-- 0.01	HETTMANNSPERGER, T.P. (1984): Statistical Inference based on Ranks, John Wiley & Sons New York, 132-140. International Mathematical and Statistical Libraries, Inc., 2500 Park West Tower One, Houston, Texas 77042-3020, USA, nakl-1 - nakl-3 MILLER, R.G. (1981): Simultaneous Statistical Inference, Springer-Verlag New York Inc., 165-167 NIJENHUIS, A. and S.W. WILF (1978): Combinatorial Algorithms, Academic Press, New York, 32-33

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 the test substance in ground Kliba maintenance diet mouse/rat “GLP” meal over a period of up to 35 days of 50 ppm stored at room temperature was demonstrated before the start of the study (BASF Project No. 01Y0741/11Y094 see PART III, Supplement) and of 30 ppm in the diet was demonstrated during the administration period as a separate study at the Analytical Chemistry Laboratory of the Experimental Toxicology and Ecology of the BASF SE, Ludwigshafen, Germany (BASF Project No. 01Y0741/11Y115, see PART III, Supplement).

4.1.2. Homogeneity control analyses

Considering the low relative standard deviation in the homogeneity analysis, it can be concluded that BAS 750 F was distributed homogeneously in ground Kliba maintenance diet mouse/rat “GLP” meal.

4.1.3. Concentration control analyses

The mean values of BAS 750 F in ground Kliba maintenance diet mouse/rat “GLP” meal were found to be in the range of 90-110% of the nominal concentrations. These results demonstrated the correctness of the concentrations of BAS 750 F in ground Kliba maintenance diet mouse/rat “GLP” meal.

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 1×10^5/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 were 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.

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

No animals died or were sacrificed moribund prematurely in the present study.

4.2.2. Clinical observations

(Tables IA 1 - IA 2)

No test substance-related, adverse findings were observed in male and female animals of test groups 1-4 (30, 100, 300 and 1000 ppm).

4.2.3. Food consumption

(Tables IA 3 - IA 4)

Food consumption was consistently decreased in male and female animals given 1000 ppm throughout the entire study period, with maximum decreases seen on day 7 in males (-41.7%) and on study day 14 in females (-45%), compared to the control group; the decreased food intake at 1000 ppm was assessed as treatment-related. In males of test groups 30, 100 or 300 ppm, food consumption was increased to a similar extent on days 7, 21 and 28, while a decrease of similar degree was seen in these test groups on day 14. In females administered 30, 100 or 300 ppm, feed intake was usually slightly lower than the control value, but still within the normal range and no dose-related change was apparent. Therefore, the changes in food consumption observed in male and female test groups 1-3 were assessed as incidental.

4.2.4. Water consumption

(Tables IA 5 - IA 6)

In male animals of test group 1 (30 ppm) water consumption was increased on study day 7 (+31.2%), decreased on study day 14 (-21.7%), increased on study day 21 (+5.1%) and decreased on study day 28 (-10.3%). In male animals of test group 2 (100 ppm) water consumption was increased on study day 7 (+9.4%), decreased on study day 14 (-41.3%), decreased on study day 21 (-7.7%) and decreased on study day 28 (-2.6%). In male animals of test group 3 (300 ppm) water consumption was increased on study day 7 (+12.5%), decreased on study day 14 (-21.7%), decreased on study day 21 (-7.7%) and decreased on study day 28 (-7.7%). In male animals of test group 4 (1000 ppm) water

consumption was decreased on study day 7 (-9.4%), decreased on study day 14 (-21.7%), decreased on study day 21 (-15.4%) and decreased on study day 28 (-28.2%).

In female animals of test group 1 (30 ppm) water consumption was increased on study day 7 (+12.9%), decreased on study day 14 (-2.6%), decreased on study day 21 (-2.6%) and decreased on study day 28 (-8.3%). In female animals of test group 2 (100 ppm) water consumption was increased on study day 7 (+12.9%), decreased on study day 14 (-7.9%), increased on study day 21 (+13.2%) and increased on study day 28 (+2.8%). In female animals of test group 3 (300 ppm) water consumption was increased on study day 7 (+9.7%), decreased on study day 14 (-15.8%), decreased on study day 21 (-26.3%) and decreased on study day 28 (-8.3%). In female animals of test group 4 (1000 ppm) water consumption was decreased on study day 7 (-12.9%), increased on study day 14 (+7.9%), decreased on study day 21 (-23.7%) and decreased on study day 28 (-19.4%).

Water consumption fluctuated during the study period in all groups including controls. No clear test substance-related, adverse change was observed.

4.2.5. Body weight data

(Tables IA- 7 – IA-10; figures 4.2.5.1. and 4.2.5.2.)

Mean body weight of males in test group 4 (1000 ppm) was significantly decreased on study day 7 (-12.7%), on study day 14 (-7.4%), on study day 21 (-10.5%) and on study day 28 (-13.1%). Mean body weight of females in test group 4 (1000 ppm) was significantly decreased on study day 7 (-13.8%), on study day 14 (-6.6%) and on study day 28 (-6.2%). These changes were regarded to be treatment-related.

In males of test group 3 (300 ppm) the mean body weight was significantly increased on study day 7 (+6.5%). In females of test group 2 (100 ppm), the mean body weight was significantly increased on study day 28 (+5.4%). Both changes were considered incidental findings. There were no other significant or relevant body weight effects in male or female treatment groups 1-3 (30, 100 or 300 ppm).

Male and female mice of test group 4 (1000 ppm) lost weight during the first treatment week, which they could regain in treatment week 2. Thereafter, body weight development stagnated in males, while in females a slight weight gain was observed which was comparable to that of the female control group. At the end of the 4-week treatment period, the mean weight of males given 1000 ppm was more or less the same as on day 0, while the mean weight of the control group males had increased by 16% during this time. Females given 1000 ppm had increased their initial weight by 5% while control group females had gained 15% weight within 4 weeks. The weight changes of the top-dose group male and females were considered treatment-related and potentially adverse, but could also partly have been caused by reduced palatability of the feed during the first treatment week.

Body weight change in females in test group 3 (300 ppm) was significantly decreased from study day 0 to 14 (-36%); this finding was assessed as incidental, due to its single

occurrence. No significant or relevant body weight changes were observed in test groups 1 and 2.

Fig. 4.2.5.1.: Mean body weights of male animals

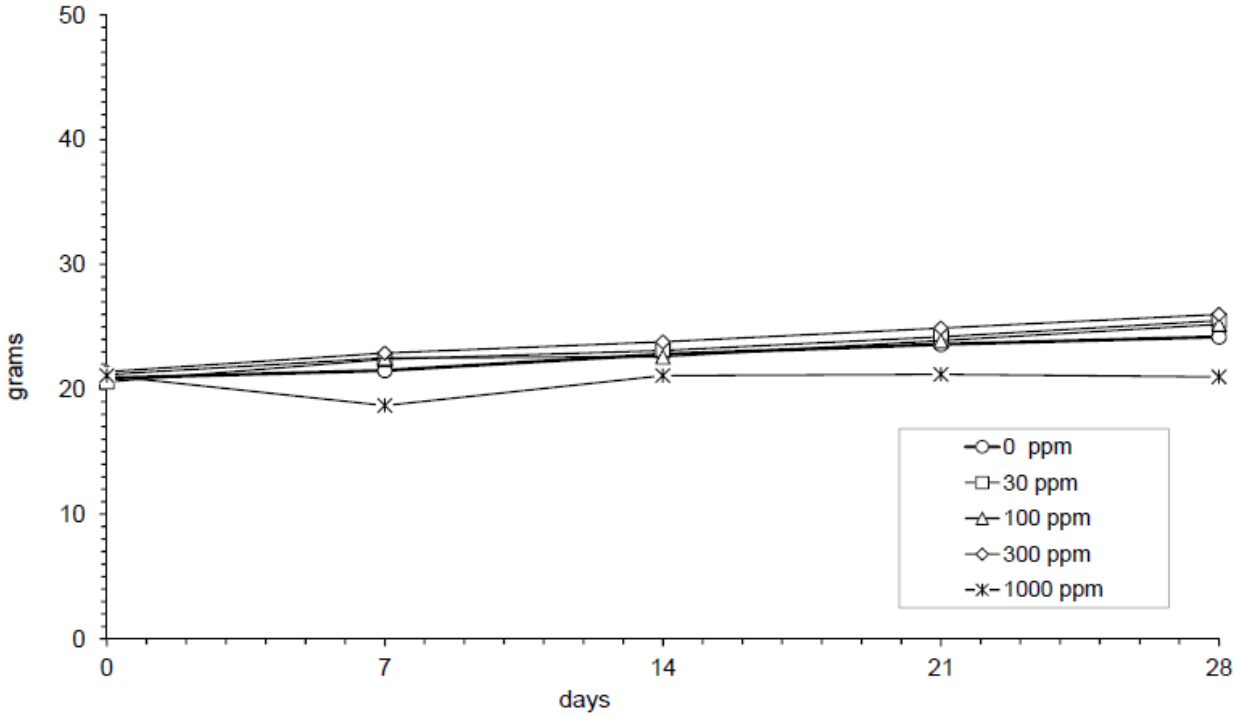
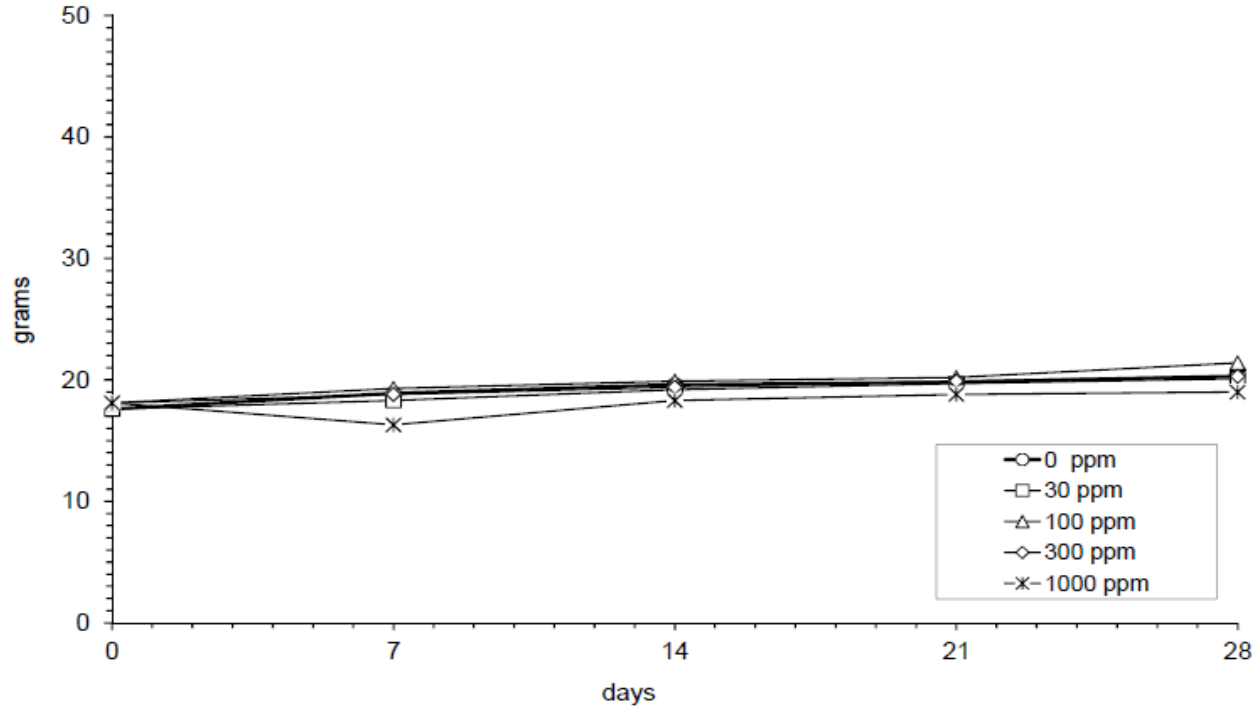


Fig. 4.2.5.2.: Mean body weights of female animals



4.2.6. Intake of test substance

(Tables IA 11 – IA 12)

The mean daily test substance intake in mg/kg body weight/day (mg/kg bw/d) over the entire study period was calculated and is shown in the following table:

Test group	Concentration in the vehicle (ppm)	Mean daily test-substance intake (mg/kg bw/d)	
		Males	Females
1	30	4.8	5.8
2	100	15.5	18.5
3	300	47.9	61.0
4	1000	128.2	145.2

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

At the end of the study, in mice of both sexes of test group 4 (1000 ppm) mean corpuscular volume (MCV) was decreased and additionally in males of the same test group mean corpuscular hemoglobin concentration (MCHC) was increased and relative reticulocyte counts were decreased. The calculated red blood cell indices (i.e., MCV and MCHC) were altered without any change of the measured red blood cell parameters (i.e., red blood cell (RBC) counts, hemoglobin and hematocrit values); the relative reticulocyte counts in males of test group 4 (1000 ppm) were within the historical control range (relative reticulocyte counts 0.6-2.9 %, PART III, Supplement). Therefore, the alterations of the red blood cell parameters were regarded as incidental and not treatment-related.

In males of test group 3 (300 ppm) total white blood cell (WBC) counts were higher compared to controls, but values were not dose-dependently changed. In males of test groups 3 and 4 (300 and 1000 ppm) absolute and relative monocyte counts and additionally in males of test group 2 (100 ppm) relative monocyte counts were increased. However, all mentioned values were within historical control ranges, apart from relative monocyte counts in males of test group 4 (1000 ppm) which were marginally above this range (absolute monocyte counts 0.02-0.13 Giga/L; relative monocyte counts 0.4-2.5 %, PART III, Supplement). In females of all dose groups (test groups 1, 2, 3 and 4; 30, 100, 300 and 1000 ppm) absolute and relative monocyte counts were also higher compared to controls, but the values were not dose-dependently changed. In females of test group 3 (300 ppm) relative basophil counts were increased, but again this parameter was not dose-dependently changed. In females of test group 4 (1000 ppm) relative neutrophil counts were decreased. Although this relative parameter was below the historical control range, corresponding absolute neutrophil counts in this test group were not significantly changed and within the historical control range (relative neutrophil counts 14.1-30.4 %; absolute neutrophil counts 0.31-1.34 Giga/L, PART III, Supplement). Therefore, all mentioned parameters of the white blood cell counts were regarded as incidental and not treatment-related.

4.3.2. Clinical chemistry

(Tables IB 5 – IB 6 Enzymes)
(Tables IB 7 – IB 8 Substrates)
(Tables IB 9 – IB 10 Electrolytes + minerals)

In males of test group 4 (1000 ppm) alanine aminotransferase (ALT) activities were increased. Additionally, in males of test groups 2, 3 and 4 (100, 300 and 1000 ppm) alkaline phosphatase (ALP) activities were higher compared to controls, but the means were within the historical control range (ALP 1.12-2.29 µkat/L, PART III, Supplement) and therefore, this alteration was regarded as incidental and not treatment-related.

In females of test group 4 (1000 ppm) glucose levels were decreased.

In male mice of test groups 2 and 3 (100 and 300 ppm) as well as in females of test groups 2, 3 and 4 (100, 300 and 1000 ppm) total protein, albumin and globulin values were decreased. All three mentioned parameters in males as well as total protein and globulin levels in females were not dose-dependently changed. Therefore, these alterations were regarded as incidental and not treatment-related. Albumin levels in females of test groups 2, 3 and 4 were dose-dependently altered, but the changes in test groups 2 and 3 were the only changed parameters in these individuals and therefore decreased albumin concentrations in females of test group 2 and 3 were regarded as treatment-related, but not adverse (ECETOC Technical Report No. 85, 2002).

In mice of both sexes of test groups 1 up to 4 (30, 100, 300 and 1000 ppm) cholesterol levels were decreased. However, in females this change was not dose-dependent and therefore it was regarded as incidental and not treatment-related. In males, cholesterol was the only change parameter in test groups 1, 2 and 3 and therefore this changes was regarded as treatment-related, but not adverse (ECETOC Technical Report No. 85, 2002). Triglycerides were decreased in males of test group 2 (100 ppm) as well as in females of all dose groups, but were not dose-dependently changed, and therefore the changes were assessed as not treatment-related. In males of all dose groups (in test group 4 not statistically significant)) total bilirubin levels were lower compared to controls but the alterations were also not dose-dependent. Therefore the changes total bilirubin were regarded as incidental and not treatment-related.

4.4. PATHOLOGY

Summary tables of the results are to 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)

4.4.1.1. Absolute organ weights

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

	Male animals				Female animals			
Test group (ppm)	1 (30)	2 (100)	3 (300)	4 (1000)	1 (30)	2 (100)	3 (300)	4 (1000)
Terminal body weight	103%	103%	107%	**88%***	101%	104%	99%	**95%***
Adrenal glands					93%	94%	97%	**87%***
Brain	105%	103%	**105%***	98%				
Heart	103%	100%	110%	**79%****				
Kidney	105%	104%	110%	**84%***				
Liver	**113%***	**120%****	**128%***	**148%****	105%	**120%***	**132%****	**163%****
Ovaries					88%	74%	90%	**72%***
Spleen	93%	88%	130%	**68%***				
Thymus					121%	**132%****	**135%****	**162%****

*p <= 0.05; **p <= 0.01

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

4.4.1.2. Relative organ weights

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

	Male animals				Female animals			
Test group (ppm)	1 (30)	2 (100)	3 (300)	4 (1000)	1 (30)	2 (100)	3 (300)	4 (1000)
Brain	102%	100%	98%	**112%***				
Liver	**112%***	**118%****	**122%***	**171%***	**105%****	116%	**133%****	**172%****
Ovaries					87%	72%	91%	**76%***
Thymus					120%	**128%***	**136%****	**171%****

*p <= 0.05; **p <= 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 in male and female test group 4 (1000 ppm) animals was regarded to be treatment-related.
Increases in liver weights in all test groups in males and in test group 3 and 4 females were regarded to be treatment-related, based on histopathological findings and comparison with historical controls. For males, the historical controls of absolute weights ranged from 854.0 mg - 1006.0 mg, and of relative weights from 3.716% - 4.603%. In this study, the weights of test groups 2 (absolute 1037.0 mg, relative 4.818%), test group 3 (absolute 1110.6 mg, relative 4.958%), and test group 4 (absolute 1276.2 mg, relative 6.959%) were above the historical range. The weight increase in test group 1 was also regarded to be treatment-related due to the histopathological correlate (hypertrophy). For females, the historical controls of absolute weights ranged from 685.0 mg - 856.2 mg, and of relative weights from 4.172% - 5.447%. In this study, the weights were as follows: test group 2 (absolute 944.6 mg, relative not significantly increased and within historical range), test group 3 (1035.8 mg, 5.939%), and test group 4 (1282.2 mg, 7.696%). The weight increase of the liver of test group 3 and 4 females was regarded to be treatment-related. Test group 2 was considered to be incidental as the more relevant relative weight (Bailey, 2004) was not significantly increased, was within the historical control range and there was no correlating histopathological finding (hypertrophy).

The increase in thymus weights in female animals was considered to be treatment-related in test group 4 only, based on comparison with historical controls. The historical control range was for absolute weights 39.2 mg - 55.0 mg, and for relative weights 0.234% - 0.315%. In this study, the controls were below this range (36.4 mg and 0.207%, respectively. Only test group 4 weights were above the historical range (58.88 mg, 0.354%).

Other weight changes did not show a clear dose response and were therefore not regarded as treatment-related, or were considered secondary to body weight reductions.

4.4.2. Gross lesions

(Table IC 9)

A focus was observed on the liver of two male and two female test group 4 (1000 ppm) animals and one test group 3 (300 ppm) male.
The cyst on the kidney of one test group 2 (100 ppm) female was considered to be incidental or spontaneous in origin and without any relation to treatment.

4.4.3. Histopathology

(Table IC 10)

Treatment-related findings were observed in livers of males of all test groups and females of test groups 3 (300 ppm) and 4 (1000 ppm) with incidences and grading according to the table below:

	Male animals					Female animals				
Test group (ppm)	0 (0)	1 (30)	2 (100)	3 (300)	4 (1000)	0 (0)	1 (30)	2 (100)	3 (300)	4 (1000)
No. of animals	5	5	5	5	5	5	5	5	5	5
Hypertrophy, centrilobular		5	5	5	5					
• Grade 1		5	1							
• Grade 2			4	1						
• Grade 3				4	5					
Hypertrophy, diffuse									5	5
• Grade 1									4	
• Grade 2									1	5
Necrosis, multifocal					4					3
• Grade 1					3					2
• Grade 2					1					1
Hyperplasia, bile duct					1			1		5
• Grade 1					1			1		5
Oval cell proliferation					2			2		4
• Grade 1					2			2		4

Bile duct hyperplasia and oval cell proliferation in group 2 (100 ppm) female animals were likely not treatment-related due to their very minimal grade and focal occurrence. 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

BAS 750 F was administered via the diet to groups of 5 male and 5 female C57BL/6 J Rj mice at concentrations of 0 (test group 0), 30 (test group 1), 100 (test group 2), 300 (test group 3) and 1000 ppm (test group 4) over a period of 4 weeks.

Regarding clinical examination the deceased body weights and body weight changes as well as the decreased food consumption in male and female animals of test group 4 (1000 ppm) over the entire study period up to -41.9% on study day 7 in males and up to -45.0% on study day 14 in female animals were assessed as substance-related and therefore as an adverse effect.

Regarding clinical pathology a dysregulation of the liver cell function in rats of both sexes of test group 4 (1000 ppm) was indicated by decreased cholesterol levels in males as well as decreased albumin and glucose levels in females. In males of the mentioned test group a slight degradation of the liver cell membranes can be assumed because of higher activities of the cytosolic liver-specific alanine aminotransferase (ALT) enzyme in blood.

Regarding pathology, target organ was the liver. Hepatocellular hypertrophy was observed in all treated males in a centrilobular pattern and more diffuse in all females of test groups 3 and 4 (300 and 1000 ppm, respectively). The hypertrophy correlated in both sexes with the observed weight increases. In test group 4 (1000 ppm), the hypertrophy was associated with multifocal hepatocellular necrosis in 4/5 male and 3/5 female animals correlating with foci observed macroscopically on the liver. Additionally, there was bile duct hyperplasia and oval cell proliferation in one or two male and 5 or 4 female animals, respectively. Findings in the liver of test group 4 in males and females were regarded as adverse as the weight increase was above historical controls, there were correlating clinical pathology findings and histopathologically observed necrosis. In test group 3 females, the weight increase was above 130%, outside of the historical-control range and therefore regarded as potentially adverse although clinical pathology findings were absent and histopathology showed hypertrophy only. Findings in test group 1, 2 and 3 males were regarded as adaptive.
The weight increase in the thymus of test group 4 females was regarded as adverse.
The terminal body weight was significantly decreased in both male (-12%) and female (-5%) test group 4 animals.

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

6. CONCLUSION

The administration of BAS 750 F via the diet to male and female C57BL/6 J Rj mice for 4 weeks caused test substance-related adverse signs of systemic toxicity in males at concentrations of 1000 ppm (128 mg/kg bw/d) and in females at 300 ppm (61 mg/kg bw/d) and 1000 ppm (145 mg/kg bw/d).

In conclusion, under the conditions of this study the no observed adverse effect level (NOAEL) for this test compound in mice is 300 ppm in male (48 mg/kg bw/d) and 100 ppm in female (19 mg/kg bw/d) C57BL/6 J Rj mice.

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
Deviation Vs Control	=	deviation versus control 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
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

8.2. LIST OF ABBREVIATIONS USED IN TABLES CLINICAL PATHOLOGY

S.d. = standard deviation
N = number of values

HEMATOLOGY:

RBC = red blood cells (erythrocytes)
HGB = hemoglobin
HCT = hematocrit
MCV = mean corpuscular volume
MCH = mean corpuscular hemoglobin
MCHC = mean corpuscular hemoglobin concentration
RET = reticulocytes
PLT = platelets
HQT = prothrombin time (Hepato Quick's test)
PTT = activated partial thromboplastin time
QT = prothrombin time (Quick's test)
WBC = white blood cells (leukocytes)
NEUTA = polymorphonuclear neutrophils (absolute)
LYMPHA = lymphocytes (absolute)
MONOA = monocytes (absolute)
EOSA = eosinophils (absolute)
BASOA = basophils (absolute)
LUCA = large unstained cells (absolute)
NEUT = polymorphonuclear neutrophils
LYMPH = lymphocytes
MONO = monocytes
EOS = eosinophils
BASO = basophils
LUC = large unstained cells

CLINICAL CHEMISTRY:

ALT = alanine aminotransferase
AST = aspartate aminotransferase
ALP = alkaline phosphatase
GGT_C = serum-γ-glutamyltransferase
UREA = urea
CREA = creatinine
GLUC = glucose
TBIL = total bilirubin
TBA = bile acids

TPROT	=	total protein
ALB	=	albumin
GLOB	=	globulins
TRIG	=	triglycerides
CHOL	=	cholesterol
NA	=	sodium
K	=	potassium
CL	=	chloride
INP	=	inorganic phosphate
CA	=	calcium

UNITS:

mmol/L	=	millimole/liter
µmol/L	=	micromole/liter
nmol/L	=	nanomole/liter
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
mL	=	milliliter
Mio/g	=	millions/gram

8.3. LIST OF ABBREVIATIONS USED IN TABLES PATHOLOGY

A.-nos.	=	Animal numbers
exam	=	examined
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/d	=	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	=	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).

