

RCC - CCR STUDY NUMBER 1155101

**SALMONELLA TYPHIMURIUM
REVERSE MUTATION ASSAY**

WITH

Lyso-Phospholipase

REPORT

**STUDY COMPLETION DATE:
April 28, 2008**



1 COPY OF GLP CERTIFICATE



HESSEN



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 88/320/EG wurde durchgeführt in

Assessment of conformity with GLP according to Chemikaliengesetz and Directive 88/320/EEC at:

Prüfeinrichtung/Test facility Prüfstandort/Test site

RCC – Cytotest Cell Research GmbH
RCC – Cytotest Cell Research GmbH
In den Leppsteinswiesen 19
64380 Rossdorf

(Unverwechselbare Bezeichnung und Adresse/Unequivocal name and address)

Prüfungen nach Kategorien/Areas of Expertise

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

- | | |
|--|--|
| 2 Prüfungen zur Bestimmung der toxikologischen Eigenschaften | 2 Toxicity studies |
| 3 Prüfungen zur Bestimmung der erbgutverändernden Eigenschaften (in vitro und in vivo) | 3 Mutagenicity studies |
| 6 Prüfungen zur Bestimmung von Rückständen | 6 Residues |
| 8 Analytische Prüfungen an biologischen Materialien | 8 Analytical studies on biological materials |
| 9 Virussicherheitsprüfungen | 9 Virus validation studies |

02.09.2006

Datum der Inspektion/Date of Inspection
(Tag Monat Jahr/day month year)

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.

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

**Hess. Ministerium für Umwelt, ländlichen Raum und Verbraucherschutz,
Mainzer Straße 80 D65189 Wiesbaden**

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

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3 PREFACE

3.1 General

Title: Salmonella typhimurium Reverse Mutation Assay
with Lyso-Phospholipase

Sponsor: AB Enzymes GmbH
Feldbergstrasse 78
D-64293 Darmstadt

Study Monitor:

Test Facility: R C C
Cytotest Cell Research GmbH (RCC-CCR)
In den Leppsteinswiesen 19
D-64380 Rossdorf

3.2 Responsibilities

Study Director:

Deputy Study Director:

Management:

Head of Quality Assurance Unit:

3.3 Schedule

Experimental Starting Date: January 30, 2008

Experimental Completion Date: February 14, 2008

3.4 Project Staff Signatures

Study Director

Management

3.5 Good Laboratory Practice

The study was performed in compliance with:

"Chemikaliengesetz" (Chemicals Act) of the Federal Republic of Germany, "Anhang 1" (Annex 1) dated July 25, 1994 („BGBl. I 1994“, pp. 1703), last revision dated June 27, 2002.

"OECD Principles of Good Laboratory Practice", as revised in 1997 [C(97)186/Final].

3.6 Guidelines

This study followed the procedures indicated by the following internationally accepted guidelines and recommendations:

"Ninth Addendum to OECD Guidelines for Testing of Chemicals", Section 4, No. 471: "Bacterial Reverse Mutation Test", adopted July 21, 1997.

"Commission Directive 2000/32/EC, L1362000, Annex 4D", dated May 19, 2000.

3.7 Archiving

RCC Cytotest Cell Research GmbH will archive the following data for 15 years:

Raw data, study plan, report, and a sample of the test item.

No data will be discarded without the sponsor's consent.

3.8 Deviations from the Study Plan

There were no deviations from the study plan.

4 STATEMENT OF COMPLIANCE

Study Number: 1155101
Test Item: Lyso-Phospholipase
Study Director: Dipl. Biol. Andrea Sokolowski
Title: Salmonella Typhimurium Reverse Mutation Assay
with Lyso-Phospholipase

This study performed in the test facility of RCC Cytotest Cell Research GmbH was conducted in compliance with Good Laboratory Practice Regulations:

"Chemikaliengesetz" (Chemicals Act) of the Federal Republic of Germany, "Anhang 1" (Annex 1) dated July 25, 1994 („BGBl. I 1994“, pp. 1703), last revision dated June 27, 2002.

"OECD Principles of Good Laboratory Practice", as revised in 1997 [C(97)186/Final].

There were no circumstances that may have affected the quality or integrity of the study.

Study Director

5 STATEMENT OF QUALITY ASSURANCE UNIT

Study Number: 1155101
Test Item: Lyso-Phospholipase
Study Director: Dipl. Biol. Andrea Sokolowski
Title: Salmonella Typhimurium Reverse Mutation Assay
with Lyso-Phospholipase

The general facilities and activities of RCC Cytotest Cell Research GmbH are inspected periodically and the results are reported to the responsible person and the management.

Study procedures were inspected periodically. The study plan and this report were audited by the Quality Assurance Unit. The dates are given below.

Phases and Dates of QAU Inspections/ Audits		Dates of Reports to the Study Director and to Management
Study Plan:	January 16, 2008	January 16, 2008
Process Inspection (preparation of the test item):	January 29, 2008	January 29, 2008
Report	March 27, 2008	March 27, 2008

This statement is to confirm that the present report reflects the raw data.

Head of Quality Assurance Unit

6 SUMMARY OF RESULTS

This study was performed to investigate the potential of Lyso-Phospholipase to induce gene mutations according to the plate incorporation test (experiment I) and the pre-incubation test (experiment II) using the *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, TA 100, and TA 102.

The assay was performed in two independent experiments both with and without liver microsomal activation. Each concentration, including the controls, was tested in triplicate. The test item was tested at the following concentrations:

Pre-Experiment/Experiment I: 3, 10; 33; 100; 333; 1000; 2500; and 5000 µg/plate

Experiment II: 33; 100; 333; 1000; 2500; and 5000 µg/plate

The plates incubated with the test item showed normal background growth up to 5000 µg/plate with and without S9 mix in all strains used.

No toxic effects, evident as a reduction in the number of revertants, occurred in the test groups with and without metabolic activation.

No substantial increase in revertant colony numbers of any of the five tester strains was observed following treatment with Lyso-Phospholipase at any dose level, neither in the presence nor absence of metabolic activation (S9 mix). There was also no tendency of higher mutation rates with increasing concentrations in the range below the generally acknowledged border of biological relevance.

Appropriate reference mutagens were used as positive controls and showed a distinct increase of induced revertant colonies.

6.1 Conclusion

In conclusion, it can be stated that during the described mutagenicity test and under the experimental conditions reported, the test item did not induce gene mutations by base pair changes or frameshifts in the genome of the strains used.

Therefore, Lyso-Phospholipase is considered to be non-mutagenic in this *Salmonella typhimurium* reverse mutation assay.

7 OBJECTIVE

7.1 Aims of the Study

The experiments were performed to assess the potential of the test item to induce gene mutations by means of two independent *Salmonella typhimurium* reverse mutation assays. Experiment I was performed as a plate incorporation assay. Since a negative result was obtained in this experiment, experiment II was performed as a pre-incubation assay.

7.2 Reasons for the Study

The most widely used assays for detecting gene mutations are those using bacteria (3). They are relatively simple and rapid to perform, and give reliable data on the ability of an agent to interact with DNA and produce mutations.

Reverse mutation assays determine the frequency with which an agent reverses or suppresses the effect of the forward mutation. The genetic target presented to an agent is therefore small, specific and selective. Several bacterial strains, or a single strain with multiple markers are necessary to overcome the effects of mutagen specificity. The reversion of bacteria from growth-dependence on a particular amino acid to growth in the absence of that amino acid (reversion from auxotrophy to prototrophy) is the most widely used marker.

The *Salmonella typhimurium* histidine (his) reversion system measures his⁻ → his⁺ reversions. The *S. typhimurium* strains are constructed to differentiate between base pair (TA 1535, TA 100, TA 102) and frameshift (TA 1537, TA 98) mutations.

According to the direct plate incorporation and the pre-incubation method the bacteria are exposed to the test item with and without metabolic activation and plated on selective medium. After a suitable period of incubation, revertant colonies are counted.

To establish a dose response effect at least six dose levels with adequately spaced concentrations were tested. The maximum dose level was 5000 µg/plate.

To validate the test, reference mutagens are tested in parallel to the test item.

8 MATERIALS AND METHODS

8.1 Test Item

Internal RCC-CCR Test Item Number: S 837411

The test item and the information concerning the test item were provided by the sponsor.

Identity:	Lyso-Phospholipase
Batch No.:	LP 07102 A3
Aggregate state at room temperature:	Solid
* Colour:	Pale brown
Purity:	Not indicated by the sponsor
Stability in solvent:	Stable in water for approx.: 1 day at room temperature 5 days in refrigerator 1 year in freezer
Storage:	At room temperature, moisture protected
Expiration Date:	November, 2009

On the day of the experiment, the test item Lyso-Phospholipase was dissolved in deionised water. The solvent was chosen because of its solubility properties and its relative nontoxicity to the bacteria (4).

No precipitation of the test item occurred up to the highest investigated dose.

*as determined by RCC-CCR Laboratory Staff

8.2 Controls

8.2.1 Negative Controls

Concurrent untreated and solvent controls were performed.

8.2.2 Positive Control Substances

Without metabolic activation

Strains: TA 1535, TA 100
Name: sodium azide, NaN_3
Supplier: SERVA, D-69042 Heidelberg
Catalogue No.: 30175
Purity: at least 99 %
Dissolved in: water deionised
Concentration: 10 µg/plate

Strains: TA 1537, TA 98
Name: 4-nitro-o-phenylene-diamine, 4-NOPD
Supplier: SIGMA, D-82041 Deisenhofen
Catalogue No.: N 9504
Purity: > 99.9 %
Dissolved in: DMSO (purity >99 %, MERCK, D-64293 Darmstadt)
Concentration: 10 µg/plate in TA 98, 50 µg/plate in TA 1537

Strain: TA 102
Name: methyl methane sulfonate, MMS
Supplier: MERCK-SCHUCHARDT, D-85662 Hohenbrunn
Catalogue No.: 820775
Purity: > 99.0 %
Dissolved in: water deionised
Concentration: 3.0 µL/plate

With metabolic activation

Strains: TA 1535, TA 1537, TA 98, TA 100, TA 102
Name: 2-aminoanthracene, 2-AA
Supplier: SIGMA, D-82041 Deisenhofen
Catalogue No.: A 1381
Purity: 97.5 %
Dissolved in: DMSO (purity >99 %, MERCK, D-64293 Darmstadt)
Concentration: 2.5 µg/plate (10.0 µg/plate in TA 102)

The stability of the positive control substances in solution was unknown but a mutagenic response in the expected range is sufficient evidence of biological stability.

8.3 Test System

8.3.1 Characterisation of the *Salmonella typhimurium* Strains

The histidine dependent strains are derived from *S. typhimurium* strain LT2 through a mutation in the histidine locus. Additionally due to the "deep rough" (*rfa*⁻) mutation they possess a faulty lipopolysaccharide envelope which enables substances to penetrate the cell wall more easily. A further mutation (deletion of the *uvrB* gene) causes an inactivation of the excision repair system. The latter alteration also includes a deletion in the nitrate reductase and biotin genes. In the strains TA 98, TA 100, and TA 102 the R-factor plasmid pKM 101 carries *umu* DC analogous genes that are involved in error-prone repair and the ampicillin resistance marker. The strain TA 102 does not contain the *uvrB*⁻-mutation and is excision repair proficient. Additionally, TA 102 contains the multicopy plasmid pAQ1 carrying the *hisG428* mutation (ochre mutation in the *hisG* gene) and a tetracycline resistance gene (5).

In summary, the mutations of the TA strains used in this study can be described as follows:

Salmonella typhimurium		
Strains	Genotype	Type of mutations indicated
TA 1537	<i>his C 3076; rfa</i> ⁻ ; <i>uvrB</i> ⁻ :	frame shift mutations
TA 98	<i>his D 3052; rfa</i> ⁻ ; <i>uvrB</i> ⁻ ;R-factor	" "
TA 1535	<i>his G 46; rfa</i> ⁻ ; <i>uvrB</i> ⁻ :	base-pair substitutions
TA 102	<i>his G 428; rfa</i> ⁻ ; <i>uvrB</i> ⁺ ;R-factor	" "
TA 100	<i>his G 46; rfa</i> ⁻ ; <i>uvrB</i> ⁻ ;R-factor	" "

Regular checking of the properties of the strains regarding the membrane permeability, ampicillin- and tetracycline-resistance as well as spontaneous mutation rates is performed in the laboratory of RCC Cytotest Cell Research GmbH according to B. Ames et al. (1) and D. Maron and B. Ames (5). In this way it was ensured that the experimental conditions set down by Ames were fulfilled.

The bacterial strains TA 1535, TA 1537, TA 98, TA 100, and TA 102 were obtained from Trinova Biochem GmbH (35394 Gießen, Germany).

8.3.2 Storage

The strain cultures were stored as stock cultures in ampoules with nutrient broth + 5 % DMSO (MERCK, D-64293 Darmstadt) in liquid nitrogen.

8.3.3 Precultures

From the thawed ampoules of the strains 0.5 mL bacterial suspension was transferred into 250 mL Erlenmeyer flasks containing 20 mL nutrient medium. A solution of 20 µL ampicillin (25 µg/mL) was added to the strains TA 98, TA 100, and TA 102. Additionally 20 µL tetracycline (2 µg/mL) was added to strain TA 102. This nutrient medium contains per litre:

8 g Merck Nutrient Broth (MERCK, D-64293 Darmstadt)
5 g NaCl (MERCK, D-64293 Darmstadt)

The bacterial cultures were incubated in a shaking water bath for 4 hours at 37° C.

8.3.4 Selective Agar

The plates with the minimal agar were obtained from E. Merck, D-64293 Darmstadt.

8.3.5 Overlay Agar

The overlay agar contains per litre:

6.0 g MERCK Agar Agar*
6.0 g NaCl*
10.5mg L-Histidine x HCl x H₂O*
12.2mg Biotin*
* (MERCK, D-64293 Darmstadt)

Sterilisations were performed at 121° C in an autoclave.

8.4 Mammalian Microsomal Fraction S9 Mix

The bacteria used in this assay do not possess the enzyme systems which, in mammals, are known to convert promutagens into active DNA damaging metabolites. In order to overcome this major drawback an exogenous metabolic system is added in form of mammalian microsome enzyme activation mixture.

8.4.1 S9 (Preparation by R C C - C C R)

Phenobarbital/β-Naphthoflavone induced rat liver S9 is used as the metabolic activation system. The S9 is prepared from 8 - 12 weeks old male Wistar Hanlbm rats, weight approx. 220 - 320 g induced by applications of 80 mg/kg b.w. Phenobarbital i.p. (Desitin; D-22335 Hamburg) and β-Naphthoflavone p.o. (Aldrich, D-89555 Steinheim) each on three consecutive days. The livers are prepared 24 hours after the last treatment. The S9 fractions are produced by dilution of the liver homogenate with a KCl solution (1+3) followed by centrifugation at 9000 g. Aliquots of the supernatant are frozen and stored in ampoules at -80° C. Small numbers of the ampoules can be kept at -20°C for up to one week. Each batch of S9 mix is routinely tested with 2-aminoanthracene as well as benzo(a)pyrene.

The protein concentration in the S9 preparation was 30.5 mg/mL (lot no. R 240807) in both experiments.

8.4.2 S9 Mix

Before the experiment an appropriate quantity of S9 supernatant was thawed and mixed with S9 co-factor solution. The amount of S9 supernatant was 10% v/v in the S9 mix. Cofactors are added to the S9 mix to reach the following concentrations in the S9 mix:

8 mM MgCl₂
33 mM KCl
5 mM Glucose-6-phosphate
5 mM NADP

in 100 mM sodium-ortho-phosphate-buffer, pH 7.4.

During the experiment the S9 mix was stored in an ice bath. The S9 mix preparation was performed according to Ames et al.(1).

8.5 Pre-Experiment for Toxicity

To evaluate the toxicity of the test item a pre-experiment was performed with all strains used. Eight concentrations were tested for toxicity and mutation induction with each 3 plates. The experimental conditions in this pre-experiment were the same as described for the experiment I below (plate incorporation test).

Toxicity of the test item can be evident as a reduction in the number of spontaneous revertants or a clearing of the bacterial background lawn.

The pre-experiment is reported as main experiment I, since the following criteria are met:

Evaluable plates (>0 colonies) at five concentrations or more in all strains used.

8.6 Dose Selection

In the pre-experiment the concentration range of the test item was 3 – 5000 µg/plate. The pre-experiment is reported as experiment I. Since no toxic effects were observed 5000 µg/plate were chosen as maximal concentration.

The concentration range included two logarithmic decades. The following concentrations were tested:

33; 100; 333; 1000; 2500; and 5000 µg/plate

8.7 Experimental Performance

For each strain and dose level, including the controls three plates were used.

The following materials were mixed in a test tube and poured onto the selective agar plates:

- 100 µL Test solution at each dose level, solvent (negative control) or reference mutagen solution (positive control),
- 500 µL S9 mix (for test with metabolic activation) or S9 mix substitution buffer (for test without metabolic activation),
- 100 µL Bacteria suspension (cf. test system, pre-culture of the strains),
- 2000 µL Overlay agar

In the pre-incubation assay 100 µL test solution, 500 µL S9 mix / S9 mix substitution buffer and 100 µL bacterial suspension were mixed in a test tube and incubated at 37°C for 60 minutes. After pre-incubation 2.0 mL overlay agar (45° C) was added to each tube. The mixture was poured on minimal agar plates.

After solidification the plates were incubated upside down for at least 48 hours at 37° C in the dark (2).

8.8 Data Recording

The colonies were counted using the Petri Viewer Mk2 (Perceptive Instruments Ltd, Suffolk CB 7BN, UK) with the software program Ames Study Manager. The counter was connected to an IBM AT compatible PC with printer which printed out both, the individual and mean values of the plates for each concentration together with standard deviations and enhancement factors as compared to the spontaneous reversion rates (see tables of results). Due to air bubbles (might be caused by the test item) the colonies were partly counted manually.

8.9 Acceptability of the Assay

The Salmonella typhimurium reverse mutation assay is considered acceptable if it meets the following criteria:

- regular background growth in the negative and solvent control
- the spontaneous reversion rates in the negative and solvent control are in the range of our historical data
- the positive control substances should produce a significant increase in mutant colony frequencies

8.10 Evaluation of Results

A test item is considered as a mutagen if a biologically relevant increase in the number of revertants exceeding the threshold of twice (strains TA 98, TA 100, and TA 102) or thrice (strains TA 1535 and TA 1537) the colony count of the corresponding solvent control is observed (3).

A dose dependent increase is considered biologically relevant if the threshold is exceeded at more than one concentration (2).

An increase exceeding the threshold at only one concentration is judged as biologically relevant if reproduced in an independent second experiment.

A dose dependent increase in the number of revertant colonies below the threshold is regarded as an indication of a mutagenic potential if reproduced in an independent second experiment. However, whenever the colony counts remain within the historical range of negative and solvent controls such an increase is not considered biologically relevant.

8.11 Biometry

According to the OECD guideline 471, a statistical analysis of the data is not mandatory.

9 DISCUSSION OF RESULTS

The test item Lyso-Phospholipase was assessed for its potential to induce gene mutations according to the plate incorporation test (experiment I) and the pre-incubation test (experiment II) using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, TA 100, and TA 102.

The assay was performed in two independent experiments both with and without liver microsomal activation. Each concentration and the controls, were tested in triplicate. The test item was tested at the following concentrations:

Pre-Experiment/Experiment I: 3, 10; 33; 100; 333; 1000; 2500; and 5000 µg/plate

Experiment II: 33; 100; 333; 1000; 2500; and 5000 µg/plate

The plates incubated with the test item showed normal background growth up to 5000 µg/plate with and without S9 mix in all strains used.

No toxic effects, evident as a reduction in the number of revertants, occurred in the test groups with and without metabolic activation.

No substantial increase in revertant colony numbers of any of the five tester strains was observed following treatment with Lyso-Phospholipase at any concentration level, neither in the presence nor absence of metabolic activation (S9 mix). There was also no tendency of higher mutation rates with increasing concentrations in the range below the generally acknowledged border of biological relevance.

In experiment II without metabolic activation, the data in solvent control of strain TA 1537 were slightly above our historical control range. Since this deviation is rather small, this effect is considered to be based upon biologically irrelevant fluctuations in the number of colonies.

Appropriate reference mutagens were used as positive controls. They showed a distinct increase in induced revertant colonies.

In conclusion, it can be stated that during the described mutagenicity test and under the experimental conditions reported, the test item did not induce gene mutations by base pair changes or frameshifts in the genome of the strains used.