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Summary - Clinical Observation

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

			0 / M 0 ppm	1/ M 30 ppm	2/ M 100 ppm	3/ M 300 ppm	4/ M 1000 ppm
day 0 [DCO] -> 29	Animals examined	N	5	5	5	5	5
	dead	N	5	5	5	5	5
	sacrificed scheduled	%	100.0	100.0	100.0	100.0	100.0
	normal	N	5	5	5	5	5
	NAD	%	100.0	100.0	100.0	100.0	100.0

Summary - Clinical Observation

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

			0 / F 0 ppm	1/ F 30 ppm	2/ F 100 ppm	3 / F 300 ppm	4/ F 1000 ppm
day 0 [DCO] -> 29	Animals examined	N	5	5	5	5	5
	dead	N	5	5	5	5	5
	sacrificed scheduled	%	100.0	100.0	100.0	100.0	100.0
	normal	N	5	5	5	5	5
	NAD	%	100.0	100.0	100.0	100.0	100.0

Study 31C0741/11C201

11-Apr-2013 13:49

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Summary Food Consumption Per Day

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

		0 / M 0 ppm	1/ M 30 ppm	2/ M 100 ppm	3/ M 300 ppm	4/ M 1000 ppm
d 6 -> 7	**Mean [g]**	3.1	3.7	3.7	3.7	1.8
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		19.4	19.4	19.4	-41.9
d 13 -> 14	**Mean [g]**	4.4	3.7	3.3	4.1	3.6
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		-15.9	-25.0	-6.8	-18.2
d 20 -> 21	**Mean [g]**	3.0	3.8	3.5	3.7	2.3
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		26.7	16.7	23.3	-23.3
d 27 -> 28	**Mean [g]**	3.8	4.2	4.2	4.1	2.8
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		10.5	10.5	7.9	-26.3

d = day

Study 31C0741/11C201

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Summary Food Consumption Per Day

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

		0 / F 0 ppm	1/ F 30 ppm	2/ F 100 ppm	3 / F 300 ppm	4/ F 1000 ppm
d 6 -> 7	**Mean [g]**	3.8	3.5	3.5	3.8	2.7
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		-7.9	-7.9	0.0	-28.9
d 13 -> 14	**Mean [g]**	4.0	3.7	3.6	3.8	2.2
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		-7.5	-10.0	-5.0	-45.0
d 20 -> 21	**Mean [g]**	3.9	3.5	3.7	3.9	2.3
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		-10.3	-5.1	0.0	-41.0
d 27 -> 28	**Mean [g]**	4.7	4.1	4.2	4.5	3.2
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		-12.8	-10.6	-4.3	-31.9

d = day

Study 31C0741/11C201

11-Apr-2013 13:53

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Summary Water Consumption Per Day

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

		0 / M 0 ppm	1/ M 30 ppm	2/ M 100 ppm	3/ M 300 ppm	4/ M 1000 ppm
d 4 -> 7	**Mean [g]**	3.2	4.2	3.5	3.6	2.9
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		31.2	9.4	12.5	-9.4
d 11 -> 14	**Mean [g]**	4.6	3.6	2.7	3.6	3.6
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		-21.7	-41.3	-21.7	-21.7
d 18 -> 21	**Mean [g]**	3.9	4.1	3.6	3.6	3.3
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		5.1	-7.7	-7.7	-15.4
d 25 -> 28	**Mean [g]**	3.9	3.5	3.8	3.6	2.8
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		-10.3	-2.6	-7.7	-28.2

d = day

Study 31C0741/11C201

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Summary Water Consumption Per Day

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

		0 / F 0 ppm	1/ F 30 ppm	2/ F 100 ppm	3 / F 300 ppm	4/ F 1000 ppm
d 4 -> 7	**Mean [g]**	3.1	3.5	3.5	3.4	2.7
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		12.9	12.9	9.7	-12.9
d 11 -> 14	**Mean [g]**	3.8	3.7	3.5	3.2	4.1
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		-2.6	-7.9	-15.8	7.9
d 18 -> 21	**Mean [g]**	3.8	3.7	4.3	2.8	2.9
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		-2.6	13.2	-26.3	-23.7
d 25 -> 28	**Mean [g]**	3.6	3.3	3.7	3.3	2.9
	S.d.					
	N	1	1	1	1	1
	Deviation Vs Control		-8.3	2.8	-8.3	-19.4

d = day

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Summary Body Weights - BW / Body Weights [g]

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

		0 / M 0 ppm	1/ M 30 ppm	2/ M 100 ppm	3/ M 300 ppm	4/ M 1000 ppm
day 0	**Mean**	20.9 n	20.6	21.2	21.4	21.1
	S.d.	0.4	0.6	0.7	0.7	0.8
	N	5	5	5	5	5
	Deviation Vs Control		-1.1	1.6	2.7	1.3
day 7	**Mean**	21.5 n	22.4	22.5	22.9 *	18.7 **
	S.d.	0.7	1.3	0.8	0.5	0.3
	N	5	5	5	5	5
	Deviation Vs Control		4.2	4.7	6.5	-12.7
day 14	**Mean**	22.8 n	23.1	22.6	23.8	21.1 *
	S.d.	1.1	1.1	1.0	0.6	0.6
	N	5	5	5	5	5
	Deviation Vs Control		1.6	-0.8	4.6	-7.4
day 21	**Mean**	23.6 n	24.2	23.9	24.9	21.2 **
	S.d.	1.5	1.1	0.9	0.5	0.8
	N	5	5	5	5	5
	Deviation Vs Control		2.4	1.0	5.5	-10.5
day 28	**Mean**	24.2 n	25.5	25.2	26.0	21.0 **
	S.d.	1.7	1.2	0.7	0.4	1.0
	N	5	5	5	5	5
	Deviation Vs Control		5.5	4.3	7.4	-13.1

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

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Summary Body Weights - BW / Body Weights [g]

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

		0 / F 0 ppm	1/ F 30 ppm	2/ F 100 ppm	3 / F 300 ppm	4/ F 1000 ppm
day 0	**Mean**	17.6 n	17.6	18.1	18.1	18.1
	S.d.	0.6	0.7	0.6	1.2	0.2
	N	5	5	5	5	5
	Deviation Vs Control		-0.1	3.0	2.7	2.6
day 7	**Mean**	18.9 n	18.3	19.3	18.8	16.3 **
	S.d.	0.6	0.7	0.7	0.8	0.3
	N	5	5	5	5	5
	Deviation Vs Control		-3.4	2.0	-0.6	-13.8
day 14	**Mean**	19.6 n	19.2	19.9	19.4	18.3 *
	S.d.	0.5	0.4	0.6	0.9	0.6
	N	5	5	5	5	5
	Deviation Vs Control		-2.0	1.6	-1.2	-6.6
day 21	**Mean**	19.8 n	19.7	20.2	19.9	18.8
	S.d.	0.6	0.5	0.6	0.8	0.6
	N	5	5	5	5	5
	Deviation Vs Control		-0.2	2.4	0.6	-5.0
day 28	**Mean**	20.3 n	20.1	21.4 *	20.3	19.0 *
	S.d.	0.5	0.5	0.7	0.9	0.4
	N	5	5	5	5	5
	Deviation Vs Control		-0.9	5.4	0.4	-6.2

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

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18-Feb-2013 10:52

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

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

		0 / M 0 ppm	1/ M 30 ppm	2/ M 100 ppm	3/ M 300 ppm	4/ M 1000 ppm
d 0 -> 7	**Mean**	0.6 n	1.7	1.3	1.4	-2.4 **
	S.d.	0.9	0.8	0.3	0.4	1.1
	N	5	5	5	5	5
	Deviation Vs Control		186.7	110.0	140.0	-500.0
d 0 -> 14	**Mean**	1.9 n	2.5	1.4	2.4	-0.1 **
	S.d.	1.3	0.6	0.5	0.8	0.8
	N	5	5	5	5	5
	Deviation Vs Control		30.5	-27.4	25.3	-103.2
d 0 -> 21	**Mean**	2.8 n	3.6	2.7	3.5	0.0 **
	S.d.	1.7	0.6	0.4	0.6	0.8
	N	5	5	5	5	5
	Deviation Vs Control		28.1	-3.6	26.6	-99.3
d 0 -> 28	**Mean**	3.3 n	4.9	4.0	4.6	-0.1 **
	S.d.	2.0	1.0	0.3	0.4	0.7
	N	5	5	5	5	5
	Deviation Vs Control		46.7	21.0	36.5	-103.0

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

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

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

		0 / F 0 ppm	1/ F 30 ppm	2/ F 100 ppm	3 / F 300 ppm	4/ F 1000 ppm
d 0 -> 7	**Mean**	1.3 n	0.7	1.1	0.7	-1.8 **
	S.d.	0.3	0.2	0.6	0.6	0.2
	N	5	5	5	5	5
	Deviation Vs Control		-48.4	-10.9	-46.9	-239.1
d 0 -> 14	**Mean**	2.0 n	1.6	1.8	1.3 *	0.2 **
	S.d.	0.1	0.6	0.2	0.4	0.4
	N	5	5	5	5	5
	Deviation Vs Control		-19.0	-10.0	-36.0	-88.0
d 0 -> 21	**Mean**	2.1 n	2.1	2.1	1.8	0.7 **
	S.d.	0.4	0.6	0.5	0.7	0.7
	N	5	5	5	5	5
	Deviation Vs Control		-0.9	-1.9	-16.8	-67.3
d 0 -> 28	**Mean**	2.6 n	2.5	3.2	2.2	0.9 **
	S.d.	0.4	0.8	0.6	0.9	0.5
	N	5	5	5	5	5
	Deviation Vs Control		-6.1	22.0	-15.2	-65.2

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

Study 31C0741/11C201

11-Apr-2013 13:55

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Summary Substance Intake (mg/kg/Day)

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

		1/ M 30 ppm	2/ M 100 ppm	3/ M 300 ppm	4/ M 1000 ppm
d 6 -> 7	**Mean**	4.9	16.5	48.6	98.2
	S.d.				
	N	1	1	1	1
d 13 -> 14	**Mean**	4.7	14.4	51.2	170.8
	S.d.				
	N	1	1	1	1
d 20 -> 21	**Mean**	4.7	14.7	44.5	108.7
	S.d.				
	N	1	1	1	1
d 27 -> 28	**Mean**	5.0	16.6	47.1	135.0
	S.d.				
	N	1	1	1	1
Mean [mg/kg/Day]	**Mean**	4.8	15.5	47.9	128.2

d = day

Study 31C0741/11C201

11-Apr-2013 13:55

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Summary Substance Intake (mg/kg/Day)

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

		1/ F 30 ppm	2/ F 100 ppm	3 / F 300 ppm	4/ F 1000 ppm
d 6 -> 7	**Mean**	5.7	18.2	60.7	165.6
	S.d.				
	N	1	1	1	1
d 13 -> 14	**Mean**	5.8	17.9	58.2	122.3
	S.d.				
	N	1	1	1	1
d 20 -> 21	**Mean**	5.4	18.3	58.9	124.6
	S.d.				
	N	1	1	1	1
d 27 -> 28	**Mean**	6.2	19.8	66.1	168.4
	S.d.				
	N	1	1	1	1
Mean [mg/kg/Day]	**Mean**	5.8	18.5	61.0	145.2

d = day

IB 1

Study 31C0741/11C201 16-May-2013 08:21

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Red blood cell parameters

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

		0 / M 0 ppm	1/ M 30 ppm	2/ M 100 ppm	3/ M 300 ppm	4/ M 1000 ppm
RBC	Mean	11.22 k	10.60	10.43	10.21	11.06
[tera/L]	S.d.	0.48	0.08	0.58	1.02	0.87
day 29	N	5	5	5	5	5
	Median	11.46	10.62	10.58	10.82	11.04
HGB	Mean	9.8 k	9.5	9.4	9.1	9.9
[mmol/L]	S.d.	0.4	0.1	0.6	0.7	0.7
day 29	N	5	5	5	5	5
	Median	10.0	9.4	9.6	9.4	10.0
HCT	Mean	0.496 k	0.473	0.470	0.461	0.474
[L/L]	S.d.	0.015	0.009	0.027	0.037	0.040
day 29	N	5	5	5	5	5
	Median	0.500	0.476	0.480	0.480	0.476
MCV	Mean	44.2 v	44.6	45.0	45.2	42.8 **
[fL]	S.d.	0.7	0.6	0.7	1.1	0.3
day 29	N	5	5	5	5	5
	Median	44.0	44.8	44.9	45.1	42.7
MCH	Mean	0.87 k	0.89	0.89	0.90	0.90
[fmol]	S.d.	0.01	0.01	0.02	0.02	0.05
day 29	N	5	5	5	5	5
	Median	0.87	0.90	0.89	0.90	0.87
MCHC	Mean	19.72 v	20.06	19.87	19.81	20.88 **
[mmol/L]	S.d.	0.35	0.23	0.04	0.17	1.23
day 29	N	5	5	5	5	5
	Median	19.77	20.03	19.86	19.85	20.40
RET	Mean	3.0 v	3.0	2.8	3.1	2.1 **
[%]	S.d.	0.3	0.1	0.1	0.8	0.1
day 29	N	5	5	5	5	5
	Median	2.9	2.9	2.8	3.1	2.1
PLT	Mean	1,536 k	1,522	1,470	1,414	1,566
[giga/L]	S.d.	107	99	126	216	353
day 29	N	5	5	5	5	5
	Median	1,578	1,498	1,456	1,472	1,618

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

IB 2

Study 31C0741/11C201

16-May-2013 08:21

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Red blood cell parameters

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

		0 / F 0 ppm	1/ F 30 ppm	2/ F 100 ppm	3 / F 300 ppm	4/ F 1000 ppm
RBC	Mean	10.47 k	10.28	10.22	10.43	10.73
[tera/L]	S.d.	0.49	0.27	0.91	0.50	0.48
day 29	N	5	5	5	5	5
	Median	10.40	10.40	9.94	10.48	10.78
HGB	Mean	9.4 k	9.4	9.3	9.4	9.6
[mmol/L]	S.d.	0.5	0.1	0.7	0.5	0.5
day 29	N	5	5	5	5	5
	Median	9.4	9.4	9.0	9.4	9.4
HCT	Mean	0.466 k	0.454	0.459	0.465	0.464
[L/L]	S.d.	0.021	0.008	0.038	0.021	0.024
day 29	N	5	5	5	5	5
	Median	0.468	0.456	0.446	0.464	0.468
MCV	Mean	44.5 v	44.2	44.9	44.6	43.3 **
[fL]	S.d.	0.3	0.8	0.4	0.2	0.5
day 29	N	5	5	5	5	5
	Median	44.4	44.0	44.9	44.6	43.2
MCH	Mean	0.90 k	0.91	0.91	0.91	0.89
[fmol]	S.d.	0.02	0.02	0.02	0.00	0.02
day 29	N	5	5	5	5	5
	Median	0.90	0.90	0.91	0.91	0.89
MCHC	Mean	20.21 k	20.64	20.37	20.36	20.51
[mmol/L]	S.d.	0.46	0.54	0.31	0.14	0.30
day 29	N	5	5	5	5	5
	Median	20.43	20.45	20.26	20.39	20.51
RET	Mean	2.5 k	2.5	3.0	2.3	2.3
[%]	S.d.	0.3	0.3	0.7	0.1	0.2
day 29	N	5	5	5	5	5
	Median	2.5	2.5	2.8	2.2	2.3
PLT	Mean	1,294 k	1,296	1,257	1,428	1,344
[giga/L]	S.d.	52	89	173	81	243
day 29	N	5	5	5	5	4
	Median	1,270	1,332	1,324	1,438	1,448

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

IB 3

Study 31C0741/11C201 16-May-2013 08:22

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White blood cell parameters

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

		0 / M 0 ppm	1/ M 30 ppm	2/ M 100 ppm	3/ M 300 ppm	4/ M 1000 ppm
WBC	Mean	5.78 v	4.29	4.51	7.96 *	4.83
[giga/L]	S.d.	1.70	1.20	2.44	1.58	1.84
day 29	N	5	5	5	5	5
	Median	5.96	4.34	4.70	8.10	4.62
NEUTA	Mean	0.43 k	0.32	0.43	0.56	0.30
[giga/L]	S.d.	0.19	0.13	0.27	0.10	0.14
day 29	N	5	5	5	5	5
	Median	0.42	0.34	0.50	0.60	0.24
LYMPHA	Mean	5.24 v	3.90	3.95	7.18	4.29
[giga/L]	S.d.	1.54	1.14	2.10	1.46	1.75
day 29	N	5	5	5	5	5
	Median	5.44	4.08	4.12	7.28	4.14
MONOA	Mean	0.02 v	0.02	0.07	0.09 **	0.11 *
[giga/L]	S.d.	0.02	0.01	0.05	0.02	0.08
day 29	N	5	5	5	5	5
	Median	0.02	0.02	0.04	0.10	0.08
EOSA	Mean	0.06 v	0.03	0.04	0.09	0.10
[giga/L]	S.d.	0.02	0.01	0.02	0.04	0.11
day 29	N	5	5	5	5	5
	Median	0.06	0.04	0.04	0.08	0.04
BASOA	Mean	0.00 k	0.00	0.00	0.02	0.00
[giga/L]	S.d.	0.00	0.00	0.00	0.03	0.00
day 29	N	5	5	5	5	5
	Median	0.00	0.00	0.00	0.00	0.00
LUCA	Mean	0.02 k	0.01	0.02	0.03	0.01
[giga/L]	S.d.	0.01	0.01	0.02	0.01	0.01
day 29	N	5	5	5	5	5
	Median	0.02	0.02	0.02	0.02	0.00
NEUT	Mean	7.4 k	7.7	9.0	7.2	7.3
[%]	S.d.	2.2	2.9	1.8	1.6	4.0
day 29	N	5	5	5	5	5
	Median	6.9	7.0	9.7	7.2	6.4
LYMPH	Mean	90.8 k	90.7	88.1	90.1	87.7
[%]	S.d.	1.9	3.0	1.6	1.4	4.4
day 29	N	5	5	5	5	5
	Median	91.4	91.1	87.6	90.1	88.0
MONO	Mean	0.3 v	0.5	1.4 **	1.1 **	2.6 *
[%]	S.d.	0.2	0.3	0.4	0.1	2.0
day 29	N	5	5	5	5	5
	Median	0.3	0.4	1.6	1.2	2.4
EOS	Mean	1.1 k	0.6	1.0	1.1	2.0
[%]	S.d.	0.3	0.2	0.5	0.3	1.6
day 29	N	5	5	5	5	5
	Median	1.0	0.7	1.0	1.1	1.4
BASO	Mean	0.1 k	0.1	0.1	0.2	0.1
[%]	S.d.	0.1	0.1	0.1	0.2	0.1
day 29	N	5	5	5	5	5
	Median	0.1	0.1	0.1	0.1	0.1
LUC	Mean	0.4 k	0.4	0.3	0.3	0.3
[%]	S.d.	0.1	0.2	0.2	0.2	0.2
day 29	N	5	5	5	5	5
	Median	0.4	0.4	0.4	0.3	0.2

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

IB 4

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White blood cell parameters

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

		0 / F 0 ppm	1/ F 30 ppm	2/ F 100 ppm	3 / F 300 ppm	4/ F 1000 ppm
WBC [giga/L] day 29	Mean	3.72 k	3.75	5.29	3.75	5.67
	S.d.	1.38	1.21	2.76	0.86	3.40
	N	5	5	5	5	5
	Median	4.00	3.52	4.16	3.50	4.14
NEUTA [giga/L] day 29	Mean	0.42 k	0.52	0.44	0.32	0.34
	S.d.	0.10	0.19	0.27	0.06	0.19
	N	5	5	5	5	5
	Median	0.46	0.54	0.34	0.32	0.28
LYMPHA [giga/L] day 29	Mean	3.23 k	3.09	4.59	3.22	5.08
	S.d.	1.25	1.05	2.56	0.84	3.21
	N	5	5	5	5	5
	Median	3.46	3.02	3.50	2.96	3.70
MONOA [giga/L] day 29	Mean	0.02 v	0.07 **	0.18 **	0.15 **	0.17 **
	S.d.	0.01	0.04	0.05	0.09	0.11
	N	5	5	5	5	5
	Median	0.02	0.06	0.18	0.12	0.12
EOSA [giga/L] day 29	Mean	0.04 k	0.06	0.06	0.04	0.06
	S.d.	0.04	0.04	0.03	0.02	0.04
	N	5	5	5	5	5
	Median	0.04	0.04	0.06	0.04	0.06
BASOA [giga/L] day 29	Mean	0.00 k	0.00	0.00	0.00	0.00
	S.d.	0.00	0.00	0.01	0.01	0.00
	N	5	5	5	5	5
	Median	0.00	0.00	0.00	0.00	0.00
LUCA [giga/L] day 29	Mean	0.01 k	0.02	0.02	0.01	0.02
	S.d.	0.01	0.00	0.02	0.01	0.02
	N	5	5	5	5	5
	Median	0.02	0.02	0.02	0.02	0.02
NEUT [%] day 29	Mean	11.9 v	14.2	8.6	9.2	6.0 **
	S.d.	2.4	4.1	2.6	3.1	2.0
	N	5	5	5	5	5
	Median	11.3	13.0	8.7	9.0	5.6
LYMPH [%] day 29	Mean	86.3 k	81.9	85.3	85.5	88.6
	S.d.	2.0	4.7	4.8	2.8	2.5
	N	5	5	5	5	5
	Median	86.7	83.1	84.4	84.6	88.9
MONO [%] day 29	Mean	0.5 v	1.8 *	4.4 **	3.9 **	3.5 **
	S.d.	0.3	0.9	2.5	1.9	2.7
	N	5	5	5	5	5
	Median	0.6	2.0	5.7	3.9	2.1
EOS [%] day 29	Mean	1.0 k	1.5	1.4	0.9	1.4
	S.d.	0.5	0.7	0.5	0.4	1.1
	N	5	5	5	5	5
	Median	1.0	1.5	1.3	0.6	1.2
BASO [%] day 29	Mean	0.1 v	0.1	0.2	0.2 *	0.1
	S.d.	0.0	0.1	0.1	0.1	0.1
	N	5	5	5	5	5
	Median	0.1	0.1	0.2	0.3	0.1
LUC [%] day 29	Mean	0.2 k	0.5	0.2	0.4	0.3
	S.d.	0.2	0.2	0.2	0.2	0.3
	N	5	5	5	5	5
	Median	0.3	0.5	0.3	0.4	0.4

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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Enzymes

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

		0 / M 0 ppm	1/ M 30 ppm	2/ M 100 ppm	3/ M 300 ppm	4/ M 1000 ppm
ALT	Mean	0.83 v	0.81	0.97	1.14	2.08 *
[µkat/L]	S.d.	0.15	0.27	0.16	0.59	0.39
day 29	N	5	3	4	5	4
	Median	0.88	0.77	0.92	0.98	2.22
AST	Mean	5.18 k	4.10	4.83	5.11	5.72
[µkat/L]	S.d.	2.25	0.61	1.36	2.00	1.92
day 29	N	5	3	4	5	4
	Median	4.19	3.90	4.87	4.47	5.69
ALP	Mean	1.56 v	1.70	1.82 *	1.87 *	2.07 *
[µkat/L]	S.d.	0.14	0.14	0.16	0.15	0.39
day 29	N	5	5	5	5	5
	Median	1.51	1.68	1.85	1.88	2.08
GGT_C	Mean	0 k	0	0	0	0
[nkat/L]	S.d.	0	0	0	0	0
day 29	N	5	5	5	5	5
	Median	0	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

IB 6

Study 31C0741/11C201 16-May-2013 09:25

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Enzymes

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

		0 / F 0 ppm	1/ F 30 ppm	2/ F 100 ppm	3 / F 300 ppm	4/ F 1000 ppm
ALT	Mean	1.15 v	1.03	1.22	1.36	2.67
[µkat/L]	S.d.	0.37	0.18	0.27	0.34	1.69
day 29	N	5	5	5	5	4
	Median	0.99	1.04	1.33	1.22	1.94
AST	Mean	5.70 k	5.86	5.48	4.87	6.46
[µkat/L]	S.d.	0.94	1.98	1.74	0.88	1.49
day 29	N	5	5	5	5	4
	Median	5.77	5.03	6.14	4.57	6.63
ALP	Mean	2.28 v	2.07	2.11	1.98	2.53
[µkat/L]	S.d.	0.19	0.13	0.24	0.24	0.25
day 29	N	5	5	5	5	5
	Median	2.16	2.07	2.11	2.08	2.51
GGT_C	Mean	0 k	0	0	0	0
[nkat/L]	S.d.	0	0	0	0	0
day 29	N	5	5	5	5	5
	Median	0	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

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Substrates

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

		0 / M 0 ppm	1/ M 30 ppm	2/ M 100 ppm	3/ M 300 ppm	4/ M 1000 ppm
UREA	Mean	12.22 k	12.44	14.15	12.28	13.14
[mmol/L]	S.d.	1.61	1.14	2.01	1.34	1.18
day 29	N	5	5	5	5	5
	Median	11.32	12.57	14.86	12.60	13.31
CREA	Mean	36.7 k	36.2	33.7	31.6	36.2
[µmol/L]	S.d.	2.0	2.9	3.5	1.9	4.6
day 29	N	5	5	5	5	5
	Median	36.4	35.8	35.7	32.3	34.6
GLUC	Mean	7.54 k	7.21	6.96	7.29	5.70
[mmol/L]	S.d.	1.01	0.57	1.67	0.99	1.27
day 29	N	5	5	5	5	5
	Median	7.11	7.15	6.41	7.06	5.09
TBIL	Mean	1.46 v	0.91 *	0.52 **	0.63 **	0.67
[µmol/L]	S.d.	0.43	0.30	0.26	0.48	0.65
day 29	N	5	5	5	5	5
	Median	1.30	0.87	0.52	0.81	0.69
TBA	Mean	5.2 k	9.2	9.4	41.2	6.4
[µmol/L]	S.d.	2.9	9.4	14.1	53.5	2.8
day 29	N	5	5	5	5	5
	Median	4.6	4.6	3.8	8.4	5.5
TPROT	Mean	49.55 v	49.89	45.88 **	44.56 **	49.67
[g/L]	S.d.	0.54	0.39	1.81	2.19	1.31
day 29	N	5	5	5	5	5
	Median	49.64	49.67	46.74	45.45	49.72
ALB	Mean	31.17 v	31.33	28.63 **	27.87 **	31.31
[g/L]	S.d.	0.81	0.72	1.63	1.21	1.06
day 29	N	5	5	5	5	5
	Median	30.97	30.85	29.51	27.75	31.70
GLOB	Mean	18.38 v	18.56	17.25 **	16.69 **	18.37
[g/L]	S.d.	0.36	0.50	0.36	1.09	0.53
day 29	N	5	5	5	5	5
	Median	18.40	18.82	17.33	16.99	18.38
CHOL	Mean	2.53 v	2.01 *	1.51 **	1.24 **	0.69 **
[mmol/L]	S.d.	0.28	0.19	0.07	0.13	0.15
day 29	N	5	5	5	5	5
	Median	2.56	2.04	1.53	1.19	0.73
TRIG	Mean	0.98 v	0.85	0.50 *	0.68	0.66
[mmol/L]	S.d.	0.25	0.14	0.11	0.10	0.23
day 29	N	5	5	5	5	5
	Median	0.99	0.86	0.44	0.62	0.68

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

IB 8

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Substrates

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

		0 / F 0 ppm	1/ F 30 ppm	2/ F 100 ppm	3 / F 300 ppm	4/ F 1000 ppm
UREA	Mean	11.32 k	11.61	10.23	10.94	10.05
[mmol/L]	S.d.	1.03	1.36	1.53	0.59	0.32
day 29	N	5	5	5	5	5
	Median	11.58	11.46	9.22	11.19	10.05
CREA	Mean	32.8 k	34.9	33.8	32.3	33.7
[µmol/L]	S.d.	1.5	0.8	4.0	3.2	3.0
day 29	N	5	5	5	5	5
	Median	33.6	34.7	31.8	31.0	34.0
GLUC	Mean	7.79 v	7.90	6.83	5.95	5.25 **
[mmol/L]	S.d.	1.15	1.45	1.80	1.04	0.81
day 29	N	5	5	5	5	5
	Median	8.45	8.03	6.59	5.83	5.60
TBIL	Mean	0.88 k	0.95	0.85	0.47	0.64
[µmol/L]	S.d.	0.31	0.18	0.29	0.24	0.30
day 29	N	5	5	5	5	5
	Median	0.95	0.91	0.90	0.56	0.52
TBA	Mean	9.9 k	9.4	40.8	7.0	9.3
[µmol/L]	S.d.	6.4	5.5	72.3	4.0	7.0
day 29	N	5	5	5	5	4
	Median	7.7	6.6	7.1	4.7	6.5
TPROT	Mean	48.29 v	46.13	43.41 *	42.71 **	43.22 *
[g/L]	S.d.	1.84	1.18	2.13	0.70	2.05
day 29	N	5	5	5	5	4
	Median	47.92	45.89	42.96	42.46	43.28
ALB	Mean	31.85 v	30.64	28.67 *	28.16 **	27.69 *
[g/L]	S.d.	1.12	0.67	1.40	0.70	1.14
day 29	N	5	5	5	5	4
	Median	31.88	30.56	28.47	28.06	27.66
GLOB	Mean	16.44 v	15.48	14.74 *	14.55 **	15.53
[g/L]	S.d.	0.93	0.61	0.77	0.41	0.92
day 29	N	5	5	5	5	4
	Median	16.27	15.53	14.57	14.46	15.62
CHOL	Mean	2.04 v	1.32 **	0.87 **	0.68 **	0.83 **
[mmol/L]	S.d.	0.22	0.14	0.12	0.16	0.08
day 29	N	5	5	5	5	5
	Median	1.95	1.38	0.81	0.70	0.78
TRIG	Mean	0.82 v	0.48 **	0.39 **	0.30 **	0.63 *
[mmol/L]	S.d.	0.14	0.13	0.17	0.08	0.08
day 29	N	5	5	5	5	5
	Median	0.79	0.45	0.31	0.30	0.58

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

IB 9

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Electrolytes + minerals

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

		0 / M 0 ppm	1/ M 30 ppm	2/ M 100 ppm	3/ M 300 ppm	4/ M 1000 ppm
NA	Mean	148.5 k	150.0	148.7	147.8	149.4
[mmol/L]	S.d.	2.0	1.1	1.4	1.9	4.7
day 29	N	5	5	5	5	5
	Median	147.9	150.0	148.7	147.1	149.9
K	Mean	6.94 k	6.01	6.88	7.14	6.21
[mmol/L]	S.d.	0.94	0.32	0.67	0.88	0.58
day 29	N	5	3	4	5	4
	Median	6.57	6.17	6.83	6.90	6.25
CL	Mean	113.3 k	115.9	116.6	114.3	115.5
[mmol/L]	S.d.	2.2	0.7	1.3	1.6	2.8
day 29	N	5	5	5	5	5
	Median	113.2	116.0	116.7	114.9	114.8
INP	Mean	2.82 k	2.97	3.25	2.89	3.10
[mmol/L]	S.d.	0.35	0.27	0.39	0.30	0.29
day 29	N	5	5	5	5	5
	Median	2.79	3.11	3.29	2.70	2.99
CA	Mean	2.42 k	2.36	2.35	2.34	2.38
[mmol/L]	S.d.	0.03	0.03	0.02	0.08	0.06
day 29	N	5	5	5	5	5
	Median	2.42	2.36	2.36	2.34	2.38