10 REFERENCES

1. Ames, B.N., J. McCann, and E. Yamasaki (1977)
Methods for detecting carcinogens and mutagens with the Salmonella/mammalian microsome mutagenicity test
In: B.J. Kilbey et al. (Eds.) "Handbook of Mutagenicity Test Procedures" Elsevier, Amsterdam, 1-17
2. de Serres F.J. and M.D. Shelby (1979)
Recommendations on data production and analysis using the Salmonella/microsome mutagenicity assay
Mutation Res. 64, 159-165
3. Hollstein, M., J. McCann, F.A. Angelosanto and W.W. Nichols (1979)
Short-term tests for carcinogens and mutagens
Mutation Res. 65, 133-226
4. Maron D.M., J. Katzenellenbogen and B.N. Ames, (1981)
Compatibility of organic solvents with the Salmonella/Microsome Test
Mutation Res. 88, 343-350
5. Maron, D.M., Ames, B.N. (1983)
Revised methods for the Salmonella mutagenicity test
Mutation Res. 113, 173-215

11 DISTRIBUTION OF THE REPORT

Sponsor	2x (copy)
Study Director	1x (original)

12 SUMMARY OF RESULTS

12.1 Summary of Results Pre-Experiment and Experiment I

Study Name: 1155101
Experiment: 1155101 VV Plate
Assay Conditions:

Study Code: CCR-RCC 1155101
Date Plated: 30/01/2008
Date Counted: 04/02/2008

Metabolic Activation	Test Group	Dose Level (µg/plate)	Revertant Colony Counts (Mean ±SD)				
			TA 1535	TA 1537	TA 98	TA 100	TA 102
Without Activation	Deionised water		18 ± 5	20 ± 6	34 ± 4	129 ± 8	435 ± 5
	Untreated		21 ± 7	17 ± 4	28 ± 5	126 ± 4	394 ± 33
	Lyso-Phospholipase	3 µg	16 ± 1	17 ± 2	27 ± 3	122 ± 10	392 ± 33
		10 µg	16 ± 5	16 ± 3	34 ± 7	115 ± 15	437 ± 8
		33 µg	19 ± 3	18 ± 1	29 ± 7	127 ± 14	444 ± 16
		100 µg	18 ± 2	21 ± 2	30 ± 6	136 ± 7	439 ± 21
		333 µg	19 ± 4	18 ± 1	32 ± 4	127 ± 16	371 ± 55
		1000 µg	13 ± 2 ^{UM}	13 ± 3 ^{UM}	28 ± 3 ^{UM}	112 ± 11 ^{UM}	346 ± 16 ^{UM}
		2500 µg	14 ± 3 ^{UM}	15 ± 3 ^{UM}	26 ± 2 ^{UM}	101 ± 9 ^{UM}	330 ± 22 ^{UM}
		5000 µg	14 ± 1 ^{UM}	13 ± 2 ^{UM}	22 ± 2 ^{UM}	104 ± 9 ^{UM}	317 ± 15 ^{UM}
		NaN3	10 µg	2150 ± 11		2250 ± 47	
		4-NOPD	10 µg		453 ± 28		
		4-NOPD	50 µg		114 ± 4		
		MMS	3.0 µL				5497 ± 509
With Activation	Deionised water		25 ± 4	30 ± 6	39 ± 3	143 ± 26	549 ± 18
	Untreated		20 ± 3	29 ± 6	45 ± 8	113 ± 15	449 ± 32
	Lyso-Phospholipase	3 µg	23 ± 3	28 ± 2	43 ± 7	137 ± 16	403 ± 32
		10 µg	23 ± 7	27 ± 8	53 ± 7	117 ± 9	490 ± 33
		33 µg	21 ± 2	29 ± 4	51 ± 6	131 ± 11	465 ± 20
		100 µg	22 ± 4	29 ± 1	43 ± 4	151 ± 6	548 ± 49
		333 µg	28 ± 5	31 ± 6	45 ± 15	123 ± 19	443 ± 42
		1000 µg	12 ± 3 ^{UM}	26 ± 2 ^{UM}	38 ± 9 ^{UM}	119 ± 11 ^{UM}	352 ± 10 ^{UM}
		2500 µg	13 ± 2 ^{UM}	22 ± 2 ^{UM}	29 ± 5 ^{UM}	114 ± 7 ^{UM}	312 ± 11 ^{UM}
		5000 µg	15 ± 1 ^{UM}	19 ± 1 ^{UM}	24 ± 2 ^{UM}	113 ± 8 ^{UM}	314 ± 7 ^{UM}
		2-AA	2.5 µg	173 ± 14	114 ± 14	820 ± 59	1085 ± 69
	2-AA	10.0 µg				2048 ± 89	

Key to Positive Controls

NaN3 sodium azide
2-AA 2-aminoanthracene
MMS methyl methane sulfonate
4-NOPD 4-nitro-o-phenylene-diamine

Key to Plate Postfix Codes

U Air bubble
M Manual count

12.2 Summary of Results Experiment II

Study Name: 1155101
Experiment: 1155101 HV2 Pre
Assay Conditions:

Study Code: CCR-RCC 1155101
Date Plated: 11/02/2008
Date Counted: 14/02/2008

Metabolic Activation	Test Group	Dose Level (µg/plate)	Revertant Colony Counts (Mean ±SD)				
			TA 1535	TA 1537	TA 98	TA 100	TA 102
Without Activation	Deionised water Untreated		13 ± 1	25 ± 10	24 ± 3	129 ± 7	446 ± 19
			14 ± 0	13 ± 2	20 ± 6	130 ± 21	411 ± 34
	Lyso-Phospholipase	33 µg	17 ± 4	20 ± 9	24 ± 2	131 ± 5	408 ± 26
		100 µg	18 ± 8	21 ± 8 ^{UM}	20 ± 3 ^{UM}	140 ± 11	448 ± 22 ^{UM}
		333 µg	16 ± 1 ^{UM}	16 ± 1 ^{UM}	16 ± 2 ^{UM}	144 ± 5 ^{UM}	426 ± 18 ^{UM}
		1000 µg	14 ± 1 ^{UM}	14 ± 2 ^{UM}	16 ± 1 ^{UM}	148 ± 3 ^{UM}	440 ± 16 ^{UM}
		2500 µg	12 ± 3 ^{UM}	11 ± 3 ^{UM}	18 ± 3 ^{UM}	149 ± 7 ^{UM}	433 ± 27 ^{UM}
		5000 µg	14 ± 3 ^{UM}	13 ± 2 ^{UM}	17 ± 2 ^{UM}	143 ± 5 ^{UM}	426 ± 15 ^{UM}
	NaN3	10 µg	2103 ± 32			2139 ± 192	
	4-NOPD	10 µg			408 ± 36		
	4-NOPD	50 µg		82 ± 5			
	MMS	3.0 µL					1427 ± 133
With Activation	Deionised water Untreated		18 ± 5	19 ± 3	28 ± 11	171 ± 10	572 ± 21
			17 ± 6	17 ± 3	31 ± 5	150 ± 12	555 ± 30
	Lyso-Phospholipase	33 µg	17 ± 3	20 ± 1	42 ± 2	158 ± 9	537 ± 57
		100 µg	18 ± 3	17 ± 3 ^{UM}	35 ± 2	171 ± 14	588 ± 12 ^{UM}
		333 µg	17 ± 4	15 ± 3 ^{UM}	37 ± 3 ^{UM}	160 ± 3 ^{UM}	585 ± 8 ^{UM}
		1000 µg	18 ± 3 ^{UM}	16 ± 2 ^{UM}	35 ± 3 ^{UM}	153 ± 10 ^{UM}	581 ± 2 ^{UM}
		2500 µg	13 ± 2 ^{UM}	16 ± 3 ^{UM}	32 ± 3 ^{UM}	142 ± 7 ^{UM}	574 ± 6 ^{UM}
		5000 µg	14 ± 2 ^{UM}	13 ± 2 ^{UM}	37 ± 3 ^{UM}	136 ± 5 ^{UM}	575 ± 11 ^{UM}
	2-AA	2.5 µg	185 ± 21	111 ± 13	872 ± 23	1204 ± 59	
	2-AA	10.0 µg					2214 ± 24

Key to Positive Controls

NaN3 sodium azide
2-AA 2-aminoanthracene
MMS methyl methane sulfonate
4-NOPD 4-nitro-o-phenylene-diamine

Key to Plate Postfix Codes

U Air bubbles
M Manual count

13 HISTORICAL CONTROL DATA

These data represent the laboratory's historical control data from January 2007 until July 2007 representing approx. 200 experiments (TA 102 the historical data are based on approx. 100 experiments).

Strain		without S9 mix				with S9 mix			
		Mean	SD	Min	Max	Mean	SD	Min	Max
TA 1535	Solvent control	17	4.51	7	40	21	4.95	8	41
	Negative control	17	4.57	9	34	21	5.55	9	42
	Positive control	1878	203.83	852	2347	270	83.95	98	636
TA1537	Solvent control	11	2.91	6	23	16	4.19	6	35
	Negative control	11	2.97	6	24	17	4.97	7	37
	Positive control	125	41.01	75	424	180	64.61	73	475
TA 98	Solvent control	32	6.78	18	66	40	6.24	24	64
	Negative control	35	6.67	17	62	41	6.56	23	67
	Positive control	534	163.95	172	1916	1193	491.42	184	2759
TA 100	Solvent control	138	25.59	84	213	157	27.89	94	254
	Negative control	145	21.66	97	210	161	25.76	94	217
	Positive control	1953	492.35	572	2943	1763	713.99	542	3886
TA 102	Solvent control	441	57.95	271	537	541	90.85	285	679
	Negative control	433	55.23	286	531	543	94.69	301	675
	Positive control	3219	268.07	1314	5519	2187	530.26	1206	3678

Mean = mean value of revertants/plate

SD = standard deviation

Min = minimal value/Max = maximal value

14 ANNEX: TABLES OF RESULTS (8 PAGES)

Pre-Experiment and Experiment I: 1155101 VV Plate Incorporation (4 pages)

Experiment II: 1155101 HV2 Pre-Incubation (4 pages)

Study Name: 1155101
Experiment: 1155101 VV Plate
Assay Conditions:

Study Code: CCR-RCC 1155101
Date Plated: 30/01/2008
Date Counted: 04/02/2008

Without metabolic activation

Strain	Compound	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 1535	Lyso-Phospholipase	3 µg	16.0	1.0	0.9	16, 17, 15
		10 µg	16.3	4.5	0.9	21, 12, 16
		33 µg	19.0	3.5	1.1	21, 15, 21
		100 µg	18.3	2.1	1.0	16, 20, 19
		333 µg	19.3	4.0	1.1	23, 20, 15
		1000 µg	13.0	1.7	0.7	14 U M, 11 U M, 14 U M
		2500 µg	14.0	3.0	0.8	14 U M, 11 U M, 17 U M
		5000 µg	14.0	1.0	0.8	13 U M, 15 U M, 14 U M
	Deionised water	18.0	4.6		17, 14, 23	
Untreated Control	21.3	7.4		27, 24, 13		
TA 1537	Lyso-Phospholipase	3 µg	17.3	1.5	0.9	17, 16, 19
		10 µg	16.3	2.5	0.8	19, 16, 14
		33 µg	18.3	1.2	0.9	19, 19, 17
		100 µg	21.0	2.0	1.1	21, 23, 19
		333 µg	17.7	1.2	0.9	17, 19, 17
		1000 µg	13.3	3.2	0.7	12 U M, 11 U M, 17 U M
		2500 µg	14.7	3.2	0.7	11 U M, 17 U M, 16 U M
		5000 µg	12.7	1.5	0.6	13 U M, 11 U M, 14 U M
	Deionised water	19.7	5.5		26, 16, 17	
Untreated Control	17.3	3.8		19, 13, 20		
TA 98	Lyso-Phospholipase	3 µg	27.3	3.1	0.8	24, 28, 30
		10 µg	34.3	6.5	1.0	34, 41, 28
		33 µg	29.0	6.6	0.9	28, 36, 23
		100 µg	30.3	5.9	0.9	37, 26, 28
		333 µg	31.7	4.0	0.9	31, 28, 36
		1000 µg	27.7	2.5	0.8	30 U M, 25 U M, 28 U M
		2500 µg	25.7	2.1	0.8	25 U M, 28 U M, 24 U M
		5000 µg	21.7	1.5	0.6	20 U M, 23 U M, 22 U M
	Deionised water	34.0	4.4		36, 29, 37	
Untreated Control	28.0	5.3		24, 34, 26		
TA 100	Lyso-Phospholipase	3 µg	122.3	10.0	0.9	123, 132, 112
		10 µg	115.0	15.0	0.9	115, 130, 100
		33 µg	126.7	13.5	1.0	140, 127, 113
		100 µg	136.3	6.7	1.1	129, 142, 138
		333 µg	126.7	16.1	1.0	115, 145, 120
		1000 µg	111.7	11.0	0.9	119 U M, 117 U M, 99 U M
		2500 µg	100.7	8.5	0.8	104 U M, 91 U M, 107 U M
		5000 µg	104.3	8.5	0.8	114 U M, 101 U M, 98 U M
	Deionised water	129.0	7.9		123, 126, 138	
Untreated Control	126.0	3.6		127, 122, 129		

Key to Plate Postfix Codes

U Air bubbles
M Manual count

Study Name: 1155101
 Experiment: 1155101 VV Plate
 Assay Conditions:

Study Code: CCR-RCC 1155101
 Date Plated: 30/01/2008
 Date Counted: 04/02/2008

Without metabolic activation

Strain	Compound	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 102	Lyso-Phospholipase	3 µg	392.0	33.0	0.9	354, 414, 408
		10 µg	437.3	7.6	1.0	434, 432, 446
		33 µg	444.0	16.1	1.0	446, 459, 427
		100 µg	439.0	20.9	1.0	415, 449, 453
		333 µg	370.7	55.2	0.9	310, 384, 418
		1000 µg	345.7	16.0	0.8	361 U M, 347 U M, 329 U M
		2500 µg	330.0	22.1	0.8	351 U M, 332 U M, 307 U M
		5000 µg	317.3	14.6	0.7	329 U M, 301 U M, 322 U M
	Deionised water		435.0	5.3		431, 441, 433
	Untreated Control		394.0	33.4		422, 357, 403
TA 1535	NaN3	10 µg	2150.0	11.1	119.4	2138, 2160, 2152
TA 1537	4-NOPD	50 µg	114.0	3.6	5.8	111, 118, 113
TA 98	4-NOPD	10 µg	452.7	28.2	13.3	485, 433, 440
TA 100	NaN3	10 µg	2249.7	46.5	17.4	2196, 2279, 2274
TA 102	MMS	3.0 µL	5496.7	509.5	12.6	6074, 5306, 5110

Key to Positive Controls

NaN3 sodium azide
 4-NOPD 4-nitro-o-phenylene-diamine
 MMS methyl methane sulfonate

Key to Plate Postfix Codes

U Air bubbles
 M Manual count

Study Name: 1155101
Experiment: 1155101 VV Plate
Assay Conditions:

Study Code: CCR-RCC 1155101
Date Plated: 30/01/2008
Date Counted: 04/02/2008

With metabolic activation

Strain	Compound	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 1535	Lyso-Phospholipase	3 µg	22.7	3.1	0.9	20, 26, 22
		10 µg	23.0	6.6	0.9	22, 17, 30
		33 µg	20.7	1.5	0.8	22, 19, 21
		100 µg	22.0	3.6	0.9	26, 21, 19
		333 µg	27.7	4.7	1.1	33, 26, 24
		1000 µg	12.0	2.6	0.5	11 U M, 10 U M, 15 U M
		2500 µg	12.7	1.5	0.5	14 U M, 11 U M, 13 U M
		5000 µg	15.3	1.2	0.6	16 U M, 16 U M, 14 U M
	Deionised water	24.7	3.8		22, 29, 23	
Untreated Control	20.0	3.0		23, 17, 20		
TA 1537	Lyso-Phospholipase	3 µg	27.7	2.1	0.9	30, 26, 27
		10 µg	27.0	7.5	0.9	19, 28, 34
		33 µg	29.3	4.0	1.0	34, 27, 27
		100 µg	28.7	1.2	0.9	30, 28, 28
		333 µg	31.0	5.6	1.0	26, 30, 37
		1000 µg	25.7	2.1	0.8	25 U M, 24 U M, 28 U M
		2500 µg	22.0	2.0	0.7	20 U M, 24 U M, 22 U M
		5000 µg	19.3	0.6	0.6	19 U M, 19 U M, 20 U M
	Deionised water	30.3	6.4		33, 23, 35	
Untreated Control	29.0	6.0		23, 29, 35		
TA 98	Lyso-Phospholipase	3 µg	43.3	6.8	1.1	51, 41, 38
		10 µg	53.3	6.8	1.4	61, 48, 51
		33 µg	51.0	5.6	1.3	45, 52, 56
		100 µg	43.3	4.0	1.1	48, 41, 41
		333 µg	44.7	15.0	1.1	36, 62, 36
		1000 µg	37.7	9.0	1.0	47 U M, 37 U M, 29 U M
		2500 µg	29.3	4.9	0.8	35 U M, 27 U M, 26 U M
		5000 µg	24.3	1.5	0.6	24 U M, 26 U M, 23 U M
	Deionised water	39.0	2.6		40, 36, 41	
Untreated Control	45.0	7.9		48, 51, 36		
TA 100	Lyso-Phospholipase	3 µg	137.3	16.3	1.0	123, 134, 155
		10 µg	116.7	8.6	0.8	109, 115, 126
		33 µg	131.3	11.2	0.9	141, 119, 134
		100 µg	151.0	6.0	1.1	157, 145, 151
		333 µg	123.3	18.5	0.9	133, 102, 135
		1000 µg	119.3	10.6	0.8	121 U M, 129 U M, 108 U M
		2500 µg	114.0	7.0	0.8	121 U M, 114 U M, 107 U M
		5000 µg	113.0	7.9	0.8	122 U M, 110 U M, 107 U M
	Deionised water	142.7	26.4		135, 121, 172	
Untreated Control	112.7	15.3		121, 122, 95		

Key to Plate Postfix Codes

U Air bubbles
M Manual count

Study Name: 1155101
Experiment: 1155101 VV Plate
Assay Conditions:

Study Code: CCR-RCC 1155101
Date Plated: 30/01/2008
Date Counted: 04/02/2008

With metabolic activation

Strain	Compound	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 102	Lyso-Phospholipase	3 µg	402.7	31.5	0.7	386, 439, 383
		10 µg	490.0	33.1	0.9	483, 526, 461
		33 µg	465.0	20.0	0.8	443, 470, 482
		100 µg	548.0	49.2	1.0	528, 604, 512
		333 µg	443.0	42.3	0.8	408, 431, 490
		1000 µg	352.3	10.3	0.6	355 U M, 361 U M, 341 U M
		2500 µg	312.3	11.0	0.6	323 U M, 313 U M, 301 U M
	5000 µg	314.0	7.0	0.6	322 U M, 309 U M, 311 U M	
	Deionised water		549.3	17.5		532, 549, 567
	Untreated Control		449.3	32.4		412, 466, 470
TA 1535	2-AA	2.5 µg	173.0	13.7	7.0	158, 185, 176
TA 1537	2-AA	2.5 µg	113.7	14.0	3.7	99, 127, 115
TA 98	2-AA	2.5 µg	820.0	59.3	21.0	809, 767, 884
TA 100	2-AA	2.5 µg	1085.0	68.9	7.6	1164, 1054, 1037
TA 102	2-AA	10.0 µg	2048.3	89.4	3.7	1978, 2149, 2018

Key to Positive Controls

2-AA 2-aminoanthracene

Key to Plate Postfix Codes

U Air bubbles
M Manual count

Study Name: 1155101
Experiment: 1155101 HV2 Pre
Assay Conditions:

Study Code: CCR-RCC 1155101
Date Plated: 11/02/2008
Date Counted: 14/02/2008

Without metabolic activation

Strain	Compound	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 1535	Lyso-Phospholipase	33 µg	16.7	3.5	1.3	13, 20, 17
		100 µg	18.3	7.6	1.4	13, 15, 27
		333 µg	16.3	1.2	1.2	15 U M, 17 U M, 17 U M
		1000 µg	14.3	0.6	1.1	14 U M, 15 U M, 14 U M
		2500 µg	12.0	2.6	0.9	10 U M, 11 U M, 15 U M
		5000 µg	14.0	2.6	1.1	17 U M, 13 U M, 12 U M
	Deionised water	13.3	0.6		13, 13, 14	
	Untreated Control	14.0	0.0		14, 14, 14	
TA 1537	Lyso-Phospholipase	33 µg	19.7	9.5	0.8	23, 27, 9
		100 µg	20.7	8.1	0.8	30 U M, 17 U M, 15 U M
		333 µg	16.3	1.2	0.7	17 U M, 15 U M, 17 U M
		1000 µg	13.7	1.5	0.5	15 U M, 14 U M, 12 U M
		2500 µg	11.3	3.2	0.5	9 U M, 15 U M, 10 U M
		5000 µg	13.3	1.5	0.5	15 U M, 12 U M, 13 U M
	Deionised water	25.0	10.1		27, 14, 34	
	Untreated Control	13.3	1.5		12, 15, 13	
TA 98	Lyso-Phospholipase	33 µg	24.3	2.3	1.0	23, 27, 23
		100 µg	20.0	2.6	0.8	22 U M, 21 U M, 17 U M
		333 µg	16.0	2.0	0.7	18 U M, 14 U M, 16 U M
		1000 µg	15.7	1.2	0.7	15 U M, 17 U M, 15 U M
		2500 µg	18.3	3.1	0.8	21 U M, 19 U M, 15 U M
		5000 µg	16.7	1.5	0.7	17 U M, 18 U M, 15 U M
	Deionised water	24.0	2.6		22, 23, 27	
	Untreated Control	20.3	5.5		26, 15, 20	
TA 100	Lyso-Phospholipase	33 µg	130.7	5.0	1.0	136, 130, 126
		100 µg	140.0	11.1	1.1	128, 150, 142
		333 µg	144.3	5.0	1.1	145 U M, 149 U M, 139 U M
		1000 µg	148.0	2.6	1.1	145 U M, 150 U M, 149 U M
		2500 µg	149.0	7.0	1.2	156 U M, 149 U M, 142 U M
		5000 µg	143.3	5.1	1.1	139 U M, 142 U M, 149 U M
	Deionised water	129.0	6.9		125, 137, 125	
	Untreated Control	129.7	21.2		115, 154, 120	
TA 102	Lyso-Phospholipase	33 µg	408.0	26.2	0.9	378, 426, 420
		100 µg	447.7	21.9	1.0	465 U M, 455 U M, 423 U M
		333 µg	426.0	17.7	1.0	410 U M, 445 U M, 423 U M
		1000 µg	439.7	15.6	1.0	456 U M, 425 U M, 438 U M
		2500 µg	432.7	27.3	1.0	425 U M, 463 U M, 410 U M
		5000 µg	426.3	14.7	1.0	421 U M, 443 U M, 415 U M
	Deionised water	446.0	18.5		432, 467, 439	
	Untreated Control	410.7	34.0		377, 410, 445	