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

IB 10

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Electrolytes + minerals

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

		0 / F 0 ppm	1/ F 30 ppm	2/ F 100 ppm	3 / F 300 ppm	4/ F 1000 ppm
NA	Mean	149.5 k	150.0	150.2	151.2	150.6
[mmol/L]	S.d.	2.2	1.9	1.8	0.9	2.3
day 29	N	5	5	5	5	5
	Median	148.7	149.8	150.7	151.5	150.0
K	Mean	6.21 k	5.94	5.72	5.48	6.57
[mmol/L]	S.d.	0.63	0.67	0.97	0.53	0.67
day 29	N	5	5	5	5	4
	Median	5.88	6.14	5.69	5.26	6.75
CL	Mean	115.5 k	115.6	116.1	116.9	115.9
[mmol/L]	S.d.	2.3	0.5	2.7	2.5	2.0
day 29	N	5	5	5	5	5
	Median	115.3	115.6	115.5	115.4	116.1
INP	Mean	2.83 k	2.92	3.02	3.01	3.19
[mmol/L]	S.d.	0.22	0.31	0.40	0.19	0.32
day 29	N	5	5	5	5	5
	Median	2.89	2.75	3.16	3.02	3.15
CA	Mean	2.29 k	2.26	2.27	2.26	2.35
[mmol/L]	S.d.	0.06	0.05	0.06	0.06	0.11
day 29	N	5	5	5	5	5
	Median	2.30	2.26	2.27	2.28	2.37

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

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
Administration via the diet

ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

Sacrifice			F1				
Sex			M				
Group			0	1	2	3	4
Terminal body weight	g	M	20.875	21.48	21.54	22.38	18.32 *
		% dev	100	103	103	107	88
		SD	1.424	0.993	0.73	0.444	0.698
		n	4	5	5	5	5
Adrenal glands	mg	M	4.22	4.04	4.52	3.96	4.9
		% dev	100	96	107	94	116
		SD	0.572	0.677	0.691	0.991	0.943
		n	5	5	5	5	5
Brain	mg	M	438.8	459.8	451.0	459.8 *	428.8
		% dev	100	105	103	105	98
		SD	10.354	15.466	8.944	9.858	13.864
		n	5	5	5	5	5
Epididymides	mg	M	48.6	55.0	50.4	53.0	46.6
		% dev	100	113	104	109	96
		SD	3.975	5.0	6.804	4.183	1.673
		n	5	5	5	5	5
Heart	mg	M	137.4	142.2	137.8	150.6	108.4 **
		% dev	100	103	100	110	79
		SD	11.971	14.202	14.957	24.317	7.701
		n	5	5	5	5	5
Kidneys	mg	M	273.8	287.8	283.8	300.2	228.8 *
		% dev	100	105	104	110	84
		SD	18.86	23.382	4.087	36.058	14.394
		n	5	5	5	5	5
Liver	mg	M	864.6	978.8 *	1037.0 **	1110.6 *	1276.2 **
		% dev	100	113	120	128	148
		SD	60.45	79.112	35.896	128.59	99.251
		n	5	5	5	5	5
Spleen	mg	M	48.8	45.4	43.0	63.6	33.2 *
		% dev	100	93	88	130	68
		SD	8.106	5.55	5.0	14.502	6.573
		n	5	5	5	5	5
Testes	mg	M	175.4	190.2	188.6	185.6	173.4
		% dev	100	108	108	106	99
		SD	17.416	8.672	23.394	15.534	7.893
		n	5	5	5	5	5

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

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
Administration via the diet

ABSOLUTE WEIGHTS - MEAN VALUES (MALE)

Sacrifice			F1				
Sex			M				
Group			0	1	2	3	4
Thymus	mg	M	32.84	38.12	29.72	40.34	31.52
		% dev	100	116	90	123	96
		SD	3.863	3.838	8.358	7.594	8.526
		n	5	5	5	5	5

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

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
Administration via the diet

ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

Sacrifice			F1				
Sex			F				
Group			0	1	2	3	4
Terminal body weight	g	M	17.56	17.68	18.22	17.44	16.66 *
		% dev	100	101	104	99	95
		SD	0.527	0.497	0.589	0.329	0.45
		n	5	5	5	5	5
Adrenal glands	mg	M	6.98	6.48	6.56	6.74	6.04 *
		% dev	100	93	94	97	87
		SD	0.614	0.743	0.518	0.27	0.134
		n	5	5	5	5	5
Brain	mg	M	451.6	454.4	449.0	450.0	435.6
		% dev	100	101	99	100	96
		SD	16.149	12.137	11.292	16.985	15.582
		n	5	5	5	5	5
Heart	mg	M	117.2	122.8	136.4	121.2	112.6
		% dev	100	105	116	103	96
		SD	8.258	19.715	18.77	19.058	15.789
		n	5	5	5	5	5
Kidneys	mg	M	238.8	236.8	250.5	244.0	223.2
		% dev	100	99	105	102	93
		SD	10.78	14.55	22.053	12.59	4.658
		n	5	5	4	5	5
Liver	mg	M	784.8	827.4	944.6 *	1035.8 **	1282.2 **
		% dev	100	105	120	132	163
		SD	29.507	22.344	84.535	44.515	51.325
		n	5	5	5	5	5
Ovaries	mg	M	13.36	11.78	9.88	12.08	9.62 *
		% dev	100	88	74	90	72
		SD	2.149	1.392	2.941	0.847	0.63
		n	5	5	5	5	5
Spleen	mg	M	49.8	48.0	54.6	47.2	41.4
		% dev	100	96	110	95	83
		SD	7.43	4.899	7.701	3.271	3.912
		n	5	5	5	5	5
Thymus	mg	M	36.4	43.88	48.22 **	49.04 **	58.88 **
		% dev	100	121	132	135	162
		SD	3.957	7.032	7.818	6.759	4.21
		n	5	5	5	5	5

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

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
Administration via the diet

ABSOLUTE WEIGHTS - MEAN VALUES (FEMALE)

Sacrifice			F1				
Sex			F				
Group			0	1	2	3	4
Uterus	mg	M	115.8	88.2	87.4	93.0	69.4
	% dev		100	76	75	80	60
		SD	52.179	24.212	27.637	19.026	9.236
		n	5	5	5	5	5

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

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
Administration via the diet

RELATIVE WEIGHTS - MEAN VALUES (MALE)

Sacrifice			F1				
Sex			M				
Group			0	1	2	3	4
Terminal body weight	%	M	100.0	100.0	100.0	100.0	100.0
		% dev	100	100	100	100	100
		n	4	5	5	5	5
Adrenal glands	%	M	0.02	0.019	0.021	0.018	0.027
		% dev	100	96	108	90	138
		SD	0.002	0.003	0.003	0.004	0.006
		n	4	5	5	5	5
Brain	%	M	2.093	2.143	2.095	2.056	2.342*
		% dev	100	102	100	98	112
		SD	0.104	0.087	0.057	0.075	0.075
		n	4	5	5	5	5
Epididymides	%	M	0.23	0.256	0.233	0.237	0.255
		% dev	100	111	101	103	111
		SD	0.022	0.021	0.025	0.017	0.016
		n	4	5	5	5	5
Heart	%	M	0.666	0.662	0.639	0.674	0.593
		% dev	100	99	96	101	89
		SD	0.039	0.055	0.062	0.118	0.054
		n	4	5	5	5	5
Kidneys	%	M	1.294	1.338	1.319	1.342	1.25
		% dev	100	103	102	104	97
		SD	0.042	0.055	0.043	0.166	0.085
		n	4	5	5	5	5
Liver	%	M	4.067	4.552*	4.818*	4.958*	6.959*
		% dev	100	112	118	122	171
		SD	0.212	0.183	0.206	0.523	0.316
		n	4	5	5	5	5
Spleen	%	M	0.222	0.211	0.199	0.284	0.181
		% dev	100	95	90	128	81
		SD	0.021	0.018	0.018	0.066	0.032
		n	4	5	5	5	5
Testes	%	M	0.828	0.886	0.874	0.829	0.948
		% dev	100	107	106	100	114
		SD	0.068	0.019	0.09	0.069	0.061
		n	4	5	5	5	5

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

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
Administration via the diet

RELATIVE WEIGHTS - MEAN VALUES (MALE)

Sacrifice			F1				
Sex			M				
Group			0	1	2	3	4
Thymus	%	M	0.157	0.178	0.138	0.181	0.171
		% dev	100	113	88	115	109
		SD	0.017	0.018	0.038	0.037	0.041
		n	4	5	5	5	5

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

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
Administration via the diet

RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

Sacrifice			F1				
Sex			F				
Group			0	1	2	3	4
Terminal body weight	%	M	100.0	100.0	100.0	100.0	100.0
		% dev	100	100	100	100	100
		n	5	5	5	5	5
Adrenal glands	%	M	0.04	0.037	0.036	0.039	0.036
		% dev	100	92	91	97	91
		SD	0.003	0.004	0.003	0.002	0.002
		n	5	5	5	5	5
Brain	%	M	2.573	2.571	2.465	2.58	2.615
		% dev	100	100	96	100	102
		SD	0.105	0.084	0.051	0.06	0.079
		n	5	5	5	5	5
Heart	%	M	0.669	0.693	0.751	0.694	0.675
		% dev	100	104	112	104	101
		SD	0.064	0.098	0.119	0.098	0.087
		n	5	5	5	5	5
Kidneys	%	M	1.36	1.34	1.357	1.399	1.34
		% dev	100	99	100	103	99
		SD	0.047	0.089	0.097	0.058	0.033
		n	5	5	4	5	5
Liver	%	M	4.469	4.68 **	5.185	5.939**	7.696**
		% dev	100	105	116	133	172
		SD	0.08	0.038	0.432	0.223	0.207
		n	5	5	5	5	5
Ovaries	%	M	0.076	0.067	0.054	0.069	0.058*
		% dev	100	87	72	91	76
		SD	0.012	0.006	0.017	0.004	0.004
		n	5	5	5	5	5
Spleen	%	M	0.283	0.272	0.3	0.271	0.249
		% dev	100	96	106	96	88
		SD	0.035	0.028	0.047	0.017	0.027
		n	5	5	5	5	5
Thymus	%	M	0.207	0.249	0.265*	0.281**	0.354**
		% dev	100	120	128	136	171
		SD	0.02	0.045	0.043	0.041	0.028
		n	5	5	5	5	5

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

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
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RELATIVE WEIGHTS - MEAN VALUES (FEMALE)

Sacrifice			F1				
Sex			F				
Group			0	1	2	3	4
Uterus	%	M	0.665	0.501	0.479	0.534	0.417
	%	dev	100	75	72	80	63
		SD	0.315	0.148	0.147	0.113	0.058
		n	5	5	5	5	5

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

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
Administration via the diet

INCIDENCE OF GROSS LESIONS

Sacrifice	F1									
Sex	M					F				
Group	0	1	2	3	4	0	1	2	3	4
Animals in selected group	5	5	5	5	5	5	5	5	5	5
No abnormalities	5	5	5	4	3	5	5	4	5	3
Kidneys	.	.	.	.	.	.	.	.	.	.
Cyst	.	.	.	.	.	.	.	1	.	.
Liver	.	.	.	.	.	.	.	.	.	.
Focus	.	.	.	1	2	.	.	.	.	2

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
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INCIDENCE AND GRADING OF FINDINGS IN SELECTED ORGANS

Sacrifice		F1									
Sex		M					F				
Group		0	1	2	3	4	0	1	2	3	4
Animals in selected group		5	5	5	5	5	5	5	5	5	5
Adrenal cortex	exam.	5	.	.	.	5	5	.	.	.	5
Adrenal medulla	exam.	5	.	.	.	5	5	.	.	.	5
Kidneys	exam.	5	.	.	.	5	5	.	1	.	5
Tubules, basophilic, (m)f		1	.	.	.	.	2	.	.	.	1
	. 1.	1	.	.	.	.	2	.	.	.	1
Hydronephrosis		.	.	.	.	.	.	.	1	.	.
	. 5.	.	.	.	.	.	.	.	1	.	.
Liver	exam.	5	5	5	5	5	5	5	5	5	5
Infiltration, lymphoid, (m)f		5	5	5	5	5	1	3	5	3	5
	. 1.	5	5	5	5	5	1	3	5	3	5
Hypertrophy, centrilobular		.	5	5	5	5	.	.	.	.	.
	. 1.	.	5	1	.	.	.	.	.	.	.
	. 2.	.	.	4	1	.	.	.	.	.	.
	. 3.	.	.	.	4	5	.	.	.	.	.
Hypertrophy, diffuse		.	.	.	.	.	.	.	.	5	5
	. 1.	.	.	.	.	.	.	.	.	4	.
	. 2.	.	.	.	.	.	.	.	.	1	5
Necrosis, (multi)focal		.	.	.	.	4	.	.	.	.	3
	. 1.	.	.	.	.	3	.	.	.	.	2
	. 2.	.	.	.	.	1	.	.	.	.	1
Hyperplasia, bile duct, dif		.	.	.	.	1	.	.	1	.	5
	. 1.	.	.	.	.	1	.	.	1	.	5
Oval cell proliferation		.	.	.	.	2	.	.	2	.	4
	. 1.	.	.	.	.	2	.	.	2	.	4
Fatty change, peripheral		.	.	.	1	.	.	.	.	.	.
	. 3.	.	.	.	1	.	.	.	.	.	.
Fatty change, (multi)focal		.	.	.	.	.	.	.	.	.	1
	. P.	.	.	.	.	.	.	.	.	.	1
Spleen	exam.	5	.	.	.	5	5	.	.	.	5
Thyroid glands	exam.	5	.	.	.	5	5	.	.	.	5

STUDY TITLE

Report

BAS 750 F

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
Administration via the diet

TEST FACILITY

BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen, Germany

TEST FACILITY PROJECT IDENTIFICATION

Project No. 31C0741/11C201

PART II OF III (TABLES SECTION; INDIVIDUAL VALUES)

CONTENTS OF PART II (TABLES SECTION; INDIVIDUAL VALUES)

Study 31C0741/11C201

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day 0 [DCO]	1	2	3	4	5	6	7 [DCO]	8	9
0 / M 0 ppm	01	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	02	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	03	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	04	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	05	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day 0 [DCO]	1	2	3	4	5	6	7 [DCO]	8	9
1/ M 30 ppm	06	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	07	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	08	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	09	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	10	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

Study 31C0741/11C201

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day 0 [DCO]	1	2	3	4	5	6	7 [DCO]	8	9
2/ M 100 ppm	11	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	12	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	13	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	14	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	15	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

Study 31C0741/11C201

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day 0 [DCO]	1	2	3	4	5	6	7 [DCO]	8	9
3/ M 300 ppm	16	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	17	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	18	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	19	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	20	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

Study 31C0741/11C201

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						0 [DCO]	1	2	3	4	5	6	7 [DCO]	8	9
4/ M 1000 ppm	21	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	22	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	23	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	24	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	25	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

Study 31C0741/11C201

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						10	11	12	13	14 [DCO]	15	16	17	18	19
0 / M 0 ppm	01	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	02	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	03	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	04	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	05	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						10	11	12	13	14 [DCO]	15	16	17	18	19
1/ M 30 ppm	06	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	07	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	08	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	09	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	10	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						10	11	12	13	14 [DCO]	15	16	17	18	19
2/ M 100 ppm	11	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	12	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	13	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	14	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	15	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						10	11	12	13	14 [DCO]	15	16	17	18	19
3/ M 300 ppm	16	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	17	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	18	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	19	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	20	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						10	11	12	13	14 [DCO]	15	16	17	18	19
	21	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	22	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
4/ M 1000 ppm	23	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	24	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	25	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						20	21 [DCO]	22	23	24	25	26	27	28 [DCO]	29
0 / M 0 ppm	01	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	02	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	03	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	04	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	05	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						20	21 [DCO]	22	23	24	25	26	27	28 [DCO]	29
1/ M 30 ppm	06	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	07	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	08	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	09	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	10	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						20	21 [DCO]	22	23	24	25	26	27	28 [DCO]	29
2/ M 100 ppm	11	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	12	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	13	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	14	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	15	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1

Study 31C0741/11C201

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						20	21 [DCO]	22	23	24	25	26	27	28 [DCO]	29
3/ M 300 ppm	16	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	17	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	18	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	19	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	20	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1

Study 31C0741/11C201

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						20	21 [DCO]	22	23	24	25	26	27	28 [DCO]	29
4/ M 1000 ppm	21	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	22	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	23	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	24	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	25	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1

Study 31C0741/11C201

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						0 [DCO]	1	2	3	4	5	6	7 [DCO]	8	9
0 / F 0 ppm	26	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	27	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	28	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	29	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	30	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

Study 31C0741/11C201

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day 0 [DCO]	1	2	3	4	5	6	7 [DCO]	8	9
1/ F 30 ppm	31	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	32	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	33	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	34	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	35	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day 0 [DCO]	1	2	3	4	5	6	7 [DCO]	8	9
2/ F 100 ppm	36	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	37	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	38	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	39	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	40	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

Study 31C0741/11C201

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						0 [DCO]	1	2	3	4	5	6	7 [DCO]	8	9
3 / F 300 ppm	41	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	42	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	43	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	44	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	45	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						0 [DCO]	1	2	3	4	5	6	7 [DCO]	8	9
4/ F 1000 ppm	46	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	47	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	48	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	49	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	50	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						10	11	12	13	14 [DCO]	15	16	17	18	19
0 / F 0 ppm	26	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	27	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	28	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	29	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	30	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						10	11	12	13	14 [DCO]	15	16	17	18	19
1/ F 30 ppm	31	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	32	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	33	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	34	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	35	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						10	11	12	13	14 [DCO]	15	16	17	18	19
2/ F 100 ppm	36	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	37	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	38	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	39	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	40	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						10	11	12	13	14 [DCO]	15	16	17	18	19
3 / F 300 ppm	41	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	42	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	43	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	44	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	45	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						10	11	12	13	14 [DCO]	15	16	17	18	19
4/ F 1000 ppm	46	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	47	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	48	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	49	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												
	50	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						20	21 [DCO]	22	23	24	25	26	27	28 [DCO]	29
0 / F 0 ppm	26	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	27	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	28	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	29	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	30	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						20	21 [DCO]	22	23	24	25	26	27	28 [DCO]	29
1/ F 30 ppm	31	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	32	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	33	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	34	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	35	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1

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Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						20	21 [DCO]	22	23	24	25	26	27	28 [DCO]	29
2/ F 100 ppm	36	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	37	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	38	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	39	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	40	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1

Study 31C0741/11C201

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						20	21 [DCO]	22	23	24	25	26	27	28 [DCO]	29
3 / F 300 ppm	41	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	42	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	43	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	44	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	45	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1

Study 31C0741/11C201

Individual Signs By Interval - Clinical Observation

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

Dose Group	Animal Number	Sign Type	Sign	Modifier	Remark	Day									
						20	21 [DCO]	22	23	24	25	26	27	28 [DCO]	29
4/ F 1000 ppm	46	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	47	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	48	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	49	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1
	50	normal	NAD			1	1	1	1	1	1	1	1	1	1
		dead	sacrificed scheduled												1

Study 31C0741/11C201

Individual Food Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 6 -> 7	d 13 -> 14	d 20 -> 21	d 27 -> 28
0 / M 0 ppm	01	04, 01, 02, 03, 05	3.1	4.4	3.0	3.8

d = day

Study 31C0741/11C201

Individual Food Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 6 -> 7	d 13 -> 14	d 20 -> 21	d 27 -> 28
1/ M 30 ppm	02	08, 09, 07, 10, 06	3.7	3.7	3.8	4.2

d = day

Study 31C0741/11C201

Individual Food Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 6 -> 7	d 13 -> 14	d 20 -> 21	d 27 -> 28
2/ M 100 ppm	03	13, 11, 12, 14, 15	3.7	3.3	3.5	4.2

d = day

Study 31C0741/11C201

Individual Food Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 6 -> 7	d 13 -> 14	d 20 -> 21	d 27 -> 28
3/ M 300 ppm	04	17, 18, 16, 19, 20	3.7	4.1	3.7	4.1

d = day

Study 31C0741/11C201

Individual Food Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 6 -> 7	d 13 -> 14	d 20 -> 21	d 27 -> 28
4/ M 1000 ppm	05	21, 22, 25, 24, 23	1.8	3.6	2.3	2.8

d = day

Study 31C0741/11C201

Individual Food Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 6 -> 7	d 13 -> 14	d 20 -> 21	d 27 -> 28
0 / F 0 ppm	06	26, 28, 29, 27, 30	3.8	4.0	3.9	4.7

d = day

Study 31C0741/11C201

Individual Food Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 6 -> 7	d 13 -> 14	d 20 -> 21	d 27 -> 28
1/ F 30 ppm	07	31, 33, 32, 34, 35	3.5	3.7	3.5	4.1

d = day

Study 31C0741/11C201

Individual Food Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 6 -> 7	d 13 -> 14	d 20 -> 21	d 27 -> 28
2/ F 100 ppm	08	36, 39, 37, 38, 40	3.5	3.6	3.7	4.2

d = day

Study 31C0741/11C201

Individual Food Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 6 -> 7	d 13 -> 14	d 20 -> 21	d 27 -> 28
3 / F 300 ppm	09	45, 44, 42, 43, 41	3.8	3.8	3.9	4.5

d = day

Study 31C0741/11C201

Individual Food Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 6 -> 7	d 13 -> 14	d 20 -> 21	d 27 -> 28
4/ F 1000 ppm	10	47, 48, 50, 49, 46	2.7	2.2	2.3	3.2

d = day

Study 31C0741/11C201

Individual Water Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 4 -> 7	d 11 -> 14	d 18 -> 21	d 25 -> 28
0 / M 0 ppm	01	04, 01, 02, 03, 05	3.2	4.6	3.9	3.9

d = day

Study 31C0741/11C201

Individual Water Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 4 -> 7	d 11 -> 14	d 18 -> 21	d 25 -> 28
1/ M 30 ppm	02	08, 09, 07, 10, 06	4.2	3.6	4.1	3.5

d = day

Study 31C0741/11C201

Individual Water Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 4 -> 7	d 11 -> 14	d 18 -> 21	d 25 -> 28
2/ M 100 ppm	03	13, 11, 12, 14, 15	3.5	2.7	3.6	3.8

d = day

Study 31C0741/11C201

Individual Water Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 4 -> 7	d 11 -> 14	d 18 -> 21	d 25 -> 28
3/ M 300 ppm	04	17, 18, 16, 19, 20	3.6	3.6	3.6	3.6

d = day

Study 31C0741/11C201

Individual Water Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 4 -> 7	d 11 -> 14	d 18 -> 21	d 25 -> 28
4/ M 1000 ppm	05	21, 22, 25, 24, 23	2.9	3.6	3.3	2.8

d = day

Study 31C0741/11C201

Individual Water Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 4 -> 7	d 11 -> 14	d 18 -> 21	d 25 -> 28
0 / F 0 ppm	06	26, 28, 29, 27, 30	3.1	3.8	3.8	3.6

d = day

Study 31C0741/11C201

Individual Water Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 4 -> 7	d 11 -> 14	d 18 -> 21	d 25 -> 28
1/ F 30 ppm	07	31, 33, 32, 34, 35	3.5	3.7	3.7	3.3

d = day

Study 31C0741/11C201

Individual Water Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 4 -> 7	d 11 -> 14	d 18 -> 21	d 25 -> 28
2/ F 100 ppm	08	36, 39, 37, 38, 40	3.5	3.5	4.3	3.7

d = day

Study 31C0741/11C201

Individual Water Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 4 -> 7	d 11 -> 14	d 18 -> 21	d 25 -> 28
3 / F 300 ppm	09	45, 44, 42, 43, 41	3.4	3.2	2.8	3.3

d = day

Study 31C0741/11C201

Individual Water Consumption Per Day [g/Day]

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

Group	Cage	Animals	d 4 -> 7	d 11 -> 14	d 18 -> 21	d 25 -> 28
4/ F 1000 ppm	10	47, 48, 50, 49, 46	2.7	4.1	2.9	2.9

d = day

Study 31C0741/11C201

Individual Body Weights - BW / Body Weights [g]

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

Dose Group	Animal Number	day 0	day 7	day 14	day 21	day 28
0 / M 0 ppm	01	20.5	22.3	23.2	24.8	25.6
	02	20.9	22.2	24.1	25.2	25.9
	03	21.4	21.2	22.5	22.6	22.9
	04	21.0	20.9	21.1	21.7	22.0
	05	20.5	20.7	22.9	23.9	24.6

Study 31C0741/11C201

Individual Body Weights - BW / Body Weights [g]

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

Dose Group	Animal Number	day 0	day 7	day 14	day 21	day 28
1/ M 30 ppm	06	20.9	22.3	22.8	23.8	24.3
	07	20.4	21.0	22.4	23.6	25.0
	08	21.6	24.5	25.0	26.1	27.5
	09	19.9	21.7	22.2	23.2	25.0
	10	20.4	22.3	23.2	24.3	25.9

Study 31C0741/11C201

Individual Body Weights - BW / Body Weights [g]

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

Dose Group	Animal Number	day 0	day 7	day 14	day 21	day 28
2/ M 100 ppm	11	21.4	22.6	22.6	24.1	25.2
	12	21.0	22.4	22.5	23.8	25.3
	13	20.5	21.9	22.3	23.5	24.9
	14	22.3	23.8	24.1	25.2	26.3
	15	20.8	21.6	21.4	22.8	24.5

Individual Body Weights - BW / Body Weights [g]

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

Dose Group	Animal Number	day 0	day 7	day 14	day 21	day 28
3/ M 300 ppm	16	22.3	23.2	24.4	25.3	26.5
	17	21.1	22.7	24.5	25.5	26.2
	18	20.6	22.1	23.3	24.3	25.3
	19	21.3	23.3	23.7	24.9	25.9
	20	21.8	23.0	23.1	24.7	26.0

Study 31C0741/11C201

Individual Body Weights - BW / Body Weights [g]

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

Dose Group	Animal Number	day 0	day 7	day 14	day 21	day 28
4/ M 1000 ppm	21	20.0	19.1	20.6	20.1	19.3
	22	21.9	18.3	20.6	21.2	21.4
	23	20.8	18.9	21.3	22.2	21.7
	24	22.0	18.8	22.0	21.4	21.4
	25	21.0	18.6	20.9	20.9	21.4

Study 31C0741/11C201

Individual Body Weights - BW / Body Weights [g]

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

Dose Group	Animal Number	day 0	day 7	day 14	day 21	day 28
0 / F 0 ppm	26	17.3	18.9	19.3	19.1	19.9
	27	17.1	18.5	19.1	19.7	20.4
	28	17.4	18.5	19.6	19.9	19.9
	29	17.8	18.7	19.7	19.5	20.1
	30	18.5	19.9	20.4	20.6	21.0

Study 31C0741/11C201

Individual Body Weights - BW / Body Weights [g]

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

Dose Group	Animal Number	day 0	day 7	day 14	day 21	day 28
1/ F 30 ppm	31	17.2	18.1	19.5	20.2	20.4
	32	16.8	17.5	18.9	18.9	19.3
	33	17.5	18.3	19.3	19.6	20.7
	34	17.8	18.1	18.7	19.8	19.9
	35	18.7	19.3	19.7	20.1	20.1

Study 31C0741/11C201

Individual Body Weights - BW / Body Weights [g]

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

Dose Group	Animal Number	day 0	day 7	day 14	day 21	day 28
2/ F 100 ppm	36	19.0	19.9	21.0	21.0	21.9
	37	18.1	19.0	19.6	19.5	20.5
	38	17.5	19.4	19.6	20.2	20.8
	39	17.7	18.2	19.4	19.8	21.7
	40	18.4	19.9	20.1	20.7	21.9

Study 31C0741/11C201

Individual Body Weights - BW / Body Weights [g]

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

Dose Group	Animal Number	day 0	day 7	day 14	day 21	day 28
3 / F 300 ppm	41	18.9	19.2	19.8	20.0	20.8
	42	19.8	19.8	20.6	21.2	21.3
	43	17.0	18.7	18.5	19.8	20.8
	44	17.0	17.6	18.7	19.1	19.3
	45	17.8	18.6	19.3	19.3	19.5

Study 31C0741/11C201

Individual Body Weights - BW / Body Weights [g]

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

Dose Group	Animal Number	day 0	day 7	day 14	day 21	day 28
4/ F 1000 ppm	46	18.0	15.9	18.0	18.4	19.1
	47	17.8	16.3	18.2	19.4	19.4
	48	18.1	16.4	18.2	19.0	18.5
	49	18.1	16.2	17.9	17.9	18.7
	50	18.4	16.7	19.3	19.2	19.3

Study 31C0741/11C201

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Red blood cell parameters

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

Dose Group	Animal Number	RBC [tera/L] day 29	HGB [mmol/L] day 29	HCT [L/L] day 29	MCV [fL] day 29	MCH [fmol] day 29	MCHC [mmol/L] day 29	RET [%] day 29	PLT [giga/L] day 29
0 / M 0 ppm	01	10.84	9.2	0.484	44.7	0.86	19.17	2.9	1,514
	02	11.56	10.0	0.508	44.0	0.87	19.77	2.8	1,578
	03	11.68	10.2	0.510	43.7	0.87	20.02	3.1	1,592
	04	11.46	10.0	0.500	43.6	0.87	20.01	2.7	1,636
	05	10.58	9.4	0.476	45.1	0.88	19.61	3.5	1,362
1/ M 30 ppm	06	10.64	9.4	0.474	44.5	0.88	19.87	2.9	1,614
	07	10.70	9.6	0.480	44.8	0.90	20.07	2.9	1,634
	08	10.62	9.6	0.478	45.1	0.90	20.03	3.0	1,460
	09	10.48	9.4	0.458	43.7	0.89	20.44	3.2	1,404
	10	10.58	9.4	0.476	45.1	0.90	19.87	2.8	1,498
2/ M 100 ppm	11	10.38	9.6	0.480	46.2	0.92	19.89	2.8	1,456
	12	10.98	9.8	0.492	44.9	0.89	19.86	2.8	1,624
	13	9.48	8.4	0.422	44.5	0.88	19.85	2.9	1,338
	14	10.58	9.4	0.476	45.0	0.89	19.84	2.6	1,360
	15	10.74	9.6	0.480	44.6	0.89	19.93	2.7	1,570
3/ M 300 ppm	16	9.64	8.8	0.448	46.4	0.91	19.63	3.8	1,288
	17	10.82	9.6	0.488	45.1	0.90	19.85	2.3	1,530
	18	8.68	8.0	0.402	46.3	0.92	19.85	4.0	1,114
	19	10.92	9.8	0.486	44.4	0.89	20.05	2.5	1,472
	20	10.98	9.4	0.480	43.8	0.86	19.66	3.1	1,668
4/ M 1000 ppm	21	10.34	9.0	0.440	42.5	0.87	20.40	2.2	1,390
	22	11.44	10.0	0.488	42.6	0.87	20.34	2.2	1,756
	23	12.30	10.8	0.532	43.2	0.88	20.40	2.0	1,072
	24	11.04	9.6	0.476	43.1	0.87	20.17	2.2	1,618
	25	10.16	10.0	0.434	42.7	0.99	23.07	2.1	1,996

Study 31C0741/11C201

Red blood cell parameters

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

Dose Group	Animal Number	RBC [tera/L] day 29	HGB [mmol/L] day 29	HCT [L/L] day 29	MCV [fL] day 29	MCH [fmol] day 29	MCHC [mmol/L] day 29	RET [%] day 29	PLT [giga/L] day 29
0 / F 0 ppm	26	10.38	9.2	0.468	45.0	0.88	19.61	2.7	1,258
	27	10.40	9.6	0.466	44.7	0.92	20.49	2.3	1,338
	28	9.80	8.8	0.434	44.2	0.90	20.43	2.4	1,242
	29	10.60	9.4	0.470	44.4	0.88	19.82	2.2	1,360
	30	11.16	10.2	0.494	44.4	0.92	20.68	2.8	1,270
1/ F 30 ppm	31	9.86	9.2	0.450	45.6	0.93	20.28	2.1	1,270
	32	10.44	9.4	0.460	44.1	0.90	20.45	3.0	1,154
	33	10.40	9.4	0.456	43.9	0.90	20.45	2.5	1,380
	34	10.52	9.4	0.462	44.0	0.90	20.44	2.4	1,332
	35	10.16	9.6	0.442	43.5	0.94	21.60	2.5	1,344
2/ F 100 ppm	36	9.84	9.0	0.444	45.1	0.91	20.17	2.7	1,346
	37	10.06	9.0	0.448	44.6	0.90	20.26	2.3	1,204
	38	11.80	10.6	0.526	44.5	0.89	20.05	2.8	1,324
	39	9.46	8.8	0.430	45.5	0.93	20.54	4.2	982
	40	9.94	9.2	0.446	44.9	0.93	20.82	2.8	1,428
3 / F 300 ppm	41	9.90	9.0	0.442	44.6	0.91	20.48	2.2	1,438
	42	9.94	9.0	0.446	44.9	0.90	20.13	2.2	1,328
	43	10.84	9.8	0.484	44.6	0.91	20.36	2.4	1,536
	44	10.98	10.0	0.488	44.5	0.91	20.39	2.2	1,464
	45	10.48	9.4	0.464	44.3	0.91	20.45	2.3	1,372
4/ F 1000 ppm	46	10.06	9.0	0.432	42.9	0.90	20.91	2.5	982
	47	11.34	10.4	0.498	44.0	0.91	20.67	2.3	542OL
	48	10.96	9.6	0.470	42.8	0.87	20.26	2.1	1,462
	49	10.50	9.4	0.454	43.2	0.89	20.51	2.1	1,498
	50	10.78	9.4	0.468	43.5	0.88	20.18	2.3	1,434

OL = Outlier

Study 31C0741/11C201

White blood cell parameters

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

Dose Group	Animal Number	WBC [giga/L] day 29	NEUTA [giga/L] day 29	LYMPHA [giga/L] day 29	MONOA [giga/L] day 29	EOSA [giga/L] day 29	BASOA [giga/L] day 29	LUCA [giga/L] day 29	NEUT [%] day 29	LYMPH [%] day 29	MONO [%] day 29	EOS [%] day 29	BASO [%] day 29	LUC [%] day 29
0 / M 0 ppm	01	7.94	0.58	7.20	0.02	0.08	0.00	0.04	7.4	90.7	0.3	1.0	0.1	0.5
	02	5.88	0.30	5.44	0.04	0.06	0.00	0.02	5.2	92.7	0.5	1.2	0.1	0.3
	03	5.98	0.42	5.46	0.02	0.06	0.00	0.02	6.9	91.4	0.4	0.9	0.1	0.3
	04	5.96	0.66	5.22	0.00	0.04	0.00	0.02	11.1	87.6	0.2	0.7	0.0	0.4
	05	3.16	0.20	2.88	0.00	0.04	0.00	0.02	6.4	91.4	0.1	1.5	0.2	0.4
1/ M 30 ppm	06	5.00	0.46	4.44	0.04	0.04	0.00	0.02	9.3	88.7	0.9	0.6	0.0	0.5
	07	4.34	0.20	4.08	0.02	0.04	0.00	0.00	4.5	94.2	0.3	0.8	0.1	0.2
	08	5.80	0.34	5.38	0.02	0.04	0.00	0.02	5.9	92.6	0.4	0.7	0.2	0.3
	09	2.70	0.18	2.46	0.02	0.02	0.00	0.00	7.0	91.1	0.7	0.8	0.0	0.4
	10	3.62	0.42	3.14	0.02	0.02	0.00	0.02	11.8	86.8	0.3	0.3	0.1	0.6
2/ M 100 ppm	11	5.72	0.60	4.94	0.10	0.06	0.00	0.02	10.4	86.5	1.6	1.0	0.0	0.5
	12	7.80	0.76	6.82	0.14	0.04	0.00	0.04	9.7	87.4	1.8	0.6	0.1	0.5
	13	4.70	0.50	4.12	0.04	0.02	0.00	0.02	10.6	87.6	0.9	0.4	0.2	0.4
	14	1.74	0.14	1.54	0.02	0.04	0.00	0.00	8.1	88.6	1.1	1.8	0.3	0.1
	15	2.58	0.16	2.32	0.04	0.02	0.00	0.00	6.4	90.6	1.6	1.0	0.1	0.2
3/ M 300 ppm	16	8.38	0.60	7.54	0.10	0.08	0.00	0.04	7.2	90.1	1.2	0.9	0.1	0.4
	17	10.24	0.62	9.26	0.12	0.16	0.06	0.02	6.1	90.5	1.2	1.5	0.5	0.3
	18	6.00	0.58	5.28	0.06	0.06	0.00	0.02	9.6	88.0	1.0	1.1	0.1	0.2
	19	8.10	0.62	7.28	0.10	0.06	0.00	0.04	7.6	89.9	1.1	0.8	0.0	0.6
	20	7.10	0.38	6.54	0.08	0.08	0.02	0.02	5.3	92.0	1.2	1.1	0.2	0.2
4/ M 1000 ppm	21	4.62	0.18	4.14	0.22	0.04	0.00	0.00	4.0	89.7	4.9	1.1	0.1	0.2
	22	6.54	0.20	6.06	0.16	0.10	0.00	0.02	3.2	92.6	2.4	1.4	0.1	0.3
	23	6.42	0.42	5.64	0.06	0.30	0.00	0.00	6.4	87.7	0.9	4.8	0.1	0.1
	24	2.02	0.24	1.62	0.08	0.04	0.00	0.02	12.1	80.6	4.3	2.2	0.2	0.6
	25	4.54	0.48	4.00	0.02	0.04	0.00	0.00	10.6	88.0	0.4	0.7	0.0	0.2

Study 31C0741/11C201

White blood cell parameters

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

Dose Group	Animal Number	WBC [giga/L] day 29	NEUTA [giga/L] day 29	LYMPHA [giga/L] day 29	MONOA [giga/L] day 29	EOSA [giga/L] day 29	BASOA [giga/L] day 29	LUCA [giga/L] day 29	NEUT [%] day 29	LYMPH [%] day 29	MONO [%] day 29	EOS [%] day 29	BASO [%] day 29	LUC [%] day 29
0 / F 0 ppm	26	4.00	0.46	3.46	0.02	0.04	0.00	0.02	11.3	86.7	0.6	0.9	0.1	0.4
	27	4.38	0.48	3.82	0.02	0.04	0.00	0.02	10.9	87.1	0.6	1.0	0.1	0.3
	28	5.36	0.46	4.76	0.02	0.10	0.00	0.02	8.6	88.7	0.5	1.9	0.0	0.3
	29	1.68	0.24	1.44	0.00	0.00	0.00	0.00	13.8	85.6	0.0	0.4	0.1	0.0
	30	3.20	0.48	2.68	0.02	0.04	0.00	0.00	14.7	83.4	0.6	1.0	0.1	0.2
1/ F 30 ppm	31	4.96	0.78	3.92	0.12	0.12	0.00	0.02	15.6	79.2	2.4	2.4	0.1	0.3
	32	5.06	0.62	4.36	0.04	0.04	0.00	0.02	12.2	86.0	0.6	0.7	0.0	0.5
	33	2.64	0.34	2.20	0.06	0.04	0.00	0.02	13.0	83.1	2.0	1.5	0.0	0.5
	34	3.52	0.34	3.02	0.10	0.02	0.00	0.02	9.6	86.1	2.9	0.8	0.2	0.4
	35	2.58	0.54	1.94	0.04	0.06	0.00	0.02	20.5	75.3	1.3	2.0	0.1	0.8
2/ F 100 ppm	36	4.16	0.34	3.50	0.24	0.04	0.00	0.02	8.2	84.4	6.0	1.1	0.1	0.3
	37	2.96	0.34	2.38	0.16	0.06	0.00	0.00	11.2	80.7	5.7	2.1	0.2	0.0
	38	7.54	0.34	7.04	0.10	0.06	0.00	0.02	4.5	93.2	1.3	0.7	0.1	0.3
	39	8.90	0.92	7.64	0.18	0.12	0.02	0.04	10.3	85.7	2.1	1.3	0.2	0.4
	40	2.90	0.26	2.40	0.20	0.04	0.00	0.00	8.7	82.6	6.7	1.7	0.2	0.2
3 / F 300 ppm	41	4.00	0.36	3.54	0.06	0.02	0.00	0.02	9.0	88.3	1.3	0.6	0.2	0.5
	42	3.20	0.32	2.68	0.12	0.06	0.00	0.00	10.1	83.9	3.9	1.6	0.3	0.3
	43	2.94	0.40	2.42	0.08	0.02	0.00	0.02	13.7	82.1	2.9	0.6	0.3	0.5
	44	5.12	0.26	4.52	0.28	0.04	0.02	0.00	5.2	88.4	5.4	0.6	0.3	0.1
	45	3.50	0.28	2.96	0.20	0.04	0.00	0.02	8.2	84.6	5.9	0.9	0.1	0.4
4/ F 1000 ppm	46	3.34	0.28	2.88	0.06	0.12	0.00	0.00	8.1	86.2	2.1	3.3	0.2	0.1
	47	11.60	0.66	10.70	0.12	0.08	0.00	0.04	5.6	92.2	1.1	0.6	0.1	0.4
	48	5.34	0.24	4.76	0.28	0.06	0.00	0.02	4.3	88.9	5.2	1.2	0.0	0.4
	49	4.14	0.34	3.70	0.08	0.02	0.00	0.00	8.1	89.5	1.7	0.5	0.1	0.1
	50	3.92	0.16	3.38	0.30	0.04	0.00	0.02	4.1	86.3	7.5	1.3	0.2	0.7

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Enzymes

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

Dose Group	Animal Number	ALT [µkat/L] day 29	AST [µkat/L] day 29	ALP [µkat/L] day 29	GGT_C [nkat/L] day 29
0 / M 0 ppm	01	0.98	9.05	1.41	0
	02	0.74	5.22	1.51	0
	03	0.88	3.52	1.45	0
	04	0.95	3.91	1.73	0
	05	0.62	4.19	1.69	0
1/ M 30 ppm	06	0.77	4.78	1.68	0
	07	1.17OL	8.78OL	1.85	0
	08	0.94OL	3.64OL	1.55	0
	09	0.56	3.61	1.82	0
	10	1.09	3.90	1.58	0
2/ M 100 ppm	11	0.91	4.45	1.79	0
	12	0.93	6.40	1.96	0
	13	1.19	5.29	1.85	0
	14	1.06OL	7.76OL	1.56	0
	15	0.83	3.17	1.92	0
3/ M 300 ppm	16	0.77	4.47	1.80	0
	17	2.16	8.62	2.08	0
	18	0.71	4.50	1.67	0
	19	1.07	4.43	1.88	0
	20	0.98	3.55	1.90	0
4/ M 1000 ppm	21	2.25	7.46	1.63	0
	22	2.19	7.31	1.78	0
	23	3.49OL	16.89OL	2.63	0
	24	2.38	4.06	2.23	0
	25	1.50	4.07	2.08	0

OL = Outlier

Study 31C0741/11C201

Enzymes

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

Dose Group	Animal Number	ALT [µkat/L] day 29	AST [µkat/L] day 29	ALP [µkat/L] day 29	GGT_C [nkat/L] day 29
0 / F 0 ppm	26	1.72	6.75	2.11	0
	27	1.32	5.77	2.42	0
	28	0.79	6.33	2.15	0
	29	0.93	4.32	2.16	0
	30	0.99	5.35	2.54	0
1/ F 30 ppm	31	1.14	9.02	2.07	0
	32	1.04	6.50	2.16	0
	33	1.25	5.03	2.22	0
	34	0.90	4.69	1.90	0
	35	0.81	4.08	1.99	0
2/ F 100 ppm	36	1.33	6.14	1.79	0
	37	1.37	7.25	2.15	0
	38	1.52	6.36	2.11	0
	39	1.01	4.91	2.46	0
	40	0.86	2.76	2.03	0
3 / F 300 ppm	41	1.22	5.81	1.85	0
	42	1.09	4.57	2.08	0
	43	1.12	4.38	1.62	0
	44	1.44	5.77	2.22	0
	45	1.92	3.84	2.11	0
4/ F 1000 ppm	46	4.54OL	15.37OL	2.51	0
	47	5.17	7.39	2.90	0
	48	2.23	7.93	2.47	0
	49	1.63	4.65	2.20	0
	50	1.66	5.87	2.58	0

OL = Outlier

Substrates

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

Dose Group	Animal Number	UREA [mmol/L] day 29	CREA [µmol/L] day 29	GLUC [mmol/L] day 29	TBIL [µmol/L] day 29	TBA [µmol/L] day 29	TPROT [g/L] day 29	ALB [g/L] day 29	GLOB [g/L] day 29	CHOL [mmol/L] day 29	TRIG [mmol/L] day 29
0 / M 0 ppm	01	11.32	39.8	7.11	2.16	9.9	49.64	30.80	18.84	2.88	0.99
	02	11.23	34.3	9.21	1.29	2.1	49.37	30.97	18.40	2.68	1.20
	03	10.71	36.7	6.61	1.54	5.1	49.71	31.56	18.15	2.39	0.93
	04	14.42	36.4	7.11	1.01	4.5	50.25	32.33	17.92	2.56	1.19
	05	13.41	36.1	7.68	1.30	4.6	48.77	30.20	18.57	2.15	0.58
1/ M 30 ppm	06	12.77	35.8	7.47	0.79	4.6	49.66	31.78	17.88	1.73	0.68
	07	12.57	36.9	6.73	1.28	25.8	50.57	32.39	18.18	2.04	0.86
	08	10.78	34.6	7.15	1.10	3.8	49.88	30.85	19.03	2.20	1.05
	09	12.13	40.8	8.05	0.50	7.5	49.66	30.77	18.89	1.91	0.79
	10	13.93	33.1	6.65	0.87	4.2	49.67	30.85	18.82	2.15	0.87
2/ M 100 ppm	11	15.59	30.3	6.20	0.48	2.2	47.52	29.94	17.58	1.53	0.41
	12	15.69	35.8	7.59	0.52	1.9	47.22	29.77	17.45	1.53	0.57
	13	10.81	29.5	6.41	0.15	34.6	43.50	26.17	17.33	1.59	0.66
	14	14.86	37.1	9.49	0.89	4.5	44.40	27.76	16.64	1.52	0.41
	15	13.81	35.7	5.11	0.54	3.8	46.74	29.51	17.23	1.40	0.44
3/ M 300 ppm	16	10.33	32.4	6.34	-0.22	125.4	43.81	27.52	16.29	1.29	0.79
	17	13.83	33.8	8.93	0.84	8.4	46.77	29.30	17.47	1.18	0.62
	18	11.67	29.0	7.06	0.79	63.9	41.12	26.12	15.00	1.19	0.62
	19	12.97	30.3	7.36	0.91	3.9	45.45	27.75	17.70	1.44	0.78
	20	12.60	32.3	6.76	0.81	4.3	45.64	28.65	16.99	1.10	0.59
4/ M 1000 ppm	21	11.67	34.6	5.83	0.69	5.9	49.72	31.70	18.02	0.77	0.73
	22	13.83	33.1	5.09	0.29	3.9	50.99	32.11	18.88	0.68	0.92
	23	14.61	44.1	7.86	1.70	5.5	47.89	29.51	18.38	0.83	0.65
	24	13.31	36.3	4.82	0.73	11.2	48.93	31.25	17.68	0.44	0.30
	25	12.28	33.0	4.89	-0.04	5.3	50.84	31.97	18.87	0.73	0.68

Study 31C0741/11C201

Substrates

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

Dose Group	Animal Number	UREA [mmol/L] day 29	CREA [µmol/L] day 29	GLUC [mmol/L] day 29	TBIL [µmol/L] day 29	TBA [µmol/L] day 29	TPROT [g/L] day 29	ALB [g/L] day 29	GLOB [g/L] day 29	CHOL [mmol/L] day 29	TRIG [mmol/L] day 29
0 / F 0 ppm	26	9.71	34.0	8.45	1.05	19.9	46.63	30.27	16.36	1.93	0.79
	27	11.16	33.6	8.91	0.95	12.2	47.92	31.65	16.27	1.95	1.06
	28	12.52	30.3	6.51	0.77	3.8	48.17	32.00	16.17	1.89	0.82
	29	11.58	32.4	8.50	0.41	5.8	47.31	31.88	15.43	2.03	0.74
	30	11.61	33.7	6.59	1.24	7.7	51.40	33.43	17.97	2.42	0.70
1/ F 30 ppm	31	13.88	36.2	9.13	0.89	5.5	45.22	29.97	15.25	1.38	0.33
	32	10.29	34.8	8.03	1.10	6.6	45.89	30.36	15.53	1.44	0.69
	33	11.46	34.7	9.28	1.15	9.2	46.18	30.56	15.62	1.22	0.42
	34	10.92	34.2	7.34	0.91	6.6	45.24	30.57	14.67	1.13	0.50
	35	11.52	34.6	5.73	0.71	19.0	48.11	31.76	16.35	1.42	0.45
2/ F 100 ppm	36	11.10	30.1	7.05	0.57	18.6	42.96	28.39	14.57	0.78	0.31
	37	12.53	39.9	9.75	0.92	7.1	42.67	28.47	14.20	0.76	0.26
	38	9.22	35.7	6.59	0.90	3.4	47.00	30.93	16.07	0.98	0.49
	39	9.19	31.7	5.11	1.29	169.7	41.29	27.08	14.21	1.03	0.64
	40	9.12	31.8	5.66	0.59	5.2	43.13	28.48	14.65	0.81	0.23
3 / F 300 ppm	41	11.24	35.1	5.83	0.05	4.2	41.90	27.44	14.46	0.46	0.33
	42	10.44	30.5	7.28	0.50	3.5	42.46	27.76	14.70	0.61	0.30
	43	11.19	31.0	6.52	0.65	11.6	42.34	28.26	14.08	0.70	0.23
	44	10.22	28.7	5.64	0.56	4.7	43.22	28.06	15.16	0.91	0.42
	45	11.63	36.2	4.49	0.58	11.2	43.62	29.29	14.33	0.71	0.23
4/ F 1000 ppm	46	10.42	34.0	5.60	1.10	6.8	40.67	26.35	14.32	0.78	0.58
	47	10.05	37.1	5.48	0.77	NM	NM	NM		0.77	0.66
	48	10.30	29.8	5.74	0.46	4.5	42.99	27.39	15.60	0.75	0.58
	49	9.87	31.6	5.62	0.35	6.2	43.57	27.93	15.64	0.93	0.75
	50	9.63	35.8	3.81	0.52	19.7	45.65	29.09	16.56	0.91	0.56

NM = Not measured

Study 31C0741/11C201

Electrolytes + minerals

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

Dose Group	Animal Number	NA [mmol/L] day 29	K [mmol/L] day 29	CL [mmol/L] day 29	INP [mmol/L] day 29	CA [mmol/L] day 29
0 / M 0 ppm	01	146.4	8.54	112.4	3.35	2.45
	02	147.9	6.99	110.9	2.79	2.43
	03	147.7	6.57	113.2	2.53	2.41
	04	148.8	6.37	113.4	2.48	2.42
	05	151.8	6.21	116.8	2.95	2.38
1/ M 30 ppm	06	148.9	6.21	116.0	2.79	2.36
	07	150.0	8.35OL	117.0	3.15	2.32
	08	149.2	6.43OL	116.0	3.11	2.39
	09	150.0	5.64	115.4	2.59	2.34
	10	151.7	6.17	115.2	3.21	2.40
2/ M 100 ppm	11	146.9	6.61	114.4	2.71	2.37
	12	148.7	7.71	116.7	3.29	2.36
	13	147.8	7.06	117.5	3.40	2.33
	14	149.9	7.95OL	116.7	3.77	2.32
	15	150.3	6.13	117.7	3.06	2.36
3/ M 300 ppm	16	146.2	6.44	112.7	2.70	2.30
	17	146.4	7.51	115.8	3.17	2.34
	18	147.1	6.37	112.4	2.65	2.23
	19	148.5	8.50	115.5	3.25	2.44
	20	150.7	6.90	114.9	2.66	2.41
4/ M 1000 ppm	21	147.3	6.65	113.3	2.76	2.39
	22	149.9	6.74	114.8	3.31	2.38
	23	142.4	10.96OL	113.0	3.48	2.31
	24	153.7	5.84	119.7	2.98	2.35
	25	153.6	5.59	116.9	2.99	2.48

OL = Outlier

Study 31C0741/11C201

Electrolytes + minerals

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

Dose Group	Animal Number	NA [mmol/L] day 29	K [mmol/L] day 29	CL [mmol/L] day 29	INP [mmol/L] day 29	CA [mmol/L] day 29
0 / F 0 ppm	26	146.9	5.75	113.6	2.89	2.21
	27	148.7	6.75	113.5	3.07	2.30
	28	148.6	7.02	115.3	2.97	2.31
	29	152.3	5.63	119.1	2.65	2.25
	30	151.1	5.88	116.0	2.55	2.37
1/ F 30 ppm	31	147.4	6.18	115.6	3.32	2.26
	32	150.6	6.84	115.9	3.17	2.20
	33	149.8	5.21	115.0	2.75	2.26
	34	149.4	6.14	115.3	2.60	2.26
	35	152.6	5.35	116.2	2.74	2.33
2/ F 100 ppm	36	151.9	5.69	120.2	3.16	2.28
	37	148.0	6.04	116.9	3.35	2.22
	38	148.6	7.03	114.4	3.06	2.36
	39	150.7	5.46	113.3	3.21	2.27
	40	151.9	4.36	115.5	2.33	2.21
3 / F 300 ppm	41	149.7	6.17	118.3	2.99	2.18
	42	151.5	5.92	120.6	3.02	2.20
	43	151.5	4.98	115.0	3.23	2.31
	44	152.0	5.26	115.1	3.08	2.32
	45	151.4	5.07	115.4	2.72	2.28
4/ F 1000 ppm	46	149.1	8.99OL	116.5	3.50	2.25
	47	148.0	6.92	116.1	2.80	2.37
	48	150.0	7.15	114.7	3.15	2.25
	49	153.1	5.63	118.7	2.97	2.39
	50	152.8	6.58	113.5	3.51	2.50

OL = Outlier

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Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 0

	Term. body weight g	Adrenal glands mg	Brain mg	Epididymides mg	Heart mg	Kidneys mg
M	20.875	4.22	438.8	48.6	137.4	273.8
SD	1.424	0.572	10.354	3.975	11.971	18.86
n	4	5	5	5	5	5
1		4.8	451.0	51.0	131.0	289.0
2	22.7	4.1	444.0	46.0	155.0	294.0
3	20.4	3.9	439.0	48.0	124.0	275.0
4	19.3	3.5	423.0	44.0	134.0	248.0
5	21.1	4.8	437.0	54.0	143.0	263.0

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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 0

		Liver mg	Spleen mg	Testes mg	Thymus mg
	M	864.6	48.8	175.4	32.84
	SD	60.45	8.106	17.416	3.863
	n	5	5	5	5
	1	931.0	58.0	185.0	32.8
	2	886.0	55.0	179.0	36.9
	3	789.0	41.0	166.0	36.5
	4	814.0	40.0	151.0	28.6
	5	903.0	50.0	196.0	29.4

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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 1

	Term. body weight g	Adrenal glands mg	Brain mg	Epididymides mg	Heart mg	Kidneys mg
M	21.48	4.04	459.8	55.0	142.2	287.8
SD	0.993	0.677	15.466	5.0	14.202	23.382
n	5	5	5	5	5	5
6	20.7	2.9	466.0	58.0	141.0	277.0
7	21.2	4.2	470.0	50.0	127.0	282.0
8	23.0	4.3	474.0	62.0	164.0	317.0
9	20.6	4.1	436.0	54.0	146.0	258.0
10	21.9	4.7	453.0	51.0	133.0	305.0

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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 1

	Liver mg	Spleen mg	Testes mg	Thymus mg
M	978.8	45.4	190.2	38.12
SD	79.112	5.55	8.672	3.838
n	5	5	5	5
6	948.0	45.0	188.0	34.4
7	920.0	43.0	188.0	43.4
8	1113.0	55.0	200.0	40.3
9	928.0	41.0	178.0	37.9
10	985.0	43.0	197.0	34.6

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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 2

	Term. body weight g	Adrenal glands mg	Brain mg	Epididymides mg	Heart mg	Kidneys mg
M	21.54	4.52	451.0	50.4	137.8	283.8
SD	0.73	0.691	8.944	6.804	14.957	4.087
n	5	5	5	5	5	5
11	22.1	4.4	458.0	56.0	137.0	287.0
12	22.2	4.3	450.0	59.0	137.0	279.0
13	20.8	5.6	454.0	46.0	141.0	282.0
14	21.9	4.6	457.0	48.0	158.0	289.0
15	20.7	3.7	436.0	43.0	116.0	282.0