Key to Plate Postfix Codes

U Air bubbles
M Manual count

Study Name: 1155101
 Experiment: 1155101 HV2 Pre
 Assay Conditions:

Study Code: CCR-RCC 1155101
 Date Plated: 11/02/2008
 Date Counted: 14/02/2008

Without metabolic activation

Strain	Compound	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 1535	NaN3	10 µg	2102.7	31.6	157.7	2110, 2068, 2130
TA 1537	4-NOPD	50 µg	82.0	5.2	3.3	76, 85, 85
TA 98	4-NOPD	10 µg	408.0	36.0	17.0	371, 443, 410
TA 100	NaN3	10 µg	2139.0	191.9	16.6	2174, 1932, 2311
TA 102	MMS	3.0 µL	1426.7	133.4	3.2	1533, 1470, 1277

Key to Positive Controls

NaN3	sodium azide
4-NOPD	4-nitro-o-phenylene-diamine
MMS	methyl methane sulfonate

Study Name: 1155101
Experiment: 1155101 HV2 Pre
Assay Conditions:

Study Code: CCR-RCC 1155101
Date Plated: 11/02/2008
Date Counted: 14/02/2008

With metabolic activation

Strain	Compound	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 1535	Lyso-Phospholipase	33 µg	17.3	3.2	1.0	15, 16, 21
		100 µg	18.3	3.2	1.0	16, 17, 22
		333 µg	17.3	3.8	1.0	19, 13, 20
		1000 µg	18.0	2.6	1.0	15 U M, 20 U M, 19 U M
		2500 µg	13.3	2.1	0.7	15 U M, 14 U M, 11 U M
		5000 µg	13.7	1.5	0.8	15 U M, 12 U M, 14 U M
	Deionised water Untreated Control		18.0 17.0	5.3 6.2		12, 20, 22 15, 12, 24
TA 1537	Lyso-Phospholipase	33 µg	20.0	1.0	1.1	20, 19, 21
		100 µg	16.7	2.9	0.9	20 U M, 15 U M, 15 U M
		333 µg	15.0	3.0	0.8	15 U M, 12 U M, 18 U M
		1000 µg	16.0	2.0	0.8	16 U M, 18 U M, 14 U M
		2500 µg	16.0	2.6	0.8	15 U M, 14 U M, 19 U M
		5000 µg	13.3	2.1	0.7	15 U M, 14 U M, 11 U M
	Deionised water Untreated Control		19.0 16.7	2.6 2.5		20, 16, 21 14, 17, 19
TA 98	Lyso-Phospholipase	33 µg	42.3	1.5	1.5	41, 42, 44
		100 µg	34.7	1.5	1.2	33, 35, 36
		333 µg	37.0	2.6	1.3	35 U M, 36 U M, 40 U M
		1000 µg	35.0	3.0	1.3	35 U M, 32 U M, 38 U M
		2500 µg	32.3	2.9	1.2	29 U M, 34 U M, 34 U M
		5000 µg	37.0	2.6	1.3	38 U M, 39 U M, 34 U M
	Deionised water Untreated Control		28.0 31.3	11.4 4.5		33, 36, 15 27, 36, 31
TA 100	Lyso-Phospholipase	33 µg	157.7	9.1	0.9	148, 159, 166
		100 µg	170.7	13.6	1.0	169, 158, 185
		333 µg	160.3	3.2	0.9	164 U M, 159 U M, 158 U M
		1000 µg	153.3	10.4	0.9	145 U M, 150 U M, 165 U M
		2500 µg	142.0	7.0	0.8	135 U M, 142 U M, 149 U M
		5000 µg	136.3	5.1	0.8	135 U M, 132 U M, 142 U M
	Deionised water Untreated Control		170.7 150.0	10.3 12.3		162, 168, 182 136, 159, 155
TA 102	Lyso-Phospholipase	33 µg	537.0	57.2	0.9	502, 506, 603
		100 µg	587.7	12.4	1.0	580, 581, 602
		333 µg	585.3	8.1	1.0	578 U M, 594 U M, 584 U M
		1000 µg	581.0	2.0	1.0	579 U M, 581 U M, 583 U M
		2500 µg	574.0	6.2	1.0	581 U M, 569 U M, 572 U M
		5000 µg	575.0	10.8	1.0	578 U M, 563 U M, 584 U M
	Deionised water Untreated Control		571.7 555.0	21.4 29.7		583, 547, 585 521, 568, 576

Key to Plate Postfix Codes

U Air bubbles
M Manual count

Study Name: 1155101
 Experiment: 1155101 HV2 Pre
 Assay Conditions:

Study Code: CCR-RCC 1155101
 Date Plated: 11/02/2008
 Date Counted: 14/02/2008

With metabolic activation

Strain	Compound	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts
TA 1535	2-AA	2.5 µg	184.7	21.2	10.3	191, 161, 202
TA 1537	2-AA	2.5 µg	111.3	13.3	5.9	126, 108, 100
TA 98	2-AA	2.5 µg	872.0	23.3	31.1	897, 851, 868
TA 100	2-AA	2.5 µg	1204.3	58.7	7.1	1186, 1270, 1157
TA 102	2-AA	10.0 µg	2214.3	23.7	3.9	2189, 2236, 2218

Key to Positive Controls

2-AA 2-aminoanthracene

RCC-CCR STUDY NUMBER 1155102

IN VITRO

**CHROMOSOME ABERRATION TEST
IN CHINESE HAMSTER V79 CELLS
WITH
LYSO-PHOSPHOLIPASE**

REPORT

Study Completion Date:

April 25, 2008



1 COPY OF THE GLP CERTIFICATE



Gute Laborpraxis/Good Laboratory Practice

GLP-Bescheinigung/Statement of GLP Compliance

(gemäß/according to § 19b Abs. 1 Chemikaliengesetz)

HESSEN



Eine GLP-Inspektion zur Überwachung der Einhaltung der GLP-Grundsätze gemäß Chemikaliengesetz bzw. Richtlinie 88/320/EG wurde durchgeführt in

Assessment of conformity with GLP according to Chemikaliengesetz and Directive 88/320/EEC at:

Prüfeinrichtung/Test facility Prüfstandort/Test site

RCC – Cytotest Cell Research GmbH
RCC – Cytotest Cell Research GmbH
In den Leppsteinswiesen 19
64380 Rossdorf

(Unverwechselbare Bezeichnung und Adresse/Unequivocal name and address)

Prüfungen nach Kategorien/Areas of Expertise (gemäß/according chem VwV-GLP Nr. 5.3/OECD guidance)

2 Prüfungen zur Bestimmung der toxikologischen Eigenschaften
3 Prüfungen zur Bestimmung der erbgutverändernden Eigenschaften (in vitro und in vivo)
6 Prüfungen zur Bestimmung von Rückständen
8 Analytische Prüfungen an biologischen Materialien
9 Virussicherheitsprüfungen

2 Toxicity studies
3 Mutagenicity studies
6 Residues
8 Analytical studies on biological materials
9 Virus validation studies

02.09.2006

Datum der Inspektion/Date of Inspection
(Tag Monat Jahr/day month year)

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.

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

**Hess. Ministerium für Umwelt, ländlichen Raum und Verbraucherschutz,
Mainzer Straße 80 D65189 Wiesbaden**

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

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3 PREFACE

3.1 General

Title: *In vitro* Chromosome Aberration Test
in Chinese Hamster V79 Cells
with Lyso-Phospholipase

Sponsor: AB Enzymes
Feldbergstrasse 78
64293 Darmstadt
Germany

Study Monitor:

Test Facility: RCC
Cytotest Cell Research GmbH (RCC-CCR)
In den Leppsteinswiesen 19
64380 Rossdorf
Germany

3.2 Responsibilities

Study Director:
Deputy Study Director:
Management:
Head of
Quality Assurance Unit:

3.3 Schedule

Experimental Starting Date: January 30, 2008

Experimental Completion Date: March 26, 2008

3.4 Project Staff Signatures

Study Director

Management

3.5 Good Laboratory Practice

The study was performed in compliance with:

"Chemikaliengesetz" (Chemicals Act) of the Federal Republic of Germany, "Anhang 1" (Annex 1), dated July 25, 1994 ("BGBl. I 1994", pp. 1703), last revision dated June 27, 2002.

"OECD Principles of Good Laboratory Practice", as revised in 1997 [C(97)186/Final].

3.6 Guidelines

This study followed the procedures indicated by the following internationally accepted guidelines and recommendations:

Ninth Addendum to the OECD Guidelines for Testing of Chemicals, February 1998, adopted July 21, 1997, Guideline No. 473 "*In vitro* Mammalian Chromosome Aberration Test".

Commission Directive 2000/32/EC, L1362000, Annex 4A: "Mutagenicity – *In vitro* Mammalian Chromosome Aberration Test", dated May 19, 2000.

3.7 Archiving

RCC Cytotest Cell Research GmbH will archive the following data for 15 years:

Raw data, study plan, report, and a sample of the test item.

Microscopic slides will be archived for at least 12 years.

No data will be discarded without the sponsor's consent.

3.8 Deviations from the Study Plan

There were no deviations from the study plan.