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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 2

	Liver mg	Spleen mg	Testes mg	Thymus mg
M	1037.0	43.0	188.6	29.72
SD	35.896	5.0	23.394	8.358
n	5	5	5	5
11	1043.0	50.0	183.0	32.0
12	1040.0	46.0	217.0	39.9
13	1078.0	39.0	188.0	22.1
14	1045.0	42.0	201.0	20.2
15	979.0	38.0	154.0	34.4

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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 3

	Term. body weight g	Adrenal glands mg	Brain mg	Epididymides mg	Heart mg	Kidneys mg
M	22.38	3.96	459.8	53.0	150.6	300.2
SD	0.444	0.991	9.858	4.183	24.317	36.058
n	5	5	5	5	5	5
16	22.7	5.0	467.0	55.0	162.0	346.0
17	22.5	4.5	457.0	51.0	155.0	284.0
18	21.7	2.4	473.0	54.0	183.0	328.0
19	22.8	4.2	451.0	58.0	125.0	286.0
20	22.2	3.7	451.0	47.0	128.0	257.0

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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 3

	Liver mg	Spleen mg	Testes mg	Thymus mg
M	1110.6	63.6	185.6	40.34
SD	128.59	14.502	15.534	7.594
n	5	5	5	5
16	1026.0	80.0	167.0	30.1
17	1228.0	66.0	192.0	45.4
18	929.0	74.0	172.0	49.5
19	1209.0	53.0	193.0	36.3
20	1161.0	45.0	204.0	40.4

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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 4

	Term. body weight g	Adrenal glands mg	Brain mg	Epididymides mg	Heart mg	Kidneys mg
M	18.32	4.9	428.8	46.6	108.4	228.8
SD	0.698	0.943	13.864	1.673	7.701	14.394
n	5	5	5	5	5	5
21	17.3	4.9	415.0	48.0	116.0	217.0
22	18.9	4.8	451.0	46.0	108.0	234.0
23	19.0	3.4	425.0	47.0	106.0	213.0
24	18.0	5.8	432.0	48.0	97.0	231.0
25	18.4	5.6	421.0	44.0	115.0	249.0

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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 4

	Liver mg	Spleen mg	Testes mg	Thymus mg
M	1276.2	33.2	173.4	31.52
SD	99.251	6.573	7.893	8.526
n	5	5	5	5
21	1127.0	32.0	179.0	21.1
22	1392.0	39.0	184.0	34.7
23	1311.0	41.0	165.0	41.3
24	1240.0	27.0	168.0	24.2
25	1311.0	27.0	171.0	36.3

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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 0

	Term. body weight g	Adrenal glands mg	Brain mg	Heart mg	Kidneys mg	Liver mg
M	17.56	6.98	451.6	117.2	238.8	784.8
SD	0.527	0.614	16.149	8.258	10.78	29.507
n	5	5	5	5	5	5
26	17.3	6.9	443.0	123.0	239.0	785.0
27	17.8	6.8	429.0	106.0	229.0	792.0
28	17.5	6.2	460.0	121.0	235.0	760.0
29	16.9	7.1	455.0	125.0	234.0	757.0
30	18.3	7.9	471.0	111.0	257.0	830.0

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Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 0

	Ovaries mg	Spleen mg	Thymus mg	Uterus mg
M	13.36	49.8	36.4	115.8
SD	2.149	7.43	3.957	52.179
n	5	5	5	5
26	15.5	48.0	31.3	180.0
27	13.2	56.0	39.4	73.0
28	10.1	51.0	40.5	77.0
29	12.9	38.0	33.3	165.0
30	15.1	56.0	37.5	84.0

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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 1

	Term. body weight g	Adrenal glands mg	Brain mg	Heart mg	Kidneys mg	Liver mg
M	17.68	6.48	454.4	122.8	236.8	827.4
SD	0.497	0.743	12.137	19.715	14.55	22.344
n	5	5	5	5	5	5
31	18.2	7.8	450.0	134.0	217.0	851.0
32	16.9	6.1	441.0	107.0	226.0	796.0
33	18.0	6.1	455.0	152.0	244.0	846.0
34	17.6	6.3	474.0	114.0	251.0	827.0
35	17.7	6.1	452.0	107.0	246.0	817.0

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Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 1

	Ovaries mg	Spleen mg	Thymus mg	Uterus mg
M	11.78	48.0	43.88	88.2
SD	1.392	4.899	7.032	24.212
n	5	5	5	5
31	13.2	53.0	46.7	102.0
32	10.5	51.0	54.1	121.0
33	13.3	50.0	37.6	64.0
34	10.5	45.0	43.9	88.0
35	11.4	41.0	37.1	66.0

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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 2

	Term. body weight g	Adrenal glands mg	Brain mg	Heart mg	Kidneys mg		Liver mg
M	18.22	6.56	449.0	136.4	250.5		944.6
SD	0.589	0.518	11.292	18.77	22.053		84.535
n	5	5	5	5	4		5
36	18.7	6.7	458.0	138.0	272.0		1028.0
37	17.3	6.6	430.0	158.0	635.0	s	924.0
38	18.0	6.7	457.0	120.0	226.0		945.0
39	18.4	5.7	451.0	151.0	238.0		815.0
40	18.7	7.1	449.0	115.0	266.0		1011.0

BASF PATHOLOGY REPORT IIC 16/68
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Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 2

	Ovaries mg	Spleen mg	Thymus mg	Uterus mg
M	9.88	54.6	48.22	87.4
SD	2.941	7.701	7.818	27.637
n	5	5	5	5
36	12.4	57.0	44.5	76.0
37	11.6	60.0	43.0	90.0
38	11.0	51.0	51.4	78.0
39	9.4	62.0	60.5	60.0
40	5.0	43.0	41.7	133.0

BASF PATHOLOGY REPORT IIC 17/68
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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 3

	Term. body weight g	Adrenal glands mg	Brain mg	Heart mg	Kidneys mg	Liver mg
M	17.44	6.74	450.0	121.2	244.0	1035.8
SD	0.329	0.27	16.985	19.058	12.59	44.515
n	5	5	5	5	5	5
41	17.8	7.0	456.0	153.0	251.0	1112.0
42	17.7	6.3	468.0	120.0	250.0	1001.0
43	17.5	6.8	461.0	119.0	252.0	1022.0
44	17.1	6.9	438.0	103.0	245.0	1009.0
45	17.1	6.7	427.0	111.0	222.0	1035.0

BASF PATHOLOGY REPORT IIC 18/68
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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 3

	Ovaries mg	Spleen mg	Thymus mg	Uterus mg
M	12.08	47.2	49.04	93.0
SD	0.847	3.271	6.759	19.026
n	5	5	5	5
41	12.2	46.0	47.1	83.0
42	13.4	49.0	45.8	103.0
43	12.0	52.0	49.9	85.0
44	11.1	44.0	60.1	121.0
45	11.7	45.0	42.3	73.0

BASF PATHOLOGY REPORT IIC 19/68
31C0741/11C201
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Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 4

	Term. body weight g	Adrenal glands mg	Brain mg	Heart mg	Kidneys mg	Liver mg
M	16.66	6.04	435.6	112.6	223.2	1282.2
SD	0.45	0.134	15.582	15.789	4.658	51.325
n	5	5	5	5	5	5
46	16.5	6.2	427.0	128.0	226.0	1276.0
47	17.2	5.9	463.0	131.0	230.0	1367.0
48	16.9	6.1	425.0	101.0	219.0	1284.0
49	16.0	6.1	432.0	97.0	220.0	1248.0
50	16.7	5.9	431.0	106.0	221.0	1236.0

BASF PATHOLOGY REPORT IIC 20/68
31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

ABSOLUTE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 4

	Ovaries mg	Spleen mg	Thymus mg	Uterus mg
M	9.62	41.4	58.88	69.4
SD	0.63	3.912	4.21	9.236
n	5	5	5	5
46	10.3	46.0	52.0	81.0
47	9.5	43.0	58.3	73.0
48	9.3	36.0	62.3	66.0
49	8.8	43.0	62.2	71.0
50	10.2	39.0	59.6	56.0

BASF PATHOLOGY REPORT IIC 21/68
31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 0

	Term. body weight %	Adrenal glands %	Brain %	Epididymides %	Heart %	Kidneys %
M	100.0	0.02	2.093	0.23	0.666	1.294
SD		0.002	0.104	0.022	0.039	0.042
n	4	4	4	4	4	4
1						
2	100.0	0.018	1.956	0.203	0.683	1.295
3	100.0	0.019	2.152	0.235	0.608	1.348
4	100.0	0.018	2.192	0.228	0.694	1.285
5	100.0	0.023	2.071	0.256	0.678	1.246

BASF PATHOLOGY REPORT IIC 22/68
31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 0

	Liver	Spleen	Testes	Thymus
	%	%	%	%
M	4.067	0.222	0.828	0.157
SD	0.212	0.021	0.068	0.017
n	4	4	4	4
1				
2	3.903	0.242	0.789	0.163
3	3.868	0.201	0.814	0.179
4	4.218	0.207	0.782	0.148
5	4.28	0.237	0.929	0.139

BASF PATHOLOGY REPORT IIC 23/68
31C0741/11C201
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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 1

	Term. body weight	Adrenal glands	Brain	Epididymides	Heart	Kidneys
	%	%	%	%	%	%
M	100.0	0.019	2.143	0.256	0.662	1.338
SD		0.003	0.087	0.021	0.055	0.055
n	5	5	5	5	5	5
6	100.0	0.014	2.251	0.28	0.681	1.338
7	100.0	0.02	2.217	0.236	0.599	1.33
8	100.0	0.019	2.061	0.27	0.713	1.378
9	100.0	0.02	2.117	0.262	0.709	1.252
10	100.0	0.021	2.068	0.233	0.607	1.393

BASF PATHOLOGY REPORT IIC 24/68
31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 1

	Liver	Spleen	Testes	Thymus
	%	%	%	%
M	4.552	0.211	0.886	0.178
SD	0.183	0.018	0.019	0.018
n	5	5	5	5
6	4.58	0.217	0.908	0.166
7	4.34	0.203	0.887	0.205
8	4.839	0.239	0.87	0.175
9	4.505	0.199	0.864	0.184
10	4.498	0.196	0.9	0.158

BASF PATHOLOGY REPORT IIC 25/68
31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 2

	Term. body weight	Adrenal glands	Brain	Epididymides	Heart	Kidneys
	%	%	%	%	%	%
M	100.0	0.021	2.095	0.233	0.639	1.319
SD		0.003	0.057	0.025	0.062	0.043
n	5	5	5	5	5	5
11	100.0	0.02	2.072	0.253	0.62	1.299
12	100.0	0.019	2.027	0.266	0.617	1.257
13	100.0	0.027	2.183	0.221	0.678	1.356
14	100.0	0.021	2.087	0.219	0.721	1.32
15	100.0	0.018	2.106	0.208	0.56	1.362

BASF PATHOLOGY REPORT IIC 26/68
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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 2

	Liver	Spleen	Testes	Thymus
	%	%	%	%
M	4.818	0.199	0.874	0.138
SD	0.206	0.018	0.09	0.038
n	5	5	5	5
11	4.719	0.226	0.828	0.145
12	4.685	0.207	0.977	0.18
13	5.183	0.188	0.904	0.106
14	4.772	0.192	0.918	0.092
15	4.729	0.184	0.744	0.166

BASF PATHOLOGY REPORT IIC 27/68
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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 3

	Term. body weight	Adrenal glands	Brain	Epididymides	Heart	Kidneys
	%	%	%	%	%	%
M	100.0	0.018	2.056	0.237	0.674	1.342
SD		0.004	0.075	0.017	0.118	0.166
n	5	5	5	5	5	5
16	100.0	0.022	2.057	0.242	0.714	1.524
17	100.0	0.02	2.031	0.227	0.689	1.262
18	100.0	0.011	2.18	0.249	0.843	1.512
19	100.0	0.018	1.978	0.254	0.548	1.254
20	100.0	0.017	2.032	0.212	0.577	1.158

BASF PATHOLOGY REPORT IIC 28/68
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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 3

	Liver	Spleen	Testes	Thymus
	%	%	%	%
M	4.958	0.284	0.829	0.181
SD	0.523	0.066	0.069	0.037
n	5	5	5	5
16	4.52	0.352	0.736	0.133
17	5.458	0.293	0.853	0.202
18	4.281	0.341	0.793	0.228
19	5.303	0.232	0.846	0.159
20	5.23	0.203	0.919	0.182

BASF PATHOLOGY REPORT IIC 29/68
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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 4

	Term. body weight %	Adrenal glands %	Brain %	Epididymides %	Heart %	Kidneys %
M	100.0	0.027	2.342	0.255	0.593	1.25
SD		0.006	0.075	0.016	0.054	0.085
n	5	5	5	5	5	5
21	100.0	0.028	2.399	0.277	0.671	1.254
22	100.0	0.025	2.386	0.243	0.571	1.238
23	100.0	0.018	2.237	0.247	0.558	1.121
24	100.0	0.032	2.4	0.267	0.539	1.283
25	100.0	0.03	2.288	0.239	0.625	1.353

BASF PATHOLOGY REPORT IIC 30/68
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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex M
Group 4

	Liver	Spleen	Testes	Thymus
	%	%	%	%
M	6.959	0.181	0.948	0.171
SD	0.316	0.032	0.061	0.041
n	5	5	5	5
21	6.514	0.185	1.035	0.122
22	7.365	0.206	0.974	0.184
23	6.9	0.216	0.868	0.217
24	6.889	0.15	0.933	0.134
25	7.125	0.147	0.929	0.197

BASF PATHOLOGY REPORT IIC 31/68
31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 0

	Term. body weight	Adrenal glands	Brain	Heart	Kidneys	Liver
	%	%	%	%	%	%
M	100.0	0.04	2.573	0.669	1.36	4.469
SD		0.003	0.105	0.064	0.047	0.08
n	5	5	5	5	5	5
26	100.0	0.04	2.561	0.711	1.382	4.538
27	100.0	0.038	2.41	0.596	1.287	4.449
28	100.0	0.035	2.629	0.691	1.343	4.343
29	100.0	0.042	2.692	0.74	1.385	4.479
30	100.0	0.043	2.574	0.607	1.404	4.536

BASF PATHOLOGY REPORT IIC 32/68
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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 0

	Ovaries %	Spleen %	Thymus %	Uterus %
M	0.076	0.283	0.207	0.665
SD	0.012	0.035	0.02	0.315
n	5	5	5	5
26	0.09	0.277	0.181	1.04
27	0.074	0.315	0.221	0.41
28	0.058	0.291	0.231	0.44
29	0.076	0.225	0.197	0.976
30	0.083	0.306	0.205	0.459

BASF PATHOLOGY REPORT IIC 33/68
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Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 1

	Term. body weight	Adrenal glands	Brain	Heart	Kidneys	Liver
	%	%	%	%	%	%
M	100.0	0.037	2.571	0.693	1.34	4.68
SD		0.004	0.084	0.098	0.089	0.038
n	5	5	5	5	5	5
31	100.0	0.043	2.473	0.736	1.192	4.676
32	100.0	0.036	2.609	0.633	1.337	4.71
33	100.0	0.034	2.528	0.844	1.356	4.7
34	100.0	0.036	2.693	0.648	1.426	4.699
35	100.0	0.034	2.554	0.605	1.39	4.616

BASF PATHOLOGY REPORT IIC 34/68
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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 1

	Ovaries %	Spleen %	Thymus %	Uterus %
M	0.067	0.272	0.249	0.501
SD	0.006	0.028	0.045	0.148
n	5	5	5	5
31	0.073	0.291	0.257	0.56
32	0.062	0.302	0.32	0.716
33	0.074	0.278	0.209	0.356
34	0.06	0.256	0.249	0.5
35	0.064	0.232	0.21	0.373

BASF PATHOLOGY REPORT IIC 35/68
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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 2

	Term. body weight	Adrenal glands	Brain	Heart	Kidneys	Liver
	%	%	%	%	%	%
M	100.0	0.036	2.465	0.751	1.357	5.185
SD		0.003	0.051	0.119	0.097	0.432
n	5	5	5	5	4	5
36	100.0	0.036	2.449	0.738	1.455	5.497
37	100.0	0.038	2.486	0.913	3.671s	5.341
38	100.0	0.037	2.539	0.667	1.256	5.25
39	100.0	0.031	2.451	0.821	1.293	4.429
40	100.0	0.038	2.401	0.615	1.422	5.406

BASF PATHOLOGY REPORT IIC 36/68
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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 2

	Ovaries %	Spleen %	Thymus %	Uterus %
M	0.054	0.3	0.265	0.479
SD	0.017	0.047	0.043	0.147
n	5	5	5	5
36	0.066	0.305	0.238	0.406
37	0.067	0.347	0.249	0.52
38	0.061	0.283	0.286	0.433
39	0.051	0.337	0.329	0.326
40	0.027	0.23	0.223	0.711

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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 3

	Term. body weight	Adrenal glands	Brain	Heart	Kidneys	Liver
	%	%	%	%	%	%
M	100.0	0.039	2.58	0.694	1.399	5.939
SD		0.002	0.06	0.098	0.058	0.223
n	5	5	5	5	5	5
41	100.0	0.039	2.562	0.86	1.41	6.247
42	100.0	0.036	2.644	0.678	1.412	5.655
43	100.0	0.039	2.634	0.68	1.44	5.84
44	100.0	0.04	2.561	0.602	1.433	5.901
45	100.0	0.039	2.497	0.649	1.298	6.053

BASF PATHOLOGY REPORT IIC 38/68
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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 3

	Ovaries %	Spleen %	Thymus %	Uterus %
M	0.069	0.271	0.281	0.534
SD	0.004	0.017	0.041	0.113
n	5	5	5	5
41	0.069	0.258	0.265	0.466
42	0.076	0.277	0.259	0.582
43	0.069	0.297	0.285	0.486
44	0.065	0.257	0.351	0.708
45	0.068	0.263	0.247	0.427

BASF PATHOLOGY REPORT IIC 39/68
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Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 4

	Term. body weight	Adrenal glands	Brain	Heart	Kidneys	Liver
	%	%	%	%	%	%
M	100.0	0.036	2.615	0.675	1.34	7.696
SD		0.002	0.079	0.087	0.033	0.207
n	5	5	5	5	5	5
46	100.0	0.038	2.588	0.776	1.37	7.733
47	100.0	0.034	2.692	0.762	1.337	7.948
48	100.0	0.036	2.515	0.598	1.296	7.598
49	100.0	0.038	2.7	0.606	1.375	7.8
50	100.0	0.035	2.581	0.635	1.323	7.401

BASF PATHOLOGY REPORT IIC 40/68
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Administration via the diet

RELATIVE WEIGHTS - INDIVIDUAL VALUES

Sacrifice F1
Sex F
Group 4

	Ovaries %	Spleen %	Thymus %	Uterus %
M	0.058	0.249	0.354	0.417
SD	0.004	0.027	0.028	0.058
n	5	5	5	5
46	0.062	0.279	0.315	0.491
47	0.055	0.25	0.339	0.424
48	0.055	0.213	0.369	0.391
49	0.055	0.269	0.389	0.444
50	0.061	0.234	0.357	0.335

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Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice          27.May.2013 HAMA
Administration via the diet

SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                    Sacrifice                  F1
                                                    Sex                         M
                                                    Group                       0
                                                    Animal                      1
..............................................................................
General information
  Sex               : Male
  Group             : 0 (0 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
  All other organs examined without microscopic findings.

                                                    Animal                      2
..............................................................................
General information
  Sex               : Male
  Group             : 0 (0 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
  All other organs examined without microscopic findings.

                                                    Animal                      3
..............................................................................
General information
  Sex               : Male
  Group             : 0 (0 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure
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                                                                     31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice          27.May.2013 HAMA
Administration via the diet

SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          M
                                                  Group                        0
                                         cont.    Animal                       3
..............................................................................
Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
  All other organs examined without microscopic findings.

                                                  Animal                       4
..............................................................................
General information
  Sex               : Male
  Group             : 0 (0 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
  All other organs examined without microscopic findings.

                                                  Animal                       5
..............................................................................
General information
  Sex               : Male
  Group             : 0 (0 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.
```

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(GROSS LESIONS AND MICROSCOPIC FINDINGS)

	Sacrifice	F1
	Sex	M
	Group	0
cont.	Animal	5

Microscopic findings
  Kidneys
    Tubules, basophilic, (multi)focal, unilateral, grade 1.
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s), grade 1.
  All other organs examined without microscopic findings.

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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                    Sacrifice                  F1
                                                    Sex                         M
                                                    Group                       1
                                                    Animal                      6
..............................................................................
General information
  Sex               : Male
  Group             : 1 (30 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 1.
  No other organs examined.

                                                    Animal                     7
..............................................................................
General information
  Sex               : Male
  Group             : 1 (30 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 1.
  No other organs examined.

                                                    Animal                     8
..............................................................................
General information
  Sex               : Male
  Group             : 1 (30 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
```

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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          M
                                                  Group                        1
                                          cont.   Animal                       8
..............................................................................
                     1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 1.
  No other organs examined.

                                                  Animal                       9
..............................................................................
General information
  Sex               : Male
  Group             : 1 (30 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 1.
  No other organs examined.

                                                  Animal                      10
..............................................................................
General information
  Sex               : Male
  Group             : 1 (30 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure
```

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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)

	Sacrifice	F1
	Sex	M
	Group	1
cont.	Animal	10

Macroscopic findings
Animal without particular findings.

Microscopic findings
Liver
Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s), grade 1.
Hypertrophy, centrilobular, grade 1.
No other organs examined.

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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          M
                                                  Group                        2
                                                  Animal                      11
..............................................................................
General information
  Sex               : Male
  Group             : 2 (100 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 2.
  No other organs examined.

                                                  Animal                      12
..............................................................................
General information
  Sex               : Male
  Group             : 2 (100 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 2.
  No other organs examined.

                                                  Animal                      13
..............................................................................
General information
  Sex               : Male
  Group             : 2 (100 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
```

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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          M
                                                  Group                        2
                                         cont.    Animal                      13
..............................................................................
                     1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 1.
  No other organs examined.

                                                  Animal                      14
..............................................................................
General information
  Sex               : Male
  Group             : 2 (100 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 2.
  No other organs examined.

                                                  Animal                      15
..............................................................................
General information
  Sex               : Male
  Group             : 2 (100 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure
```

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(GROSS LESIONS AND MICROSCOPIC FINDINGS)

	Sacrifice	F1
	Sex	M
	Group	2
cont.	Animal	15

Macroscopic findings
Animal without particular findings.

Microscopic findings
Liver
Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s), grade 1.
Hypertrophy, centrilobular, grade 2.
No other organs examined.

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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          M
                                                  Group                        3
                                                  Animal                      16
..............................................................................
General information
  Sex               : Male
  Group             : 3 (300 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 3.
  No other organs examined.

                                                  Animal                      17
..............................................................................
General information
  Sex               : Male
  Group             : 3 (300 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 3.
  No other organs examined.

                                                  Animal                      18
..............................................................................
General information
  Sex               : Male
  Group             : 3 (300 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
```

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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          M
                                                  Group                        3
                                         cont.    Animal                      18
..............................................................................
                     1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 2.
  No other organs examined.

                                                  Animal                      19
..............................................................................
General information
  Sex               : Male
  Group             : 3 (300 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 3.
  No other organs examined.

                                                  Animal                      20
..............................................................................
General information
  Sex               : Male
  Group             : 3 (300 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure
```

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(GROSS LESIONS AND MICROSCOPIC FINDINGS)

	Sacrifice	F1
	Sex	M
	Group	3
cont.	Animal	20

Macroscopic findings
Liver
Focus, caudate process, on the margin, diameter 4.0 mm, yellow.
All other organs without macroscopic findings.

Microscopic findings
Liver
Gross lesion(s) evaluated histopathologically.
Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s), grade 1.
Hypertrophy, centrilobular, grade 3.
Fatty change, peripheral, grade 3, correlates to gross lesion Focus.
* Focally.
No other organs examined.

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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          M
                                                  Group                        4
                                                  Animal                      21
..............................................................................
General information
  Sex              : Male
  Group            : 4 (1000 ppm)
  Sacrifice        : Final sacrifice group
  Necropsy status  : Planned sacrifice
  Date of death    : 19.Feb.2013
                     29 days after start of exposure
                     1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Adrenal medulla
    Unilaterally investigated or present. No histopathologic findings noted.
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 3.
    Necrosis, (multi)focal, grade 1.
  All other organs examined without microscopic findings.

                                                  Animal                      22
..............................................................................
General information
  Sex              : Male
  Group            : 4 (1000 ppm)
  Sacrifice        : Final sacrifice group
  Necropsy status  : Planned sacrifice
  Date of death    : 19.Feb.2013
                     29 days after start of exposure
                     1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 3.
    Necrosis, (multi)focal, grade 1.
  All other organs examined without microscopic findings.
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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                    Sacrifice                F1
                                                    Sex                       M
                                                    Group                     4
                                                    Animal                   23
..............................................................................
General information
  Sex               : Male
  Group             : 4 (1000 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Liver
    Focus, left lateral lobe, diameter 2.0 mm, yellow.
  All other organs without macroscopic findings.

Microscopic findings
  Liver
    Gross lesion(s) evaluated histopathologically.
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 3.
    Necrosis, (multi)focal, grade 2, correlates to gross lesion Focus.
    Hyperplasia bile duct, diffuse, grade 1.
    Oval cell proliferation, grade 1.
  All other organs examined without microscopic findings.

                                                    Animal                   24
..............................................................................
General information
  Sex               : Male
  Group             : 4 (1000 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Liver
    Focus, right medial lobe, diameter 2.0 mm, yellow.
  All other organs without macroscopic findings.
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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                 Sacrifice                   F1
                                                 Sex                          M
                                                 Group                        4
                                        cont.    Animal                      24
..............................................................................
Microscopic findings
  Liver
    Gross lesion(s) evaluated histopathologically.
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 3.
    Necrosis, (multi)focal, grade 1, correlates to gross lesion Focus.
    Oval cell proliferation, grade 1.
  All other organs examined without microscopic findings.

                                                 Animal                      25
..............................................................................
General information
  Sex               : Male
  Group             : 4 (1000 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, centrilobular, grade 3.
  All other organs examined without microscopic findings.
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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          F
                                                  Group                        0
                                                  Animal                      26
..............................................................................
General information
  Sex               : Female
  Group             : 0 (0 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  All organs examined without pathologic findings.

                                                  Animal                      27
..............................................................................
General information
  Sex               : Female
  Group             : 0 (0 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Kidneys
    Tubules, basophilic, (multi)focal, grade 1.
  All other organs examined without microscopic findings.

                                                  Animal                      28
..............................................................................
General information
  Sex               : Female
  Group             : 0 (0 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure
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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          F
                                                  Group                        0
                                         cont.    Animal                      28
..............................................................................
Macroscopic findings
  Animal without particular findings.

Microscopic findings
  All organs examined without pathologic findings.

                                                  Animal                      29
..............................................................................
General information
  Sex               : Female
  Group             : 0 (0 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  All organs examined without pathologic findings.

                                                  Animal                      30
..............................................................................
General information
  Sex               : Female
  Group             : 0 (0 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Kidneys
    Tubules, basophilic, (multi)focal, unilateral, grade 1.
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
  All other organs examined without microscopic findings.
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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                    Sacrifice                F1
                                                    Sex                       F
                                                    Group                     1
                                                    Animal                   31
..............................................................................
General information
  Sex               : Female
  Group             : 1 (30 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
  No other organs examined.

                                                    Animal                   32
..............................................................................
General information
  Sex               : Female
  Group             : 1 (30 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
  No other organs examined.

                                                    Animal                   33
..............................................................................
General information
  Sex               : Female
  Group             : 1 (30 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure
```

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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          F
                                                  Group                        1
                                         cont.    Animal                      33
..............................................................................
Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
  No other organs examined.

                                                  Animal                      34
..............................................................................
General information
  Sex               : Female
  Group             : 1 (30 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  All organs examined without pathologic findings.

                                                  Animal                      35
..............................................................................
General information
  Sex               : Female
  Group             : 1 (30 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  All organs examined without pathologic findings.
```

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SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          F
                                                  Group                        2
                                                  Animal                      36
..............................................................................
General information
  Sex               : Female
  Group             : 2 (100 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
  No other organs examined.

                                                  Animal                      37
..............................................................................
General information
  Sex               : Female
  Group             : 2 (100 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Kidneys
    Cyst, left side, diameter 8.0 mm.
  All other organs without macroscopic findings.

Microscopic findings
  Kidneys
    Unilaterally investigated or present. Gross lesion(s) evaluated
    histopathologically.
    Hydronephrosis, unilateral, grade 5, correlates to gross lesion Cyst.
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Oval cell proliferation, grade 1.
  No other organs examined.
```

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BASF                              PATHOLOGY REPORT                  IIC       61/68
                                                                     31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice          27.May.2013 HAMA
Administration via the diet

SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          F
                                                  Group                        2
                                                  Animal                      38
..............................................................................
General information
  Sex               : Female
  Group             : 2 (100 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
  No other organs examined.

                                                  Animal                      39
..............................................................................
General information
  Sex               : Female
  Group             : 2 (100 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hyperplasia bile duct, diffuse, grade 1.
  No other organs examined.

                                                  Animal                      40
..............................................................................
General information
  Sex               : Female
  Group             : 2 (100 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure
```

BASF PATHOLOGY REPORT IIC 62/68
31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)

	Sacrifice	F1
	Sex	F
	Group	2
cont.	Animal	40

Macroscopic findings
Animal without particular findings.

Microscopic findings
Liver
Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s), grade 1.
Oval cell proliferation, grade 1.
No other organs examined.

```
BASF                              PATHOLOGY REPORT                  IIC       63/68
                                                                     31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice          27.May.2013 HAMA
Administration via the diet

SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          F
                                                  Group                        3
                                                  Animal                      41
..............................................................................
General information
  Sex               : Female
  Group             : 3 (300 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, diffuse, grade 2.
  No other organs examined.

                                                  Animal                      42
..............................................................................
General information
  Sex               : Female
  Group             : 3 (300 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Hypertrophy, diffuse, grade 1.
  No other organs examined.

                                                  Animal                      43
..............................................................................
General information
  Sex               : Female
  Group             : 3 (300 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure
```

```
BASF                              PATHOLOGY REPORT                  IIC       64/68
                                                                     31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice          27.May.2013 HAMA
Administration via the diet

SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          F
                                                  Group                        3
                                         cont.    Animal                      43
..............................................................................
Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, diffuse, grade 1.
  No other organs examined.

                                                  Animal                      44
..............................................................................
General information
  Sex               : Female
  Group             : 3 (300 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, diffuse, grade 1.
  No other organs examined.

                                                  Animal                      45
..............................................................................
General information
  Sex               : Female
  Group             : 3 (300 ppm)
  Sacrifice         : Final sacrifice group
  Necropsy status   : Planned sacrifice
  Date of death     : 19.Feb.2013
                      29 days after start of exposure
                      1 day after end of exposure
```

BASF PATHOLOGY REPORT IIC 65/68
31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice 27.May.2013 HAMA
Administration via the diet

SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)

	Sacrifice	F1
	Sex	F
	Group	3
cont.	Animal	45

Macroscopic findings
Animal without particular findings.

Microscopic findings
Liver
Hypertrophy, diffuse, grade 1.
No other organs examined.

```
BASF                              PATHOLOGY REPORT                  IIC       66/68
                                                                     31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice          27.May.2013 HAMA
Administration via the diet

SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          F
                                                  Group                        4
                                                  Animal                      46
..............................................................................
General information
  Sex              : Female
  Group            : 4 (1000 ppm)
  Sacrifice        : Final sacrifice group
  Necropsy status  : Planned sacrifice
  Date of death    : 19.Feb.2013
                     29 days after start of exposure
                     1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, diffuse, grade 2.
    Necrosis, (multi)focal, grade 1.
    Hyperplasia bile duct, diffuse, grade 1.
    Oval cell proliferation, grade 1.
  All other organs examined without microscopic findings.

                                                  Animal                      47
..............................................................................
General information
  Sex              : Female
  Group            : 4 (1000 ppm)
  Sacrifice        : Final sacrifice group
  Necropsy status  : Planned sacrifice
  Date of death    : 19.Feb.2013
                     29 days after start of exposure
                     1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, diffuse, grade 2.
    Hyperplasia bile duct, diffuse, grade 1.
  All other organs examined without microscopic findings.
```

```
BASF                              PATHOLOGY REPORT                  IIC       67/68
                                                                     31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice          27.May.2013 HAMA
Administration via the diet

SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          F
                                                  Group                        4
                                                  Animal                      48
..............................................................................
General information
  Sex              : Female
  Group            : 4 (1000 ppm)
  Sacrifice        : Final sacrifice group
  Necropsy status  : Planned sacrifice
  Date of death    : 19.Feb.2013
                     29 days after start of exposure
                     1 day after end of exposure

Macroscopic findings
  Animal without particular findings.

Microscopic findings
  Liver
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, diffuse, grade 2.
    Hyperplasia bile duct, diffuse, grade 1.
    Oval cell proliferation, grade 1.
  All other organs examined without microscopic findings.

                                                  Animal                      49
..............................................................................
General information
  Sex              : Female
  Group            : 4 (1000 ppm)
  Sacrifice        : Final sacrifice group
  Necropsy status  : Planned sacrifice
  Date of death    : 19.Feb.2013
                     29 days after start of exposure
                     1 day after end of exposure

Macroscopic findings
  Liver
    Focus, left lateral lobe and right medial lobe, few (2-5), diameter 2.0 mm,
    yellow.
  All other organs without macroscopic findings.

Microscopic findings
  Liver
    Gross lesion(s) evaluated histopathologically.
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, diffuse, grade 2.
    Necrosis, (multi)focal, grade 2, correlates to gross lesion Focus.
    Hyperplasia bile duct, diffuse, grade 1.
    Oval cell proliferation, grade 1.
```

```
BASF                              PATHOLOGY REPORT                  IIC       68/68
                                                                     31C0741/11C201
Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice          27.May.2013 HAMA
Administration via the diet

SINGLE ANIMAL SHEET
(GROSS LESIONS AND MICROSCOPIC FINDINGS)
------------------------------------------------------------------------------
                                                  Sacrifice                   F1
                                                  Sex                          F
                                                  Group                        4
                                         cont.    Animal                      49
..............................................................................
    Fatty change, (multi)focal, correlates to gross lesion Focus.
  All other organs examined without microscopic findings.

                                                  Animal                      50
..............................................................................
General information
  Sex              : Female
  Group            : 4 (1000 ppm)
  Sacrifice        : Final sacrifice group
  Necropsy status  : Planned sacrifice
  Date of death    : 19.Feb.2013
                     29 days after start of exposure
                     1 day after end of exposure

Macroscopic findings
  Liver
    Focus, left lateral lobe, diameter 2.0 mm, yellow.
  All other organs without macroscopic findings.