4 STATEMENT OF COMPLIANCE

Study Number: 1155102

Test Item: Lyso-Phospholipase

Study Director:

Title: *In vitro* Chromosome Aberration Test
in Chinese Hamster V79 Cells
with Lyso-Phospholipase

This study performed in the test facility of RCC Cytotest Cell Research GmbH was conducted in compliance with Good Laboratory Practice Regulations:

"Chemikaliengesetz" (Chemicals Act) of the Federal Republic of Germany, "Anhang 1" (Annex 1), dated July 25, 1994 ("BGBl. I 1994", pp. 1703), last revision dated June 27, 2002.

"OECD Principles of Good Laboratory Practice", as revised in 1997 [C(97)186/Final].

There were no circumstances that may have affected the quality or integrity of the study.

Study Director

5 STATEMENT OF QUALITY ASSURANCE UNIT

Study Number: 1155102
Test Item: Lyso-Phospholipase
Study Director:
Title: *In vitro* Chromosome Aberration Test
in Chinese Hamster V79 Cells
with Lyso-Phospholipase

The general facilities and activities of RCC Cytotest Cell Research GmbH are inspected periodically and the results are reported to the responsible person and the Management.

Study procedures were inspected periodically. The study plan and this report were audited by the Quality Assurance Unit. The dates are given below.

Phases and Dates of QAU Inspections/ Audits		Dates of Reports to the Study Director and to Management
Study Plan:	January 22, 2008	January 22, 2008
Study Inspection: (initial weight, preparation of the stock solution)	March 05, 2008	March 05, 2008
Report:	April 16, 2008	April 16, 2008

This statement is to confirm that the present report reflects the raw data.

Head of Quality Assurance Unit

6 SUMMARY OF RESULTS

The test item Lyso-Phospholipase, dissolved in deionised water, was assessed for its potential to induce structural chromosome aberrations in V79 cells of the Chinese hamster *in vitro* in two independent experiments. The following study design was performed:

	Without S9 mix		With S9 mix
	Exp. I	Exp. II	Exp. I and II
Exposure period	4 hrs	18 hrs	4 hrs
Recovery	14 hrs	-	14 hrs
Preparation interval	18 hrs	18 hrs	18 hrs

In each experimental group two parallel cultures were set up. Per culture 100 metaphases were scored for structural chromosome aberrations.

The highest applied concentration in the pre-test on toxicity (5000 µg/mL) was chosen with respect to the current OECD Guideline 473.

Dose selection for the cytogenetic experiments was performed considering the toxicity data. The chosen treatment concentrations are described in chapter 8.6 (page 15). The scored experimental points and the results are summarised in Table 1 (page 23).

No toxic effects indicated by reduced mitotic indices and/or reduced cell numbers of below 50 % of control were observed after treatment up to the highest required test item concentration.

In both independent experiments, no biologically relevant increase in the number of cells carrying structural chromosomal aberrations was observed after treatment with the test item. However, in Experiment II in the presence of S9 mix a single significant increase (2.0 %) was observed but this value was clearly within the laboratory's historical control data range (0.0 – 4.0 % aberrant cells, excluding gaps) and is regarded as biologically irrelevant.

No relevant increase in the frequencies of polyploid metaphases was found after treatment with the test item as compared to the frequencies of the controls.

Appropriate mutagens were used as positive controls. They induced statistically significant increases ($p < 0.05$) in cells with structural chromosome aberrations.

6.1 Conclusion

In conclusion, it can be stated that under the experimental conditions reported, the test item did not induce structural chromosome aberrations as determined by the chromosome aberration test in V79 cells (Chinese hamster cell line) *in vitro*.

Therefore, Lyso-Phospholipase is considered to be non-clastogenic in this chromosome aberration test with and without S9 mix when tested up to the highest required concentration.

7 INTRODUCTION

According to national and international acts chemicals have to be tested before introduction to the market for a possible hazard to humans and the environment. Genotoxicity studies provide important information for the assessment of the mutagenic potential of these substances (1, 4). The *in vitro* Chromosome Aberration Test performed in this study is an essential part of genotoxicity test batteries of substances.

This *in vitro* test is a test for the detection of structural chromosomal aberrations. Such aberrations are frequently lethal to the damaged cells (8, 10). However, cytogenetic damage in somatic cells is an indicator of a potential to induce subtler chromosomal damage that may be compatible with cell division. Similar damage induced in germ cells may lead to heritable cytogenetic abnormalities. Heritable cytogenetic abnormalities are known to have deleterious effects in man, e.g. induction of neoplastic events or birth defects. Also, chromosome abnormalities in somatic cells may become one of the reasons why a transformed cell population may develop into cancer.

Chromosome aberrations are generally scored in first post treatment mitoses. With the majority of chemical mutagens induced structural aberrations are of the chromatid type, but chromosome type aberrations also occur.

For treatment, cell populations should be in exponential growth to guarantee that there are cells in all stages of the cell cycle (i.e. an asynchronous population). Since the normal cell cycle time is 12 hours (see page 13) and the guidelines require fixation times of about 1.5-fold of the normal cell cycle, a fixation time of around 18 hours is appropriate. Because there may be chemicals which induce a very extensive mitotic delay at clastogenic concentrations or may be clastogenic only when cells have passed through more than one cell cycle after the beginning of treatment an additional later sampling time (28 hours) should be included (3). Due to the limited capacity of the V79 cells for metabolic activation of potential mutagens an exogenous metabolic activation system is included (7).

The frequency of polyploid and endoreduplicated cells should also be scored so that the level in control cultures can be monitored and their induction by the test item can be recorded especially when a late sampling time is used.

To validate the test reference mutagens were tested in parallel to the test item.

7.1 Aims of the Study

This *in vitro* test was performed to assess the potential of Lyso-Phospholipase to induce structural chromosome aberrations. Evaluation of cytogenetic damage induced in V79 cells (cell line from the lung of the Chinese Hamster) in the absence and the presence of metabolic activation was performed in two independent experiments at one preparation interval (18 hours) in Experiment I and at two preparation intervals (18 hours and 28 hours) in Experiment II.

8 MATERIALS AND METHODS

8.1 Test Item

Internal RCC-CCR Test Item Number: S 837411

The test item and the information concerning the test item were provided by the sponsor.

Identity:	Lyso-Phospholipase
Batch No.:	LP 07102 A3
Aggregate state at room temperature:	Solid
* Colour:	Pale brown
Purity:	Not indicated by the sponsor
Stability in solvent:	Stable in water for approx.: 1 day at room temperature 5 days in refrigerator 1 year in freezer
Storage:	At room temperature, moisture protected
Expiration Date:	November 2009

On the day of the experiment (immediately before treatment), the test item was dissolved in deionised water. The final concentration of deionised water in the culture medium was 10 % (v/v). The solvent was chosen to its solubility properties and its relative non-toxicity to the cell cultures.

*As determined by RCC-CCR Laboratory Staff

8.2 Controls

8.2.1 Solvent Controls

Concurrent solvent controls (deionised water) were performed.

8.2.2 Positive Control Substances

Without metabolic activation

Name: EMS; ethylmethane sulfonate
Supplier: ACROS ORGANICS, 2440 Geel, Belgium
Purity: $\geq 98\%$
Lot no.: A0236026
Expiration Date: April 2008
Dissolved in: Nutrient medium
Final Concentration: 500 - 900 $\mu\text{g}/\text{mL}$ (4.0 - 7.2 mM)

Solutions were prepared on the day of experiment. The stability of the positive control substance in solution was proven by the mutagenic response in the expected range.

With metabolic activation

Name: CPA; cyclophosphamide
Supplier: Aldrich Chemie, 89555 Steinheim, Germany
Purity: $\geq 98\%$
Lot no.: 075K1661
Expiration Date: July 2009
Dissolved in: Saline (0.9 % [w/v])
Final Concentration: 1.4 - 2.0 $\mu\text{g}/\text{mL}$ (5.0 - 7.0 μM)

The dilutions of the stock solutions were prepared on the day of experiment. The stability of CPA in solution at room temperature is good. At 25° C only 3.5 % of its potency is lost after 24 hours (6).

8.3 Test System

8.3.1 Reasons for the Choice of the Cell Line V79

The V79 cell line has been used successfully for many years in *in vitro* experiments. The high proliferation rate (doubling time of clone V79/D3 in stock cultures: 12 hours, determined on January 02, 2006) and a reasonable plating efficiency of untreated cells (as a rule more than 70 %) both necessary for the appropriate performance of the study, support the use of this cell line. The cells have a stable karyotype with a modal chromosome number of 22.

Lacking metabolic activities of cells under *in vitro* conditions are a disadvantage of tests with cell cultures as many chemicals only develop a mutagenic potential when they are metabolized by the mammalian organism. However, metabolic activation of chemicals can be achieved at least partially by supplementing the cell cultures with liver microsome preparations (S9 mix).

8.3.2 Cell Cultures

Large stocks of the V79 cell line (supplied by Laboratory for Mutagenicity Testing, LMP, Technical University Darmstadt, 64287 Darmstadt, Germany) were stored in liquid nitrogen in the cell bank of RCC Cytotest Cell Research GmbH allowing the repeated use of the same cell culture batch in experiments. Before freezing each batch was screened for mycoplasma contamination and checked for karyotype stability. Consequently, the parameters of the experiments remain similar because of standardized characteristics of the cells.

Thawed stock cultures were propagated at 37° C in 80 cm² plastic flasks (GREINER, 72632 Frickenhausen, Germany). About 5 x 10⁵ cells per flask were seeded into 15 mL of MEM (Minimal Essential Medium; SEROMED; 12247 Berlin, Germany) supplemented with 10 % fetal calf serum (FCS; PAA Laboratories GmbH, 35091 Cölbe, Germany). The cells were sub-cultured twice weekly. The cell cultures were incubated at 37° C in a humidified atmosphere with 1.5 % carbon dioxide (98.5 % air).

8.4 Mammalian Microsomal Fraction S9 Mix

8.4.1 S9 (Preparation by RCC Cytotest Cell Research)

Phenobarbital/ β -Naphthoflavone induced rat liver S9 was used as the metabolic activation system. The S9 was prepared from 8 - 12 weeks old male Wistar Hanlbm rats, weight approx. 220 - 320 g induced by applications of 80 mg/kg b.w. Phenobarbital i.p. (Desitin; 22335 Hamburg, Germany) and β -Naphthoflavone p.o. (Aldrich, 89555 Steinheim, Germany) each, on three consecutive days. The livers were prepared 24 hours after the last treatment.

The S9 fractions were produced by dilution of the liver homogenate with a KCl solution (1:3 parts) followed by centrifugation at 9000 g. Aliquots of the supernatant were frozen and stored in ampoules at -80° C. Small numbers of the ampoules were kept at -20°C for up to one week.