Microscopic findings
  Kidneys
    Tubules, basophilic, (multi)focal, unilateral, grade 1.
  Liver
    Gross lesion(s) evaluated histopathologically.
    Infiltration, lymphoid cell and/or presence of Kupffer cell granuloma(s),
    grade 1.
    Hypertrophy, diffuse, grade 2.
    Necrosis, (multi)focal, grade 1, correlates to gross lesion Focus.
    Hyperplasia bile duct, diffuse, grade 1.
    Oval cell proliferation, grade 1.
  All other organs examined without microscopic findings.
```

STUDY TITLE

Report

BAS 750 F

Repeated-dose 28-day toxicity study in C57BL/6 J Rj mice
Administration via the diet

TEST FACILITY

BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen, Germany

TEST FACILITY PROJECT IDENTIFICATION

Project No. 31C0741/11C201

PART III OF III (SUPPLEMENT)

CONTENTS OF PART III (SUPPLEMENT)

The Chemical Company

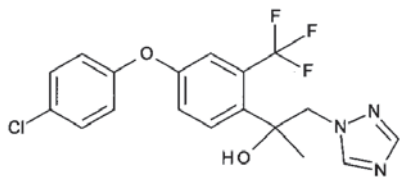
BASF SE
APR/DP - Product Characterization & Performance Management
BASF SE - Crop Protection - Speyerer Strasse 2, D-67117 Limburgerhof, Germany

11/0741-6
added 17.08.12

Certificate of Analysis

Reg.No. :	**5834378**	**Batch No. :**	**COD-001662**
Substance Type :	TGAI (=TC)	**Date of Production :**	August 07, 2012
Date of Initial Analysis :	August 10, 2012	**Study Code :**	429913_4

Purity : 95.5 % (tolerance ± 1.0%)



CL-No.	
CAS No.	
Core Project	FL1226
Internal (Metabolite) Code	
Molecular Formula	$C_{18}H_{15}ClF_3N_3O_2$
Molecular Weight	397.8

IUPAC-Name :	2-[4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl]-1-(1H-1,2,4-triazol-1-yl)propan-2-ol
Determination by :	HPLC
Homogeneity :	given

Additional Information

Storage Advice :	keep at room temperature (typically +25°C) or cooler
Expiration Date :	August 31, 2013
Remarks :	content of water = 0.2%

Recipients should ensure that the label information on the corresponding substance container(s) correspond(s) with that on this Certificate of Analysis

Study Director : Daum, Ansgar

Study Completion Date : August 16, 2012

Issued on : August 17, 2012

Issued by :

This document has been computer generated and is based on the GLP-studies cited above
Released August 16, 2012 by Daum, Ansgar

The Chemical Company

STUDY TITLE

ANALYTICAL REPORT

Reg.No. 5834378

Stability Analysis in

Ground Kliba maintenance diet mouse/ rat „GLP“ meal

AUTHOR(S)

Eric Grauert
Dr. Hennicke Kamp

STUDY COMPLETION DATE

28 August 2013

TEST FACILITY

BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen, Germany

TEST FACILITY PROJECT IDENTIFICATION

Project No.: 01Y0741/11Y094

SPONSOR

BASF SE
67056 Ludwigshafen, Germany

.

The Chemical Company

Report; Project No.: 01Y0741/11Y094

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Report; Project No.: 01Y0741/11Y094

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: 28 Aug 2013

Typed name of Study Director: Eric Grauert

Typed name of Laboratory: BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen
Germany

The Chemical Company

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The Chemical Company

SIGNATURE PAGE

Study Director: 28.08.13 Grauert
Eric Grauert

Management: 23.08.13 H. Kamp
Dr. Hennicke Kamp

The Chemical Company

STATEMENT OF THE QUALITY ASSURANCE UNIT

The Quality Assurance Unit (QAU) performed the inspections given below, and reported any inspection results to the Study Director and to Management. The conduct of this short-term study was not inspected; the processes of the laboratory and of the study involved are inspected in regular intervals.

The final report reflects the raw data.

Phase of study	Date of inspection (mm-dd-yyyy)	Reported to Study Director and to Management (mm-dd-yyyy)
Study Plan:	06-05-2012	06-05-2012
Report:	07-02-2013	07-02-2013

Ludwigshafen, 23 Aug 2013

Werner

Werner

The Chemical Company

GLP CERTIFICATE (FROM THE COMPETENT AUTHORITY)

RheinlandPfalz

Gute Laborpraxis / Good Laboratory Practice

GLP-Bescheinigung / Statement of GLP Compliance

(gem. /according to § 19 Abs. 1 Chemikaliengesetz)

Eine GLP-Inspektion zur Überwachung und 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
(gem. / 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)
19.05.2009 & 06. bis 08.07.2009

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

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

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.
Eine erneute behördliche Überprüfung der Einhaltung der GLP-Grundsätze durch die Prüfeinrichtung ist so rechtzeitig zu beantragen, dass die Folgeinspektion spätestens vier Jahre nach dem Beginn der o.g. Inspektion stattfinden kann. Ohne diesen Antrag wird die Prüfeinrichtung nach Ablauf der Frist aus dem deutschen GLP-Überwachungsprogrann genommen und diese GLP-Bescheinigung verliert ihre Gültigkeit:

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 Priciples of the GLP has to be applied for in time to allow for a follow-up inspection to take place within four years after commencing the above mentioned 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

22.10.2009

Dr. Pia Hirsch - stellv. Präsidentin -
(Name und Funktion der verantwortlichen Person / name and function of responsible person)

Siegel

Landesamt für Umwelt, Wasserwirtschaft und Gewerbeaufsicht
Kaiser-Friedrich-Straße 7
55116 Mainz

(Name und Adresse der GLP-Überwachungsbehörde / Name and adress of the GLP Monitoring Authority)

Landesamt für Umwelt, Wasserwirtschaft und Gewerbeaufsicht

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CONTENTS

The Chemical Company

1. INTRODUCTION

In the context of toxicological studies the stability of the test substance Reg.No. 5834378 in the vehicle ground Kliba maintenance diet mouse/ rat „GLP“ meal has to be verified. The results of these analyses are reported and discussed.

2. RETENTION OF RECORDS

GLP-relevant records and materials are stored at BASF SE for at least the period of time specified in the GLP principles. Details concerning responsibilities or locations of archiving can be seen from the respective SOPs and from the raw data.

3. TIME SCHEDULE

Study initiation date:	05 June 2012
Experimental starting date:	06 June 2012
Experimental completion date:	11 July 2012

4. MATERIAL AND METHODS

4.1. TEST ITEM

The analyses of the test item (= test substance) were carried out at the test facility Crop Protection - Ecology and Environmental Analytics of BASF SE, Speyerer Straße 2, 67117 Limburgerhof, Germany.

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Name of test substance:	Reg.No. 5834378
Test substance No.:	11/0741-3
Batch identification:	L84-176
CAS No.:	unknown
Purity:	97.7 % (tolerance +-1.0%) (according to the project number ASAP12_091)
Homogeneity:	Homogenous (visual)
Storage stability:	Stable until: 01 April 2014 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

Date of production:	16 March 2012
Physical state/ Appearance:	Solid, white
Storage conditions	Room temperature

4.2. SAMPLE DATA

Sponsor:	Dr. Buesen; Mr. Lang
Vehicle:	Ground Kliba maintenance diet mouse/ rat „GLP“ meal
Target concentration:	50 ppm
Duration of the stability test period:	35 days
Storage conditions of the samples during the stability period:	Room temperature

4.3. TEST SUBSTANCE PREPARATION

50 mg of the test substance was mixed with 1 kg ground Kliba maintenance diet mouse/ rat „GLP“ meal. The final nominal concentration was 50 ppm.

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4.4. SAMPLE PREPARATION AND ANALYSIS

The sample preparation and analysis of the test substance was carried out according to the valid control procedure 11/0741_02-01 and 11/0741_02-02.

A detailed description of the control procedure is given in the appendix of this report.

4.5. LIST OF DEVIATIONS

4.5.1. LIST OF DEVIATIONS FROM THE CONTROL PROCEDURE

There were no deviations from the described control procedure 11/0741_02-02.

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5. RESULTS AND DISCUSSION

5.1. ANALYSIS OF STABILITY

The results obtained for the stability of the test substance in ground Kliba maintenance diet mouse/ rat „GLP“ meal are summarized in the following table.

All calculated values in the table are rounded. Calculations were performed with a full set of decimal places.

Nominal concentration [ppm]	Time after starting [days]	Analytical value [ppm]		Nominal concentration [%]		
		Individual samples	Mean		Mean	RSD
50	0	51.6; 46.7; 48.6; 53.1; 50.2	50.0	103.2; 93.4; 97.2; 106.2; 100.4	100.1	5.0
50	7	48.8; 49.1; 48.7	48.9	97.6; 98.2; 97.5	97.8	0.4
50	12	51.1; 49.0; 50.6; 48.3	49.8	102.1, 97.9; 101.2; 96.6	99.5	2.6
50	35	46.0; 50.3, 49.7; 49.9	49.0	91.9; 100.5, 99.4; 99.8	97.9	4.1

5.2. DISCUSSION

Based on the analytical results it is concluded, that Reg.No. 5834378 is stable in ground Kliba maintenance diet mouse/ rat „GLP“ meal over a period of 35 days at ambient temperature. All determined concentrations were in the range between 90 % and 110 % of the nominal concentration.

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FIGURES

Figure 1: Chromatogram of matrix solution (measured on 13 June 2012)

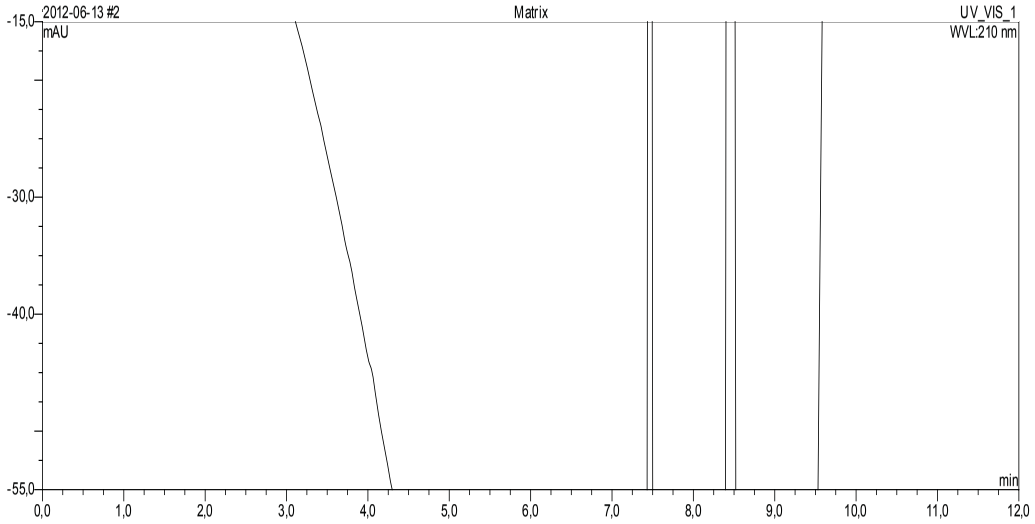
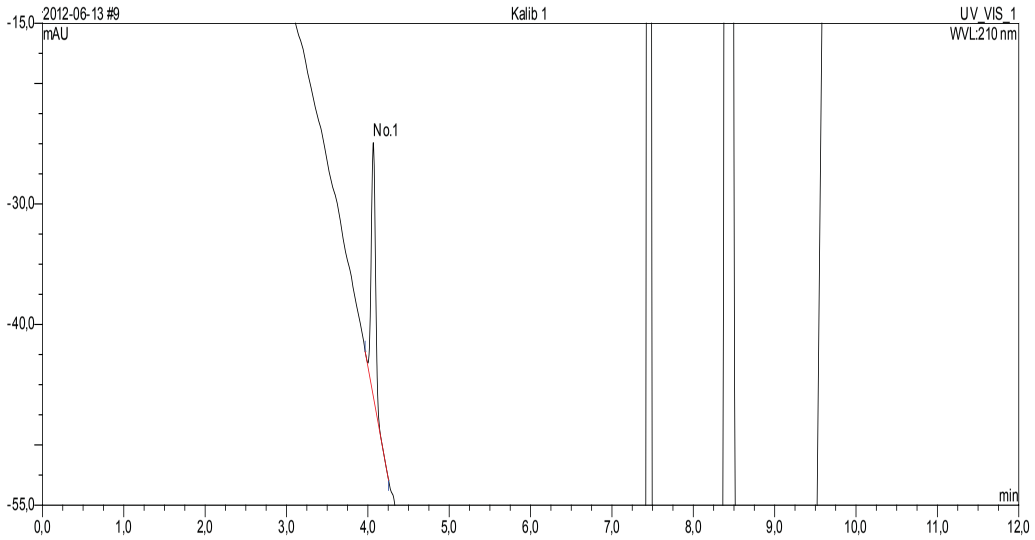


Figure 2: Chromatogram of calibration solution 1 (0.2052 mg/100 mL, measured on 13 June 2012)



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Report; Project No.: 01Y0741/11Y094

Figure 3: Chromatogram sample solution day 35 (measured on 11 July 2012)

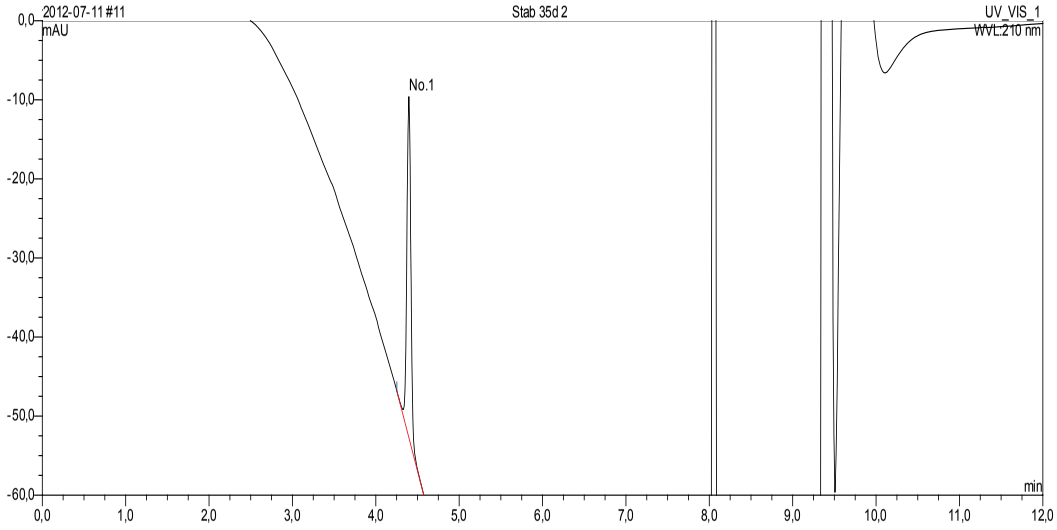
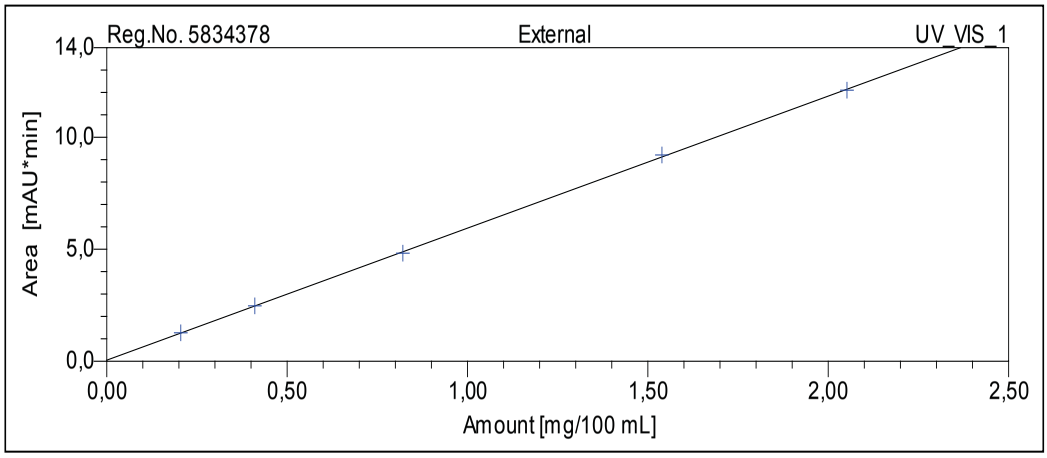


Figure 4: Calibration curve (measured on 13 June 2012, Concentration range 0.2052 – 2.052 mg/100 mL)



6. APPENDIX

6.1. CONTROL PROCEDURE 11/0741_02-02

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Report; Project No.: 01Y0741/11Y094

BASF SE
Test Facility
Experimental Toxicology and Ecology / Analytical Chemistry

The Chemical Company

CONTROL TEST

Test substance number: 11/0741 | No.: 11/0741_02-02

Name of test substance: Reg.No. 5834378 | Effective from: 08 Jun 2012

Control procedure: Content (HPLC) / ground Kliba maintenance diet mouse/rat "GLP" meal |

Technique	HPLC
System:	Agilent 1200 with autosampler, DAD, Dionex Chromeleon – Software (Dionex), or equivalent system
Column:	Length: 150 mm Inner diameter: 4.6 mm
Stationary Phase:	Ascentis Express C18, 2.7µ
Mobile Phase A:	1000 mL acetonitrile are mixed with 1 mL trifluoroacetic acid (TFA)
Mobile Phase B:	1000 mL water are mixed with 1 mL trifluoroacetic acid (TFA)

Gradient:

Time (min)	Mobile Phase A (%)	Mobile Phase B (%)
0	50	50
5	90	10
7	90	10
7.5	50	50
12	50	50

Injection volume:	10 µL
Flow rate:	1.0 mL/min
Detection:	210 nm
Column temperature:	Ambient
Run time:	Approx. 12 min

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Report; Project No.: 01Y0741/11Y094

Extraction solution: 1000 mL acetonitrile are mixed with 10 mL formic acid (HCOOH)

Sample solution: Concentration range (50 – 249 ppm)
10 g of the sample are weighed into a 50 mL polypropylene centrifuge tube with a screw cap. The sample is extracted 3 times with 30 mL extraction solution for 30 minutes using a lab shaker. After centrifugation at 4500 rpm for 5 min the supernatants are collected in a 100 mL volumetric flask. The combined extracts are diluted with extraction solution to 100 mL.

The samples are filtered (cellulose filter, 0.2 µm) prior HPLC analysis.

Annotation: If the amount of test substance in the sample solution is outside the calibration range (calibration solutions 1 – 5), an adequate dilution step with matrix solution has to be performed to match the described concentration range.

Matrix solution: The preparation of the matrix solution has to be performed according to the procedure described for sample solution preparation

Stock solution: Approx. 50 mg test substance are dissolved to a final volume of 100 mL with acetonitrile (50 mg/100 mL).

Calibration solution 1: 0.02 mL stock solution are diluted with matrix solution to 5 mL (0.2 mg/100 mL)

Calibration solution 2: 0.04 mL stock solution are diluted with matrix solution to 5 mL (0.4 mg/100 mL)

Calibration solution 3: 0.08 mL stock solution are diluted with matrix solution to 5 mL (0.8 mg/100 mL)

Calibration solution 4: 0.15 mL stock solution are diluted with matrix solution to 5 mL (1.5 mg/100 mL)

Calibration solution 5: 0.2 mL stock solution are diluted with matrix solution to 5 mL (2.0 mg/100 mL)

System-suitability solution:
System-suitability solution is prepared with a second independent weighing according to calibration solution 3 (0.8 mg/100 mL)

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Report; Project No.: 01Y0741/11Y094

Procedure	After conditioning the HPLC system, sample solutions, matrix solution, calibration solutions and system-suitability solution are injected according to the sequence described in the raw data. All solutions are injected at least once.

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Report; Project No.: 01Y0741/11Y094

Retention time:

Test substance : Reg.No. 5834378:
Approx. 4 min

System suitability: The calculated content of the system-suitability solution has to be in the range from 95 % to 105 %.

The coefficient of determination (R^2) has to be ≥ 0.990. If the correlation coefficient (R) is used, this value has to be ≥ 0.995.

Calculation:

The concentration control measurements are based on external calibration (calibration solutions 1 – 5).

The calculation of the content is performed electronically. (e.g. Dionex Chromeleon – Software, Microsoft Excel). Basic formulas for calculations are described below (e.g. Dionex Chromeleon – Software)

Formulas:

Calibration curve

$Y = a \cdot x + b$

a = slope of calibration curve
b = intercept

Analysed concentration (C_A)

$$C_A = \frac{(Y - b)}{a} \bullet \frac{V \bullet d}{w} \bullet Rf$$

w = weight sample
V = final sample volume
d = dilution factor
Rf = recovery factor (see recovery factor table below)

Recovery factor

Concentration [ppm]	Recovery [%]	Mean [%] (RSD [%])	Recovery-factor
50.0	87.5, 79.2, 82.4, 90.0, 85.1	84.8 (5.0)	1.18

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CONTROL TEST

Test substance number: 11/0741	No.: 11/0741_02-02
Name of test substance: Reg.No. 5834378	Effective from: 08 Jun 2012
Control procedure: Content (HPLC) / ground Kliba maintenance diet mouse/rat "GLP" meal	Page 5 of 6

Figure 1.1: Example chromatogram matrix solution (04 Jun 2012, Project no.: 01Y0741/11Y094) for illustration

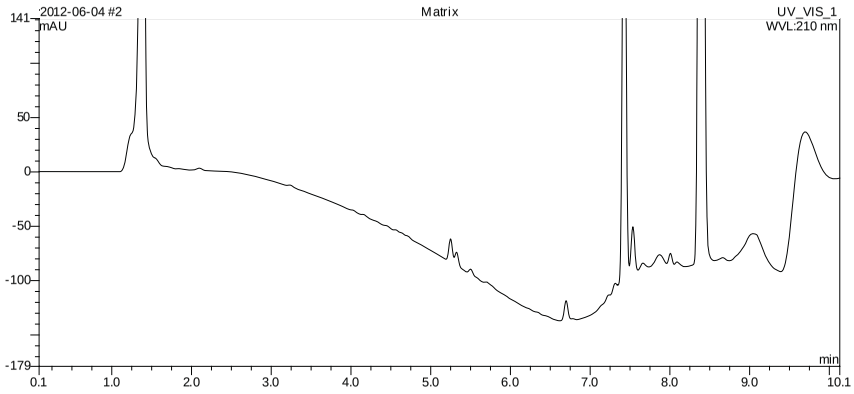
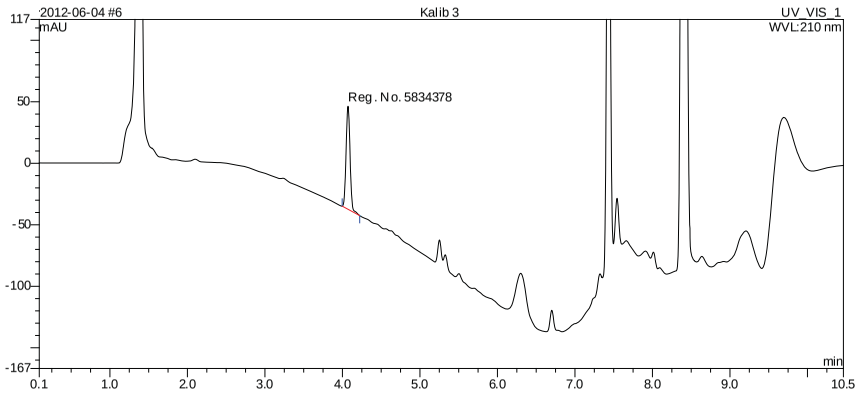


Figure 1.2: Example chromatogram calibration solution (04 Jun 2012, Project no.: 01Y0741/11Y094) for illustration



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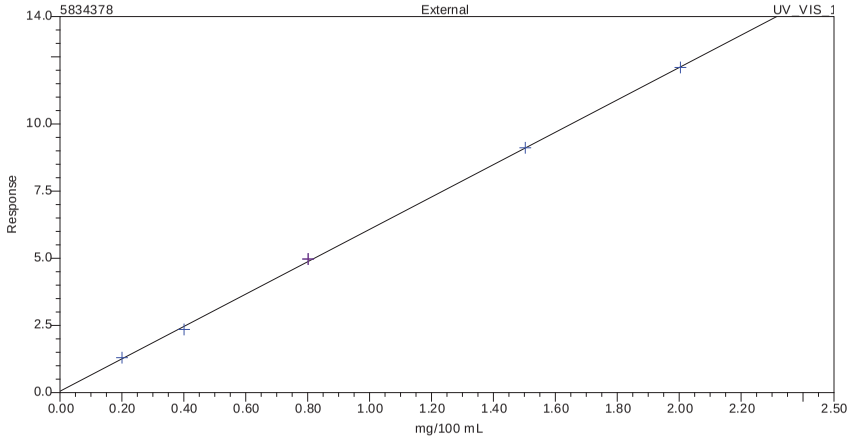
CONTROL TEST

Test substance number: 11/0741	No.: 11/0741_02-02
Name of test substance: Reg.No. 5834378	Effective from: 08 Jun 2012
Control procedure: Content (HPLC) / ground Kliba maintenance diet mouse/rat "GLP" meal	Page 6 of 6

Figure 1.3 Example calibration curve (04 Jun 2012, Project no.: 01Y0741/11Y094) for illustration



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STUDY TITLE

ANALYTICAL REPORT

Reg.No. 5834378

Stability Analysis in

Ground Kliba maintenance diet mouse/ rat „GLP“ meal

AUTHOR(S)

Dr. Matthias Becker
Dr. Hennicke Kamp

STUDY COMPLETION DATE

30 August 2013

TEST FACILITY

BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen, Germany

TEST FACILITY PROJECT IDENTIFICATION

Project No.: 01Y0741/11Y115

SPONSOR

BASF SE
67056 Ludwigshafen, Germany

.

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Report; Project No.: 01Y0741/11Y115

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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: 30 Aug. 2013

Typed name of Study Director: Dr. Matthias Becker

Typed name of Laboratory: BASF SE
Experimental Toxicology and Ecology
67056 Ludwigshafen
Germany

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SIGNATURE PAGE

Study Director: ..... 30 Aug. 2013
Dr. Matthias Becker

Management: ..... 27. Aug 2013
Dr. Hennicke Kamp

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STATEMENT OF THE QUALITY ASSURANCE UNIT

The Quality Assurance Unit (QAU) performed the inspections given below, and reported any inspection results to the Study Director and to Management. The conduct of this short-term study was not inspected; the processes of the laboratory and of the study involved are inspected in regular intervals.

The final report reflects the raw data.

Phase of study	Date of inspection (mm-dd-yyyy)	Reported to Study Director and to Management (mm-dd-yyyy)
Study Plan:	01-17-2013	01-17-2013
Report:	07-03-2013	07-03-2013

Ludwigshafen, 28 Aug 2013 N. Keller

N. Keller

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GLP CERTIFICATE (FROM THE COMPETENT AUTHORITY)

RheinlandPfalz

Gute Laborpraxis / Good Laboratory Practice

GLP-Bescheinigung / Statement of GLP Compliance

(gem. /according to § 19 Abs. 1 Chemikaliengesetz)

Eine GLP-Inspektion zur Überwachung und 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
(gem. / 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)
19.05.2009 & 06. bis 08.07.2009

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

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

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.
Eine erneute behördliche Überprüfung der Einhaltung der GLP-Grundsätze durch die Prüfeinrichtung ist so rechtzeitig zu beantragen, dass die Folgeinspektion spätestens vier Jahre nach dem Beginn der o.g. Inspektion stattfinden kann. Ohne diesen Antrag wird die Prüfeinrichtung nach Ablauf der Frist aus dem deutschen GLP-Überwachungsprogrann genommen und diese GLP-Bescheinigung verliert ihre Gültigkeit:

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 Priciples of the GLP has to be applied for in time to allow for a follow-up inspection to take place within four years after commencing the above mentioned 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

22.10.2009

Dr. Pia Hirsch - stellv. Präsidentin -
(Name und Funktion der verantwortlichen Person / name and function of responsible person)

Siegel

Landesamt für Umwelt, Wasserwirtschaft und Gewerbeaufsicht
Kaiser-Friedrich-Straße 7
55116 Mainz

(Name und Adresse der GLP-Überwachungsbehörde / Name and adress of the GLP Monitoring Authority)

Landesamt für Umwelt, Wasserwirtschaft und Gewerbeaufsicht

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Report; Project No.: 01Y0741/11Y115

CONTENTS

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Report; Project No.: 01Y0741/11Y115

1. INTRODUCTION

In the context of toxicological studies the stability of the test substance Reg.No. 5834378 in the vehicle ground Kliba maintenance diet mouse/ rat „GLP“ meal has to be verified. The results of these analyses are reported and discussed.

2. RETENTION OF RECORDS

GLP-relevant records and materials are stored at BASF SE for at least the period of time specified in the GLP principles. Details concerning responsibilities or locations of archiving can be seen from the respective SOPs and from the raw data.

3. TIME SCHEDULE

Study initiation date:	15 January 2013
Experimental starting date:	18 January 2013
Experimental completion date:	19 February 2013

4. MATERIAL AND METHODS

4.1. TEST ITEM

The analyses of the test item (= test substance) were carried out at the test facility Crop Protection - Ecology and Environmental Analytics of BASF SE, Speyerer Straße 2, 67117 Limburgerhof, Germany.

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Report; Project No.: 01Y0741/11Y115

Name of test substance:	Reg.No. 5834378
Test substance No.:	11/0741-6
Batch identification:	COD-001662
CAS No.:	Unknown
Purity:	95.5 % (tolerance +- 1.0%) (according to the project number 429913_4)
Homogeneity:	Homogeneous
Storage stability:	stable until: 31 August 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

Date of production:	07 August 2012
Physical state/ Appearance:	Solid/ beige
Storage conditions	Room temperature

4.2. SAMPLE DATA

Sponsor:	Dr. Stark; Ms. Neber
Vehicle:	Ground Kliba maintenance diet mouse/ rat „GLP“ meal
Target concentration:	30 ppm
Duration of the stability test period:	32 days
Storage conditions of the samples during the stability period:	Room temperature

4.3. TEST SUBSTANCE PREPARATION

30 mg of the test substance was mixed with 1 kg ground Kliba maintenance diet mouse/ rat „GLP“ meal. The final nominal concentration was 30 ppm.

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4.4. SAMPLE PREPARATION AND ANALYSIS

The sample preparation and analysis of the test substance was carried out according to the valid control procedures 11/0741_02-05 and 11/0741_02-06.

A detailed description of the recent control procedure is given in the appendix of this report.

4.5. LIST OF DEVIATIONS

4.5.1. LIST OF DEVIATIONS FROM THE CONTROL PROCEDURE

There were no deviations from the described control procedure 11/0741_02-06.

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Report; Project No.: 01Y0741/11Y115

5. RESULTS AND DISCUSSION

5.1. ANALYSIS OF STABILITY

The results obtained for the stability of the test substance in ground Kliba maintenance diet mouse/ rat „GLP“ meal are summarized in the following table.

All calculated values in the table are rounded. Calculations were performed with a full set of decimal places.

Nominal concentration [ppm]	Time after starting [days]	Analytical value [ppm]		Nominal concentration [%]		
		Individual samples	Mean		Mean	RSD
30	0	29.6; 30.1; 30.9; 30.1	30.2	98.5; 100.3; 103.1; 100.3	100.6	1.9
30	4	27.0; 27.2; 24.9; 26.3; 25.7	26.2	90.0; 90.6; 83.1; 87.6; 85.6	87.4	3.6
30	10	28.2; 28.3; 28.9; 28.2; 28.6	28.4	94.1; 94.2; 96.4; 93.9; 95.5	94.8	1.2
30	32	27.5; 27.6; 27.9; 28.1; 27.7	27.8	91.6; 92.0; 92.9; 93.6; 92.2	92.5	0.9

5.2. DISCUSSION

Based on the analytical results it is concluded that Reg.No. 5834378 is stable in ground Kliba maintenance diet mouse/ rat „GLP“ meal over a period of 32 days at room temperature.

The mean values of Reg.No. 5834378 in ground Kliba maintenance diet mouse/ rat „GLP“ meal, with the exception of stability day 4, were found to be in the range of 90 – 110 % of the nominal concentration.

The determined mean concentration of stability day 4 can be neglected, because all other mean concentrations were in accordance with the requirements (90 – 110 % of the nominal concentration).

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FIGURES

Figure 1: Chromatogram of matrix solution (measured on 19 Feb 2013)

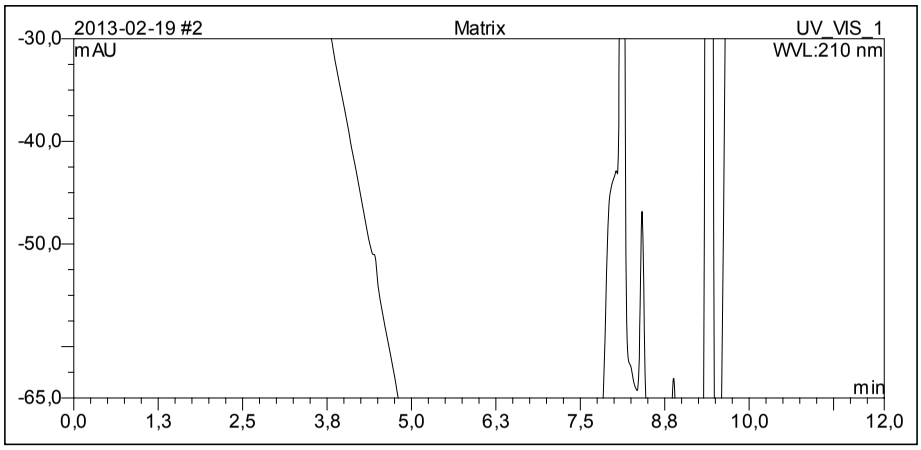

Figure 2: Chromatogram of calibration solution 1 (0.204 mg/100 mL, measured on 19 Feb 2013)

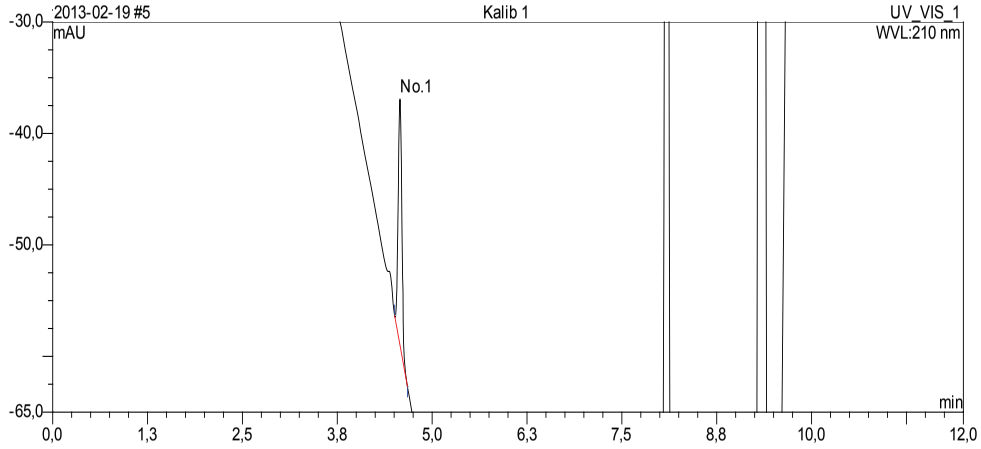

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Figure 3: Chromatogram sample solution day 32 (measured on 19 Feb 2013)

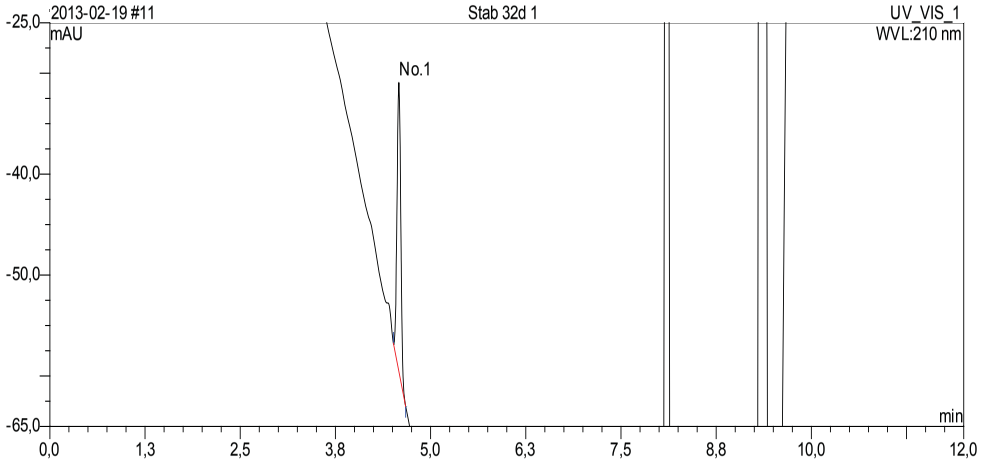
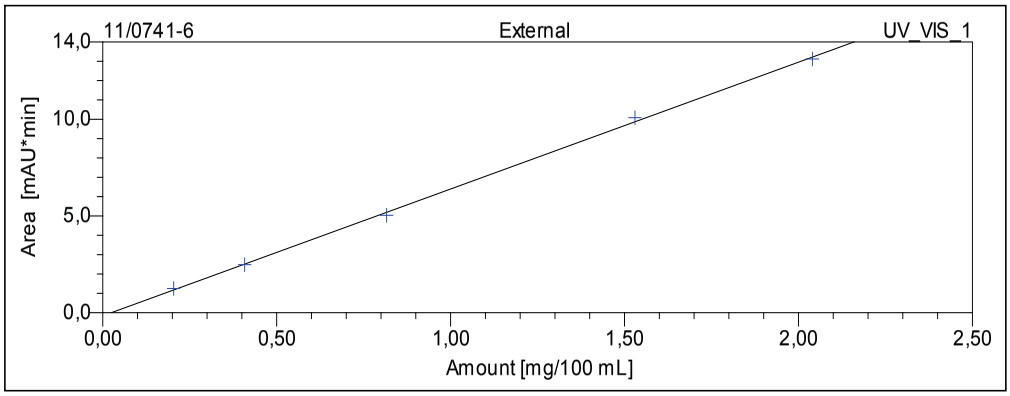


Figure 4: Calibration curve (measured on 19 Feb 2013, Concentration range 0.204 – 2.040 mg/100 mL)



6. APPENDIX

6.1. CONTROL PROCEDURE 11/0741_02-06

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Report; Project No.: 01Y0741/11Y115

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Experimental Toxicology and Ecology / Analytical Chemistry

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CONTROL TEST

Test substance number: 11/0741	No.: 11/0741_02-06
Name of test substance: Reg.No. 5834378	Effective from: 22 Jan 2013
Control procedure: Content (HPLC) / ground Kliba maintenance diet mouse/rat "GLP" meal	Page 1 of 7

Technique	HPLC
System:	Agilent 1200 with autosampler, DAD, Dionex Chromeleon – Software (Dionex), or equivalent system
Column:	Length: 150 mm Inner diameter: 4.6 mm
Stationary Phase:	Ascentis Express C18, 2.7µ
Mobile Phase A:	1000 mL acetonitrile are mixed with 1 mL trifluoroacetic acid (TFA)
Mobile Phase B:	1000 mL water are mixed with 1 mL trifluoroacetic acid (TFA)

Gradient:

Time (min)	Mobile Phase A (%)	Mobile Phase B (%)
0	50	50
5	90	10
7	90	10
7.5	50	50
12	50	50

Injection volume:	10 µL
Flow rate:	1.0 mL/min
Detection:	210 nm
Column temperature:	Ambient
Run time:	Approx. 12 min

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Report; Project No.: 01Y0741/11Y115

Extraction solution: 1000 mL acetonitrile are mixed with 10 mL formic acid (HCOOH)

Sample solution: Concentration range (30 – 6249 ppm)
10 g of the sample are weighed into a 50 mL polypropylene centrifuge tube with a screw cap. The sample is extracted 3 times with 30 mL extraction solution for 30 minutes using a lab shaker. After centrifugation at 4500 rpm for 5 min the supernatants are collected in a 100 mL volumetric flask. The combined extracts are diluted with extraction solution to 100 mL.

The samples are filtered (cellulose filter, 0.2 µm) prior HPLC analysis.

Annotation: If the amount of test substance in the sample solution is outside the calibration range (calibration solutions 1 – 5), an adequate dilution step with matrix solution has to be performed to match the described concentration range.

Matrix solution: The preparation of the matrix solution has to be performed according to the procedure described for sample solution preparation

Stock solution: Approx. 50 mg test substance are dissolved to a final volume of 100 mL with acetonitrile (50 mg/100 mL).

Calibration solution 1: 0.02 mL stock solution are diluted with matrix solution to 5 mL (0.2 mg/100 mL)

Calibration solution 2: 0.04 mL stock solution are diluted with matrix solution to 5 mL (0.4 mg/100 mL)

Calibration solution 3: 0.08 mL stock solution are diluted with matrix solution to 5 mL (0.8 mg/100 mL)

Calibration solution 4: 0.15 mL stock solution are diluted with matrix solution to 5 mL (1.5 mg/100 mL)

Calibration solution 5: 0.2 mL stock solution are diluted with matrix solution to 5 mL (2.0 mg/100 mL)

System-suitability solution:
System-suitability solution is prepared with a second independent weighing according to calibration solution 3 (0.8 mg/100 mL)

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Report; Project No.: 01Y0741/11Y115

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CONTROL TEST

Test substance number: 11/0741	No.: 11/0741_02-06
Name of test substance: Reg.No. 5834378	Effective from: 22 Jan 2013
Control procedure: Content (HPLC) / ground Kliba maintenance diet mouse/rat "GLP" meal	Page 3 of 7

Procedure	After conditioning the HPLC system, sample solutions, matrix solution, calibration solutions and system-suitability solution are injected according to the sequence described in the raw data. All solutions are injected at least once.

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Report; Project No.: 01Y0741/11Y115

Retention time:

Test substance : Reg.No. 5834378:
Approx. 4 min

System suitability: The calculated content of the system-suitability solution has to be in the range from 95 % to 105 %.

The coefficient of determination (R^2) has to be ≥ 0.990. If the correlation coefficient (R) is used, this value has to be ≥ 0.995.

Calculation:

The concentration control measurements are based on external calibration (calibration solutions 1 – 5).

The calculation of the content is performed electronically. (e.g. Dionex Chromeleon – Software, Microsoft Excel). Basic formulas for calculations are described below (e.g. Dionex Chromeleon – Software)

Formulas:

Calibration curve

$Y = a \cdot x + b$

a = slope of calibration curve
b = intercept

Analysed concentration (C_A)

$$C_A = \frac{(Y - b)}{a} \bullet \frac{V \bullet d}{w} \bullet Rf$$

w = weight sample
V = final sample volume
d = dilution factor
Rf = recovery factor (see recovery factor table below)

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CONTROL TEST

Test substance number: 11/0741 — No.: 11/0741_02-06

Name of test substance: Reg.No. 5834378 — Effective from: 22 Jan 2013

Control procedure: Content (HPLC) / ground Kliba maintenance diet mouse/rat "GLP" meal — Page 5 of 7

Recovery factor:

Concentration [ppm]	Recovery [%]	Mean [%] (RSD [%])	Recovery-factor
30 - 49	98.5; 100.3; 103.1: 100.3	100.6 (1.9)	1.00
50 - 249	95.8; 102.5; 100.5; 99.9; 103.1	100.3 (2.9)	1.00
249 - 1249	105.9; 101.0; 95.9; 100.8	100.9 (4.0)	1.00
1250 - 6249	101.3; 90.2; 98.4; 98.4	97.1 (4.9)	1.03

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Report; Project No.: 01Y0741/11Y115

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CONTROL TEST

Test substance number: 11/0741	No.: 11/0741_02-06
Name of test substance: Reg.No. 5834378	Effective from: 22 Jan 2013
Control procedure: Content (HPLC) / ground Kliba maintenance diet mouse/rat "GLP" meal	Page 6 of 7

Figure 1.1: Example chromatogram matrix solution (21 Sep 2012, Project no.: 30C0741/11S172) for illustration

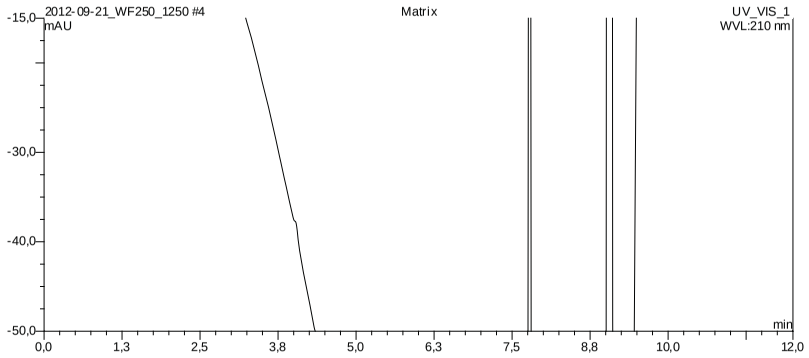
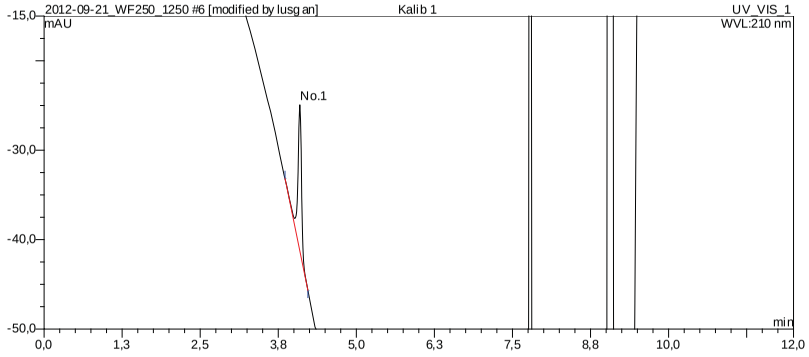


Figure 1.2: Example chromatogram calibration solution (21 Sep 2012, Project no.: 30C0741/11S172) for illustration



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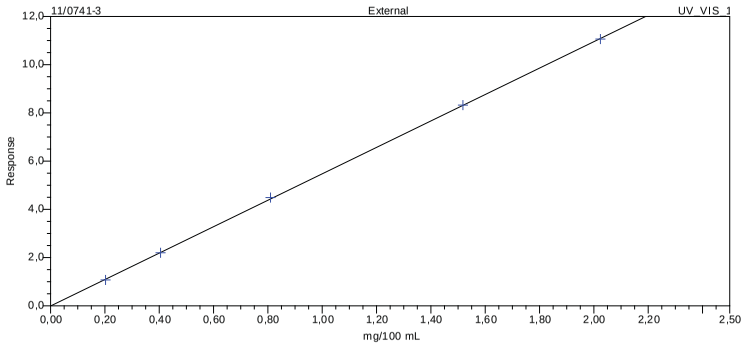
Report; Project No.: 01Y0741/11Y115

Figure 1.3 Example calibration curve (21 Sep 2012, Project no.: 30C0741/11S172) for illustration



Homogeneity and Concentration Control Analysis of Reg. No. 5834378 in Ground Kliba maintenance diet mouse/rat „GLP“ meal

1. PROJECT AND TEST SUBSTANCE INFORMATION

Project No.:	31C0741/11C201
Test item (= test substance):	Reg. No. 5834378
Batch No.:	COD-001662

2. SAMPLE DATA

2.1. HOMOGENEITY AND CONCENTRATION CONTROL ANALYSIS

Vehicle:	ground Kliba maintenance diet mouse/rat „GLP“ meal
Storage conditions of the samples until analysis:	freezer

3. MATERIAL AND METHODS

3.1. SAMPLE PREPARATION AND ANALYSIS

The sample preparation and analysis of the test substance was carried out according to the valid control procedure 11/0741_02-06.

A detailed description of the control procedure is given in the appendix of this report.

3.2. LIST OF DEVIATIONS

3.2.1. List of deviations from the control procedure

There was one deviation from the described control procedure 11/0741_02-06.

4. RESULTS AND DISCUSSION

4.1. HOMOGENEITY AND CONCENTRATION CONTROL ANALYSIS

The results obtained for the homogeneity and concentration control analysis of Reg. No. 5834378 in ground Kliba maintenance diet mouse/rat „GLP“ meal are summarized in the following tables:

All calculated values in the table are rounded. Calculations were performed with a full set of decimal places.

Date of sample preparation:	**18 Jan 2013**
Date of sampling:	**18 Jan 2013**
Date of receipt of sample in analytical laboratory:	**18 Jan 2013**
Starting date of analytical determination:	**24 Jan 2013**

Name	Amount	Nominal Conc	Nominal Conc	Mean	RSD
	ppm	ppm	%	%	%
Probe 3	27.188	30	90.6%		
Probe 4	29.081	30	96.9%		
Probe 5	27.707	30	92.4%	93.3%	3.5%
Probe 6	97.188	100	97.2%		
Probe 7	293.502	300	97.8%		
Probe 10	982.241	1000	98.2%		
Probe 8	987.211	1000	98.7%		
Probe 9	970.202	1000	97.0%	98.0%	0.9%

Date of sample preparation: **24 Jan 2013**
Date of sampling: **24 Jan 2013**
Date of receipt of sample in analytical laboratory: **24 Jan 2013**
Starting date of analytical determination: **04 Feb 2013**

Name	Amount	Nominal Conc	Nominal Conc	Mean	RSD
	ppm	ppm	%	%	%
sample 13	29.829	30	99.4%		
sample 14	29.561	30	98.5%		
sample 15	29.267	30	97.6%	98.5%	1.0%
sample 16	91.246	100	91.2%		
sample 17	284.077	300	94.7%		
sample 18	969.896	1000	97.0%		
sample 19	992.972	1000	99.3%		
sample 20	987.378	1000	98.7%	98.3%	1.2%

Considering the low relative standard deviation in the homogeneity analysis, it can be concluded that Reg. No. 5834378 was distributed homogeneously in Ground Kliba maintenance diet mouse/rat „GLP“ meal.

The values of Reg. No. 5834378 in Ground Kliba maintenance diet mouse/rat „GLP“ meal were found to be in the range of 90 % – 110 % of the nominal concentrations.

These results demonstrated the correctness of the concentrations of Reg. No. 5834378 in Ground Kliba maintenance diet mouse/rat „GLP“ meal.

Figures of the calibration curve and examples of chromatograms will follow within this report.

Figure 1: Chromatogram of matrix solution (measured on 24 Jan 2013)

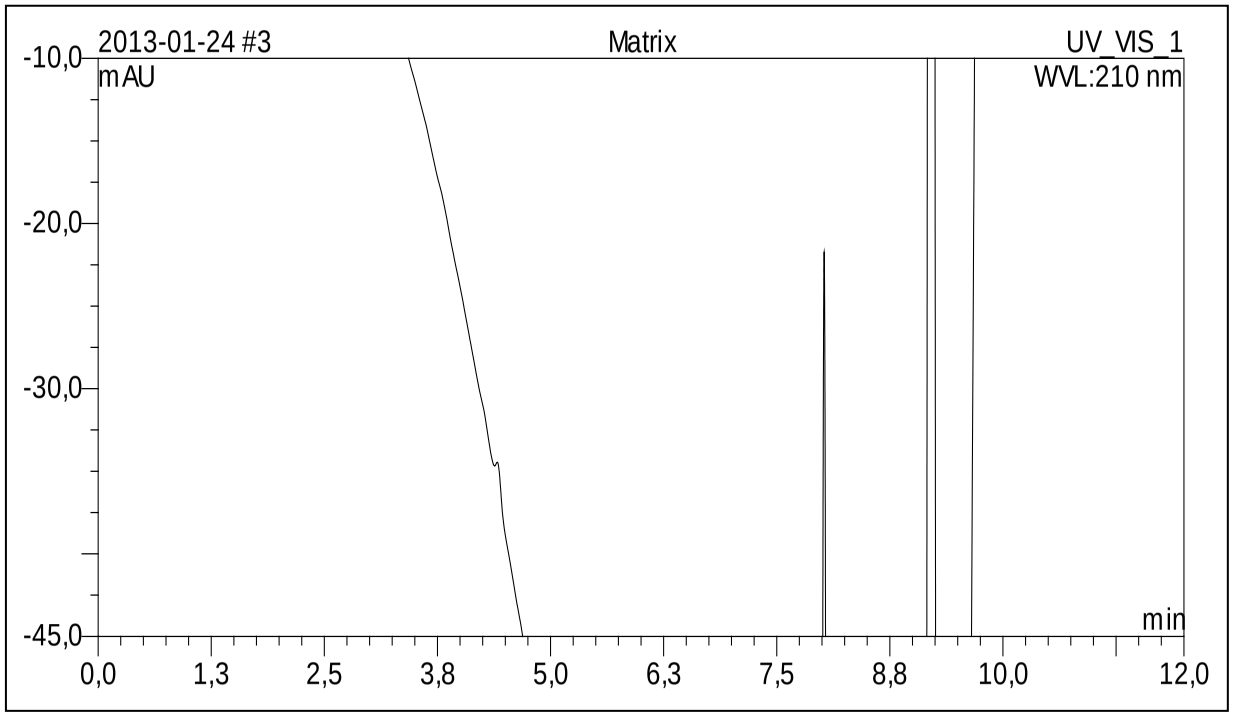


Figure 2: Chromatogram of calibration solution 1 (0.2116 mg/100 mL, measured on 24 Jan 2013)

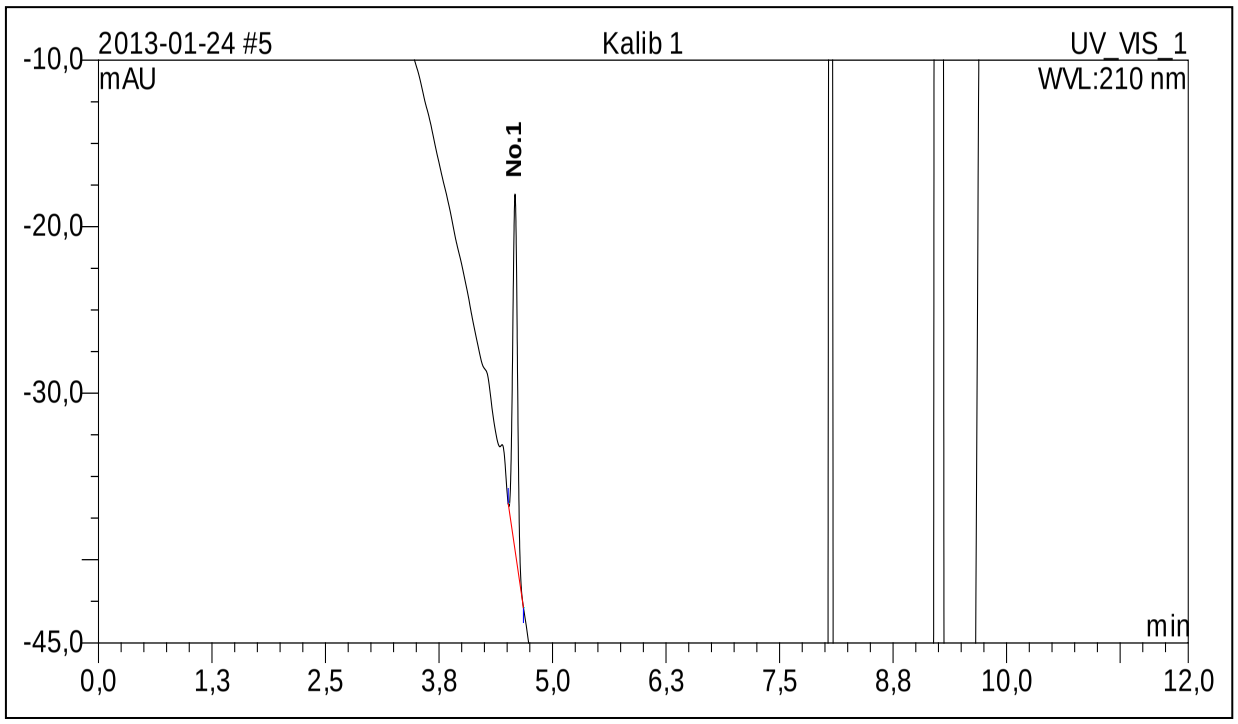


Figure 3: Chromatogram of sample 7 (measured on 24 Jan 2013)

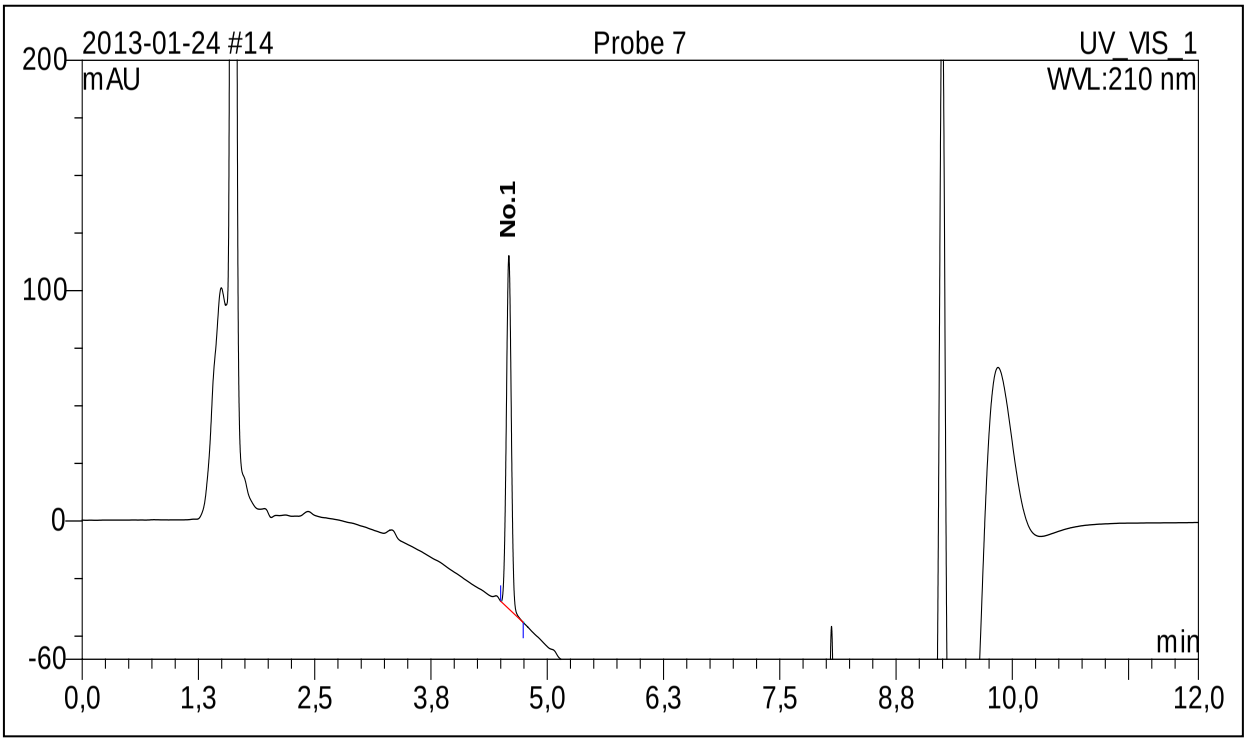
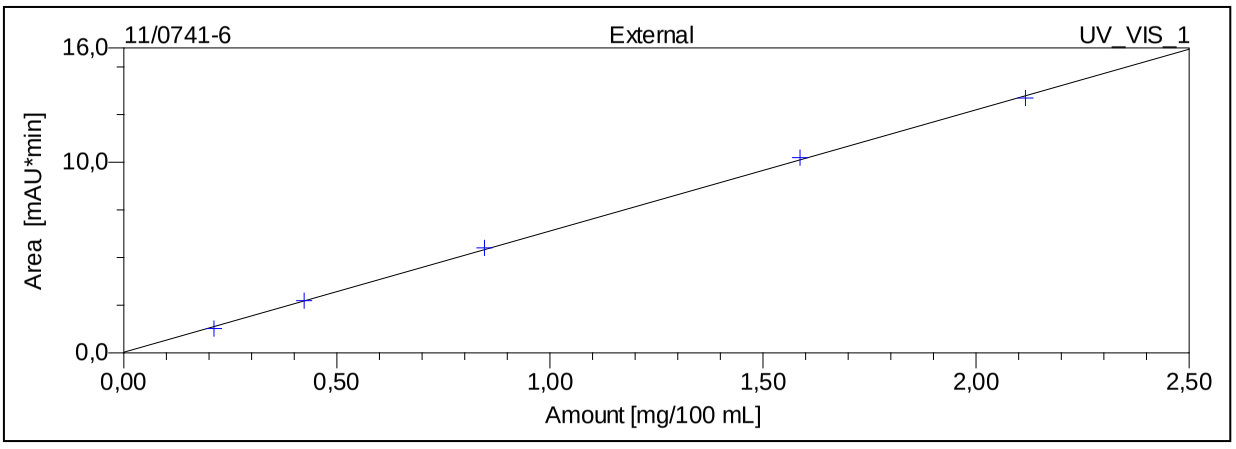


Figure 4: Calibration curve (measured on 24 Jan 2013, Concentration range 0.2116 – 2.116 mg/100 mL)



5. APPENDIX

5.1. CONTROL PROCEDURE 11/0741_02-06

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CONTROL TEST

Test substance number: 11/0741	No.: 11/0741_02-06
Name of test substance: Reg.No. 5834378	Effective from: 22 Jan 2013
Control procedure: Content (HPLC) / ground Kliba maintenance diet mouse/rat "GLP" meal	Page 1 of 7

Technique	HPLC
System:	Agilent 1200 with autosampler, DAD, Dionex Chromeleon – Software (Dionex), or equivalent system
Column:	Length: 150 mm Inner diameter: 4.6 mm
Stationary Phase:	Ascentis Express C18, 2.7µ
Mobile Phase A:	1000 mL acetonitrile are mixed with 1 mL trifluoroacetic acid (TFA)
Mobile Phase B:	1000 mL water are mixed with 1 mL trifluoroacetic acid (TFA)

Gradient:

Time (min)	Mobile Phase A (%)	Mobile Phase B (%)
0	50	50
5	90	10
7	90	10
7.5	50	50
12	50	50

Injection volume:	10 µL
Flow rate:	1.0 mL/min
Detection:	210 nm
Column temperature:	Ambient
Run time:	Approx. 12 min

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Extraction solution: 1000 mL acetonitrile are mixed with 10 mL formic acid (HCOOH)

Sample solution: Concentration range (30 – 6249 ppm)
10 g of the sample are weighed into a 50 mL polypropylene centrifuge tube with a screw cap. The sample is extracted 3 times with 30 mL extraction solution for 30 minutes using a lab shaker. After centrifugation at 4500 rpm for 5 min the supernatants are collected in a 100 mL volumetric flask. The combined extracts are diluted with extraction solution to 100 mL.

The samples are filtered (cellulose filter, 0.2 µm) prior HPLC analysis.

Annotation: If the amount of test substance in the sample solution is outside the calibration range (calibration solutions 1 – 5), an adequate dilution step with matrix solution has to be performed to match the described concentration range.

Matrix solution: The preparation of the matrix solution has to be performed according to the procedure described for sample solution preparation

Stock solution: Approx. 50 mg test substance are dissolved to a final volume of 100 mL with acetonitrile (50 mg/100 mL).

Calibration solution 1: 0.02 mL stock solution are diluted with matrix solution to 5 mL (0.2 mg/100 mL)

Calibration solution 2: 0.04 mL stock solution are diluted with matrix solution to 5 mL (0.4 mg/100 mL)

Calibration solution 3: 0.08 mL stock solution are diluted with matrix solution to 5 mL (0.8 mg/100 mL)

Calibration solution 4: 0.15 mL stock solution are diluted with matrix solution to 5 mL (1.5 mg/100 mL)

Calibration solution 5: 0.2 mL stock solution are diluted with matrix solution to 5 mL (2.0 mg/100 mL)

System-suitability solution:
System-suitability solution is prepared with a second independent weighing according to calibration solution 3 (0.8 mg/100 mL)

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Procedure	After conditioning the HPLC system, sample solutions, matrix solution, calibration solutions and system-suitability solution are injected according to the sequence described in the raw data. All solutions are injected at least once.

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Retention time:

Test substance : Reg.No. 5834378:
Approx. 4 min

System suitability: The calculated content of the system-suitability solution has to be in the range from 95 % to 105 %.

The coefficient of determination (R^2) has to be ≥ 0.990. If the correlation coefficient (R) is used, this value has to be ≥ 0.995.

Calculation:

The concentration control measurements are based on external calibration (calibration solutions 1 – 5).

The calculation of the content is performed electronically. (e.g. Dionex Chromeleon – Software, Microsoft Excel). Basic formulas for calculations are described below (e.g. Dionex Chromeleon – Software)

Formulas:

Calibration curve

$Y = a \cdot x + b$

a = slope of calibration curve
b = intercept

Analysed concentration (C_A)

$$C_A = \frac{(Y - b)}{a} \bullet \frac{V \bullet d}{w} \bullet Rf$$

w = weight sample
V = final sample volume
d = dilution factor
Rf = recovery factor (see recovery factor table below)

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Control procedure: Content (HPLC) / ground Kliba maintenance diet mouse/rat "GLP" meal Page 5 of 7

Recovery factor:

Concentration [ppm]	Recovery [%]	Mean [%] (RSD [%])	Recovery-factor
30 - 49	98.5; 100.3; 103.1: 100.3	100.6 (1.9)	1.00
50 - 249	95.8; 102.5; 100.5; 99.9; 103.1	100.3 (2.9)	1.00
249 - 1249	105.9; 101.0; 95.9; 100.8	100.9 (4.0)	1.00
1250 - 6249	101.3; 90.2; 98.4; 98.4	97.1 (4.9)	1.03

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Name of test substance: Reg.No. 5834378	Effective from: 22 Jan 2013
Control procedure: Content (HPLC) / ground Kliba maintenance diet mouse/rat "GLP" meal	Page 6 of 7

Figure 1.1: Example chromatogram matrix solution (21 Sep 2012, Project no.: 30C0741/11S174) for illustration

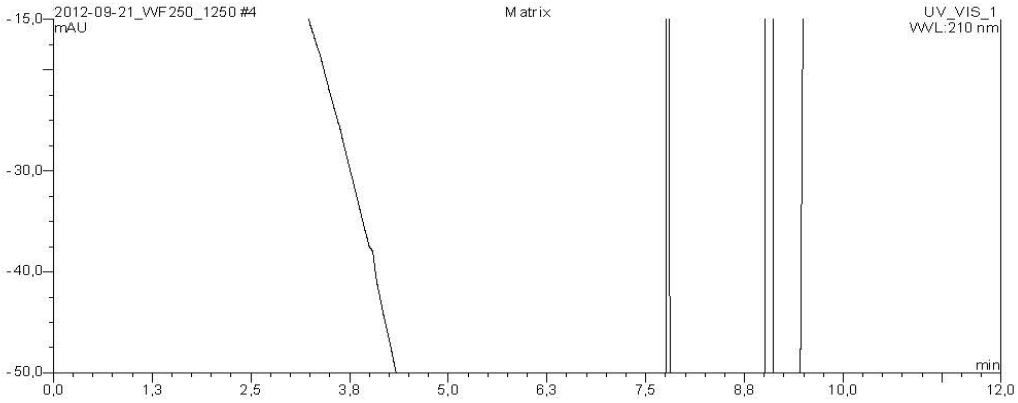
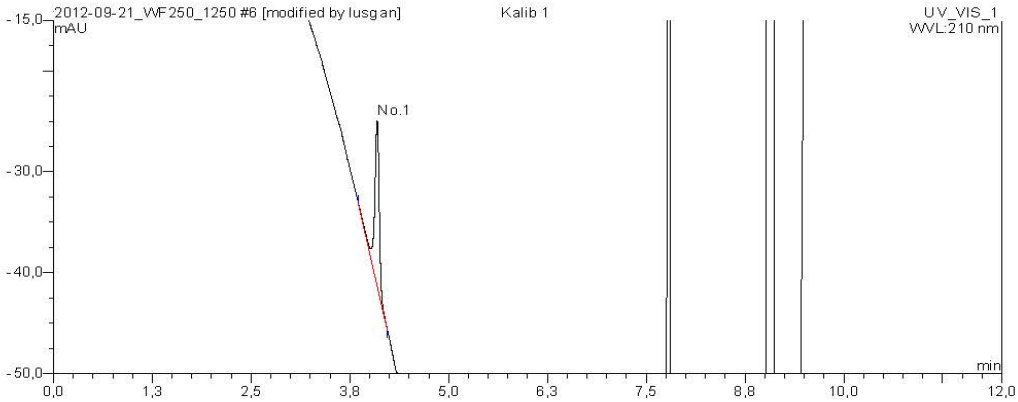


Figure 1.2: Example chromatogram calibration solution (21 Sep 2012, Project no.: 30C0741/11S174) for illustration



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CONTROL TEST

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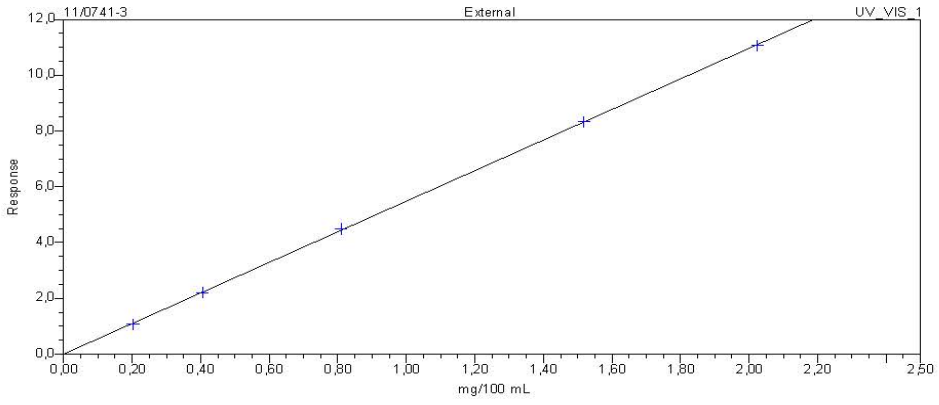
Figure 1.3 Example calibration curve (21 Sep 2012, Project no.: 30C0741/11S174) for illustration



HISTORICAL CONTROL DATA OF CLINICAL PATHOLOGY TESTING [1)]

Species:	Mouse
Sex:	Male
Strain:	C57BL/6 J Rj
Age:	10 weeks
Study period:	4 weeks
Fasting before blood sampling:	16 hours
Anaesthesia	Isoflurane
Data print out at	10-Jul-13
Clinical Chemistry Instrument:	Hitachi 917, Roche
Haematology Analyzer	ADVIA 120, Bayer

Parameter:				RETI	MONO	MONO	ALP
Unit:				%	%	GIGA/L	MYKAT/L
Study No,	Animals examined	administration via	sampling month				
04S001	5	diet	03/10	0.7	0.8	0.04	2.29
07C014	5	diet	09/10	0.7	1.3	0.06	1.82
07S015	5	diet	08/10	0.6	1.2	0.06	1.78
08C009	5	diet	08/10	1.5	2.5	0.13	1.68
96S001	8	diet	10/10	0.7	1.1	0.05	1.80
03106	5	diet	11/09	2.9	1.0	0.05	1.12
00C001	5	diet	03/11	0.6	0.9	0.02	1.77
09S078	5	diet	09/11	2.6	0.4	0.02	1.95
	N			8	8	8	8
	Mean			1.3	1.2	0.05	1.78
	Minimum			0.6	0.4	0.02	1.12
	Maximum			2.9	2.5	0.13	2.29

1) Source: All data were collected and archived at the test facility Experimental Toxicology and Ecology, BASF SE, 67056 Ludwigshafen, Germany, in accordance with the OECD principles of Good Laboratory Practice (GLP) and the GLP principles of the German "Chemikaliengesetz" (Chemicals Act)

HISTORICAL CONTROL DATA OF CLINICAL PATHOLOGY TESTING[1)]

Species:	Mouse
Sex:	Female
Strain:	C57BL/6 J Rj
Age:	10 weeks
Study period:	4 weeks
Fasting before blood sampling:	16 hours
Anaesthesia	Isoflurane
Data print out at	10-Jul-13
Haematology Analyzer	ADVIA 120, Bayer

Parameter:				NEUT	NEUT
Unit:				%	GIGA/L
Study No,	Animals examined	administration via	sampling month		
04S001	5	diet	03/10	24.5	0.67
07C014	5	diet	09/10	28.7	1.34
07S015	5	diet	08/10	21.7	0.45
08C009	5	diet	08/10	28.0	1.02
96S001	8	diet	10/10	20.7	0.31
03106	5	diet	11/09	30.4	0.65
00C001	5	diet	03/11	22.0	0.33
09S078	5	diet	09/11	14.1	0.46
	N			8	8
	Mean			23.8	0.65
	Minimum			14.1	0.31
	Maximum			30.4	1.34

1) Source: All data were collected and archived at the test facility Experimental Toxicology and Ecology, BASF SE, 67056 Ludwigshafen, Germany, in accordance with the OECD principles of Good Laboratory Practice (GLP) and the GLP principles of the German "Chemikaliengesetz" (Chemicals Act)

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Historical Control Data

C57BL / 6 J Rj

Liver - m

6/14/2008 - 6/14/2013

Species mouse **Duration** 4 weeks

study	application	study start	study end	No	abs. in mg	SD abs. in mg	rel.wght	SD rel.wght	age	supplier
01S002	feeding	2/1/2010	3/1/2010	8	901.500	92.961	4.603	0.216	5-7 weeks (35-49 days)	Janvier
08C009	feeding	7/1/2010	8/1/2010	5	1006.000	62.933	4.519	0.212	5-7 weeks (35-49 days)	Janvier
09S078	feeding	8/1/2011	9/1/2011	5	866.800	33.237	4.202	0.167	5-7 weeks (35-49 days)	Janvier
11S214	feeding	5/1/2013	6/1/2013	5	913.600	62.991	4.569	0.320	5-7 weeks (35-49 days)	Janvier
11S218	feeding	5/1/2013	6/1/2013	5	895.000	53.791	4.408	0.305	5-7 weeks (35-49 days)	Janvier
12S072	feeding	12/1/2012	1/1/2013	5	854.000	94.013	3.716	0.251	5-7 weeks (35-49 days)	Janvier

total no of animals 33 **max abs. wght.** 1006.000 mg **max rel. wght.** 4.603 %

total no of studies 6 **min abs. wght.** 854.000 mg **min rel. wght.** 3.716 %

mean abs. wght. 906.150 mg **mean rel. wght.** 4.336 %

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Historical Control Data

C57BL / 6 J Rj

Liver - f

6/14/2008 - 6/14/2013

Species mouse **Duration** 4 weeks

study	application	study start	study end	No	abs. in mg	SD abs. in mg	rel.wght	SD rel.wght	age	supplier
08C009	feeding	7/1/2010	8/1/2010	5	685.000	63.691	4.172	0.388	5-7 weeks (35-49 days)	Janvier
08S025	feeding	10/1/2012	11/1/2012	8	758.000	49.000	4.411	0.352	5-7 weeks (35-49 days)	Janvier
09S078	feeding	8/1/2011	9/1/2011	5	781.000	33.705	4.667	0.285	5-7 weeks (35-49 days)	Janvier
11S214	feeding	5/1/2013	6/1/2013	5	856.200	136.564	5.447	0.708	5-7 weeks (35-49 days)	Janvier
11S218	feeding	5/1/2013	6/1/2013	5	776.200	46.381	4.770	0.253	5-7 weeks (35-49 days)	Janvier
12S072	feeding	12/1/2012	1/1/2013	5	758.400	67.818	4.240	0.170	5-7 weeks (35-49 days)	Janvier

total no of animals 33 **max abs. wght.** 856.200 mg **max rel. wght.** 5.447 %

total no of studies 6 **min abs. wght.** 685.000 mg **min rel. wght.** 4.172 %

mean abs. wght. 769.133 mg **mean rel. wght.** 4.618 %

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Historical Control Data

C57BL / 6 J Rj

Thymus - f

6/14/2008 - 6/14/2013

Species mouse **Duration** 4 weeks

study	application	study start	study end	No	abs. in mg	SD abs. in mg	rel.wght	SD rel.wght	age	supplier
02C014	feeding	4/1/2012	5/1/2012	8	41.000	4.036	0.253	0.021	5-7 weeks (35-49 days)	Janvier
08C009	feeding	7/1/2010	8/1/2010	5	41.400	3.507	0.252	0.024	5-7 weeks (35-49 days)	Janvier
08S025	feeding	10/1/2012	11/1/2012	8	41.125	7.643	0.239	0.042	5-7 weeks (35-49 days)	Janvier
09S078	feeding	8/1/2011	9/1/2011	5	39.200	1.924	0.234	0.009	5-7 weeks (35-49 days)	Janvier
11S214	feeding	5/1/2013	6/1/2013	5	39.800	5.404	0.254	0.037	5-7 weeks (35-49 days)	Janvier
11S218	feeding	5/1/2013	6/1/2013	5	40.400	3.647	0.248	0.024	5-7 weeks (35-49 days)	Janvier
12S072	feeding	12/1/2012	1/1/2013	5	44.500	11.445	0.248	0.055	5-7 weeks (35-49 days)	Janvier
98S001	feeding	1/1/2011	2/1/2011	8	55.000	5.928	0.315	0.040	5-7 weeks (35-49 days)	Janvier

total no of animals	**49**	**max abs. wght.**	**55.000 mg**	**max rel. wght.**	**0.315 %**
total no of studies	**8**	**min abs. wght.**	**39.200 mg**	**min rel. wght.**	**0.234 %**
		mean abs. wght.	**42.803 mg**	**mean rel. wght.**	**0.255 %**

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Report; Project No.: 31C0741/11C201