The protein concentration was 28.3 mg/mL (Lot no. 191007) in the pre-test and in Experiment I and 31.0 mg/mL (Lot no. 150208) in Experiment II.

8.4.2 S9 Mix

An appropriate quantity of S9 supernatant was thawed and mixed with S9 cofactor solution to result in a final protein concentration of 0.75 mg/mL in the cultures. Cofactors were added to the S9 mix to reach the following concentrations:

8 mM MgCl₂
33 mM KCl
5 mM glucose-6-phosphate
4 mM NADP

in 100 mM sodium-ortho-phosphate-buffer, pH 7.4.

During the experiment the S9 mix was stored in an ice bath. The S9 mix preparation was performed according to Ames et al. (1).

8.5 Range-finder

A pre-test on cell growth inhibition with 4 hours and 24 hours treatment was performed in order to determine the toxicity of the test item (2). Cytotoxicity was determined using concentrations separated by no more than a factor of 2 - $\sqrt{10}$. The general experimental conditions in this pre-test were the same as described below for the cytogenetic main experiment. The following method was used:

In a quantitative assessment, exponentially growing cell cultures (seeding about 40,000 cells/ slide, with regard to the culture time 48 hours) were treated with the test item for simulating the conditions of the main experiment. A qualitative evaluation of cell number and cell morphology was made 4 hours and 24 hours after start of treatment. The cells were stained 24 hours after start of treatment. Using a 400-fold microscopic magnification the cells were counted in 10 coordinate defined fields of the slides (2 slides per treatment group). The cell number of the treatment groups is given as % cells in relation to the control.

8.6 Dose Selection

The highest concentration used in the cytogenetic experiments was chosen with regard to the current OECD Guideline for *in vitro* mammalian cytogenetic tests requesting for the top concentration clear toxicity with reduced cell numbers or mitotic indices below 50 % of control, whichever is the lowest concentration, and/or the occurrence of precipitation. In case of non-toxicity the maximum concentration should be 5 mg/mL, 5 µL/mL or 10 mM, whichever is the lowest, if formulation in an appropriate solvent is possible.

In the pre-test 5000 µg/mL of Lyso-Phospholipase was applied as top concentration for treatment of the cultures. Test item concentrations between 39.1 and 5000 µg/mL (with and without S9 mix) were chosen for the evaluation of cytotoxicity.

Using reduced cell numbers as an indicator for toxicity in the pre-test, no cytotoxicity indicated by reduced cell numbers was observed up to the highest test item concentration. Considering the toxicity data of the pre-test, 5000 µg/mL (with and without S9 mix) was chosen as top concentration in Experiment I.

Dose selection of Experiment II was also influenced by test item toxicity. In the range finding experiment no reduced cell numbers were observed after 24 hours exposure up to the highest concentration. Therefore, 5000 µg/mL was chosen as top treatment concentration for continuous exposure in the absence of S9 mix. In the presence of S9 mix 5000 µg/mL was chosen as top treatment concentration with respect to the results obtained in Experiment I.

Doses applied in the Chromosome aberration test with Lyso-Phospholipase

Preparation interval	Exposure period	Exp.	Concentration in µg/mL					
			Without S9 mix					
18 hrs	4 hrs	I	156.3	312.5	625.0	1250.0	2500.0	5000.0
18 hrs	18 hrs	II	156.3	312.5	625.0	1250.0	2500.0	5000.0
			With S9 mix					
18 hrs	4 hrs	I	156.3	312.5	625.0	1250.0	2500.0	5000.0
18 hrs	4 hrs	II	156.3	312.5	625.0	1250.0	2500.0	5000.0

Scored experimental points are shown in bold characters

^P Precipitation occurred 4 hours after start of treatment

8.7 Experimental Performance

8.7.1 Seeding of the Cultures

Exponentially growing stock cultures more than 50 % confluent were treated with trypsin-EDTA-solution at 37° C for approx. 5 minutes. Then the enzymatic treatment was stopped by adding complete culture medium and a single cell suspension was prepared. The trypsin concentration for all sub-culturing steps was 0.5 % (w/v) in Ca-Mg-free salt solution (Invitrogen GIBCO, 76131 Karlsruhe, Germany).

Prior to the trypsin treatment the cells were rinsed with Ca-Mg-free salt solution. The Ca-Mg-free salt solution was composed as follows (per litre):

NaCl	8000 mg
KCl	200 mg
KH ₂ P ₀ ₄	200 mg
Na ₂ HP ₀ ₄	150 mg

The cells were seeded into Quadriperm dishes (Heraeus, 63450 Hanau, Germany) that contained microscopic slides (at least 2 chambers per dish and test group). In each chamber 1×10^4 - 6×10^4 cells were seeded with regard to the preparation time. The medium was MEM with 10 % FCS (complete medium).

8.7.2 Treatment

Exposure period 4 hours

The culture medium of exponentially growing cell cultures was replaced with serum-free medium (for treatment with S9 mix) or complete medium (for treatment without S9 mix) with 10 % FCS (v/v), containing the test item. For the treatment with metabolic activation 50 µL S9 mix per mL medium were used. Concurrent solvent and positive controls were performed. After 4 hours the cultures were washed twice with "Saline G" and then the cells were cultured in complete medium for the remaining culture time.

The "Saline G" solution was composed as follows (per litre):

NaCl	8000 mg
KCl	400 mg
Glucose x H ₂ O	1100 mg
Na ₂ HP ₀ ₄ x 7H ₂ O	290 mg
KH ₂ P ₀ ₄	150 mg

pH was adjusted to 7.2

All cultures were incubated at 37° C in a humidified atmosphere with 1.5 % CO₂ (98.5 % air).

8.7.3 Preparation of the Cultures

Colcemid was added (0.2 µg/mL culture medium) to the cultures 15.5 hours after the start of the treatment. The cells on the slides were treated 2.5 hours later, in the chambers with hypotonic solution (0.4 % KCl) for 20 min at 37° C. After incubation in the hypotonic solution the cells were fixed with a mixture of methanol and glacial acetic acid (3:1 parts, respectively). Per experiment two slides per group were prepared. After preparation the cells were stained with Giemsa (E. Merck, 64293 Darmstadt, Germany).

8.7.4 Evaluation of Cell Numbers

For evaluation of cytotoxicity indicated by reduced cell numbers two additional cultures per test item and solvent control group, not treated with colcemid, were set up in parallel. These cultures were stained after 18 hours, in order to determine microscopically the cell number within 10 defined fields per coded slide. The cell number of the treatment groups is given in percentage compared to the respective solvent control.

8.7.5 Analysis of Metaphase Cells

Evaluation of the cultures was performed (according to standard protocol of the "Arbeitsgruppe der Industrie, Cytogenetik" [5]) using NIKON microscopes with 100x oil immersion objectives. Breaks, fragments, deletions, exchanges, and chromosome disintegrations were recorded as structural chromosome aberrations. Gaps were recorded as well but not included in the calculation of the aberration rates. 100 well spread metaphases per culture were scored for cytogenetic damage on coded slides.

Only metaphases with characteristic chromosome numbers of 22 ± 1 were included in the analysis. To describe a cytotoxic effect the mitotic index (% cells in mitosis) was determined. In addition, the number of polyploid cells in 500 metaphases per culture was determined (% polyploid metaphases; in the case of this aneuploid cell line polyploid means a near tetraploid karyotype).

8.8 Data Recording

The data generated were recorded in the raw data file. The results are presented in tabular form, including experimental groups with the test item, solvent, and positive controls.

8.9 Acceptability of the Test

The chromosome aberration test performed in our laboratory is considered acceptable if it meets the following criteria:

- a) The number of structural aberrations found in the solvent controls falls within the range of the laboratory's historical control data range: 0.0 - 4.0 % aberrant cells, excluding gaps.
- b) The positive control substances should produce significant increases in the number of cells with structural chromosome aberrations, which are within the range of the laboratory's historical control data:

Test group Final concentration	Aberrant cells in % (excl. gaps) range	Test group Final concentration	Aberrant cells in % (excl. gaps) range
Without S9 mix		With S9 mix	
EMS 200 – 900 µg/mL	7.5 - 68.0 %	CPA 1.0 – 2.0 µg/mL	6.5 - 100.0 %

8.10 Evaluation of Results

A test item is classified as non-clastogenic if:

- the number of induced structural chromosome aberrations in all scored dose groups is in the range of the laboratory's historical control data range (0.0 - 4.0 % aberrant cells, excluding gaps).

and/or

- no significant increase of the number of structural chromosome aberrations is observed.

A test item is classified as clastogenic if:

- the number of induced structural chromosome aberrations is not in the range of the laboratory's historical control data range (0.0 - 4.0 % aberrant cells, excluding gaps).

and

- either a concentration-related or a significant increase of the number of structural chromosome aberrations is observed.

Statistical significance was confirmed by means of the Fisher's exact test (9) ($p < 0.05$). However, both biological and statistical significance should be considered together. If the criteria mentioned above for the test item are not clearly met, the classification with regard to the historical data and the biological relevance is discussed and/or a confirmatory experiment is performed.

Although the inclusion of the structural chromosome aberrations is the purpose of this study, it is important to include the polyploids and endoreduplications. The following criterion is valid:

A test item can be classified as aneugenic if:

- the number of induced numerical aberrations is not in the range of the laboratory's historical control data range (0.0 – 5.2 % polyploid cells).

9 RESULTS AND DISCUSSION

The test item Lyso-Phospholipase, dissolved in deionised water, was assessed for its potential to induce structural chromosome aberrations in V79 cells of the Chinese hamster *in vitro* in the absence and the presence of metabolic activation by S9 mix.

Two independent experiments were performed. In Experiment I, the exposure period was 4 hours with and without metabolic activation. In Experiment II the exposure period was 4 hours with S9 mix and 18 hours without S9 mix. The chromosomes were prepared 18 hours after start of treatment with the test item.

In each experimental group two parallel cultures were set up. Per culture 100 metaphases were scored for structural chromosome aberrations.

In a range finding pre-test on toxicity cell numbers were scored 24 hours after start of treatment as an indicator for cytotoxicity. Concentrations between 39.1 and 5000 µg/mL were applied. No toxic effects were observed up to the highest required concentration in the absence and presence of S9 mix (see Table 2, page 24). Neither precipitation in culture medium nor relevant influence of the test item on the pH value or osmolarity was observed (solvent control 300 mOsm, pH 7.3 versus 307 mOsm and pH 7.3 at 5000 µg/mL).

In both independent experiments no precipitation of the test item in culture medium was observed.

In this study, neither reduced mitotic indices nor reduced cell numbers could be observed up to the highest required concentration of the test item (see Table 3, 4, and 7, pages 25, 26, and 29).

In both experiments in the absence and presence of S9 mix, a no biologically relevant increase in the number of cells carrying structural chromosome aberrations was observed (see Table 5 – 6 and Table 8 – 9, pages 27, 28, 30, and 31). The aberration rates of the cells after treatment with the test item (0.0 - 2.0 % aberrant cells, excluding gaps) were within the range of the solvent control values (0.0 - 2.0 % aberrant cells, excluding gaps) and within the range of the laboratory's historical control data range (0.0 - 4.0 % aberrant cells, excluding gaps). A single significant increase was observed in Experiment II in the presence of S9 mix after treatment with 5000 µg/mL (see Table 9 and 11, pages 31 and 32). Although this increase of 2.0 % aberrant cells was statistically significant compared to the low response (0.0 % aberrant cells) in the solvent control data, this response is within the historical control data range (0.0 - 4.0 % aberrant cells). Therefore, this observation has to be regarded as biologically irrelevant.

Table 4 and 7, pages 26 and 29, show the occurrence of polyploid metaphases. In both experiments, no biologically relevant increase in the rate of polyploid metaphases was found after treatment with the test item (1.2 - 3.5 %) as compared to the rates of the solvent controls (1.8 - 3.7 %).

In both experiments, either EMS (500 or 900 µg/mL) or CPA (1.4 or 2.0 µg/mL) were used as positive controls and showed distinct increases in the number of cells with structural chromosome aberrations.

In conclusion, it can be stated that under the experimental conditions reported, the test item Lyso-Phospholipase did not induce structural chromosome aberrations in V79 cells (Chinese hamster cell line) when tested up to the highest required concentration.

10 DISTRIBUTION OF THE REPORT

Sponsor	2x (1x copy, 1x electronic copy as PDF-file)
Study Director	1x (original)

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12 ANNEX I: TABLES OF RESULTS

12.1 Summary of Results

Table 1: Summary of results of the chromosome aberration study with Lyso-Phospholipase

Exp.	Preparation interval	Test item concentration in µg/mL	Polyploid cells in %	Cell numbers in % of control	Mitotic indices in %		Aberrant cells in %		
					of control	incl. gaps*	excl. gaps*	with exchanges	
Exposure period 4 hrs without S9 mix									
I	18 hrs	Solvent control ¹	3.2	100.0	100.0	0.0	0.0	0.0	
		Positive control ²	2.9	n.t.	108.3	10.5	10.0^S	3.5	
		1250.0	2.6	76.5	102.7	0.5	0.5	0.0	
		2500.0	2.6	106.6	101.2	0.5	0.0	0.0	
		5000.0	2.1	108.6	97.6	1.0	1.0	0.5	
Exposure period 18 hrs without S9 mix									
II	18 hrs	Solvent control ¹	1.8	100.0**	100.0	2.5	1.5	0.0	
		Positive control ³	0.7	n.t.	94.1	24.0	21.5^S	6.5	
		1250.0	2.2	111.5**	108.1	1.5	1.5	0.0	
		2500.0	1.8	104.7**	111.6	2.5	1.0	0.0	
		5000.0	1.2	85.5**	111.9	1.5	1.5	0.0	
Exposure period 4 hrs with S9 mix									
I	18 hrs	Solvent control ¹	3.7	100.0	100.0	2.5	2.0	1.0	
		Positive control ⁴	2.9	n.t.	113.7	13.0	12.0^S	5.5	
		1250.0	3.5	69.2	102.5	0.5	0.0	0.0	
		2500.0	3.4	78.0	106.5	2.0	1.5	0.0	
		5000.0	3.2	71.1	111.2	0.5	0.5	0.0	
II	18 hrs	Solvent control ¹	2.1	100.0	100	1.5	0.0	0.0	
		Positive control ⁵	1.7	n.t.	92.4	13.5	13.0^S	2.5	
		1250.0	1.6	108.4	93.0	1.0	1.0	0.0	
		2500.0	1.8	89.5	87.6	2.0	1.0	0.0	
		5000.0	2.5	74.0	91.9	3.0	2.0^S	0.5	

* Inclusive cells carrying exchanges

** Cell count on spread slides

n.t. Not tested

^S Aberration frequency statistically significant higher than corresponding control values¹ Deionised water 10.0 % (v/v)² EMS 900.0 µg/mL³ EMS 500.0 µg/mL⁴ CPA 1.4 µg/mL⁵ CPA 2.0 µg/mL

12.2 Pre-Test on Toxicity

In the pre-test the toxicity of the test item was examined using the determination of the cell number. Cell numbers of two cultures (10 coordinate defined fields per culture) were determined for each experimental group.

Table 2: Cytotoxicity of Lyso-Phospholipase to cultures of Chinese hamster cell line V79

Without S9 mix, 4 hrs exposure			With S9 mix, 4 hrs exposure		
Concentration in µg/mL	Number of cells	% of solvent control	Concentration in µg/mL	Number of cells	% of solvent control
Solvent control	1151	100.0	Solvent control	833	100.0
39.1	1016	88.3	39.1	729	87.5
78.1	993	86.3	78.1	761	91.4
156.3	960	83.4	156.3	981	117.8
312.5	774	67.3	312.5	830	99.6
625.0	1002	87.0	625.0	855	102.6
1250.0	880	76.5	1250.0	1010	121.3
2500.0	1001	87.0	2500.0	932	111.9
5000.0	996	86.5	5000.0	969	116.4

Without S9 mix; 24 hrs exposure

Concentration in µg/mL	Number of cells	% of solvent control
Solvent control	639	100.0
39.1	620	97.0
78.1	484	75.8
156.3	536	83.9
312.5	556	87.0
625.0	564	88.3
1250.0	646	101.1
2500.0	878	137.5
5000.0 ^P	721	112.8

^P Precipitation occurred at the end of treatment

12.3 Experiments I and II: Determination of Toxicity

The toxicity of the test item was examined using the determination of the cell number. Cell numbers of two cultures (10 coordinate defined fields per culture) were determined for each experimental group, except the positive control.

Table 3: Number of cells in % of solvent control

Without S9 mix							
Experiment I: 4 hrs exposure				Experiment II: continuous exposure			
Preparation interval	Concentration in µg/mL	Number of cells	Cells in % of solvent control	Preparation interval	Concentration in µg/mL	Number of cells*	Cells in % of solvent control
18 hrs	Solvent control	1061	100.0	18 hrs	Solvent control	709	100.0
"	156.3	855	80.6	"	156.3	768	108.3
"	312.5	924	87.1	"	312.5	644	90.8
"	625.0	829	78.1	"	625.0	658	92.7
"	1250.0	812	76.5	"	1250.0	791	111.5
"	2500.0	1131	106.6	"	2500.0	743	104.7
"	5000.0	1153	108.6	"	5000.0	606	85.5
With S9 mix							
Experiment I: 4 hrs exposure				Experiment II: 4 hrs exposure			
Preparation interval	Concentration in µg/mL	Number of cells	Cells in % of solvent control	Preparation interval	Concentration in µg/mL	Number of cells	Cells in % of solvent control
18 hrs	Solvent control	1004	100.0	18 hrs	Solvent control	467	100.0
"	156.3	837	83.3	"	156.3	509	109.1
"	312.5	710	70.7	"	312.5	432	92.5
"	625.0	842	83.8	"	625.0	391	83.8
"	1250.0	695	69.2	"	1250.0	506	108.4
"	2500.0	783	78.0	"	2500.0	418	89.5
"	5000.0	714	71.1	"	5000.0	345	74.0

Experimental groups scored for cytogenetic damage are shown in bold characters

* Cell count on spread slides

P Precipitation occurred 4 hours after start of treatment

12.4 Experiment I

Table 4: Number of polyploid cells and mitotic index;
preparation interval 18 hrs with and without S9 mix

Treatment group	Conc. per mL	S9 mix	Exposure period/ Recovery	Polyploid cells*				Mitotic indices**			
				Culture 1	Culture 2	Total	%	Absolute 1	Absolute 2	Mean	%***
Solv. control [#]	10.0 %	-	4 / 14 hrs	19	13	32	3.2	15.8	18.1	17.0	100.0
Pos. control ^{###}	900.00 µg	-	4 / 14 hrs	14	15	29	2.9	18.4	18.3	18.4	108.3
Test item	1250.0 µg	-	4 / 14 hrs	14	12	26	2.6	16.7	18.1	17.4	102.7
"	2500.0 µg	-	4 / 14 hrs	13	13	26	2.6	17.8	16.5	17.2	101.2
"	5000.0 µg	-	4 / 14 hrs	8	13	21	2.1	16.1	17.0	16.6	97.6
Solv. control [#]	10.0 %	+	4 / 14 hrs	16	21	37	3.7	15.4	16.8	16.1	100.0
Pos. control ^{###}	1.4 µg	+	4 / 14 hrs	12	17	29	2.9	18.1	18.5	18.3	113.7
Test item	1250.0 µg	+	4 / 14 hrs	16	19	35	3.5	17.1	15.9	16.5	102.5
"	2500.0 µg	+	4 / 14 hrs	19	15	34	3.4	16.0	18.3	17.2	106.5
"	5000.0 µg	+	4 / 14 hrs	18	14	32	3.2	17.6	18.2	17.9	111.2

* The number of polyploid cells was determined of each test group in a sample of 500 cells per culture

** The mitotic index was determined in a sample of 1000 cells per culture of each test group in %

*** For the positive control groups and the test item groups, the relative values of the mitotic index are related to the solvent controls

Deionised water

EMS

CPA

Table 5: Structural chromosome aberrations Experiment I;
preparation interval 18 hrs without S9 mix: exposure period 4 hrs

Slide no.	Cells scored	% Aberrant cells			Aberrations											
		incl. gaps*	excl. gaps*	with ex-changes	Gaps		Chromatid type				Chromosome type				Other	
					g	ig	b	f	d	ex	ib	if	id	cx	ma	cd
Without S9 mix																
Solvent control: Deionised water 10.0 %																
1	100				0	0	0	0	0	0	0	0	0	0	0	0
2	100				0	0	0	0	0	0	0	0	0	0	0	0
1 + 2	200	0.0	0.0	0.0	0	0	0	0	0	0	0	0	0	0	0	0
Positive control: EMS 900.00 µg / mL																
1	100				0	0	3	1	0	5	1	0	0	0	0	0
2	100				2	0	3	1	0	2	5	0	0	0	0	0
1 + 2	200	10.5	10.0	3.5	2	0	6	2	0	7	6	0	0	0	0	0
Test item: 1250.0 µg / mL																
1	100				0	0	0	0	0	0	0	0	0	0	0	0
2	100				0	0	0	1	0	0	0	0	0	0	0	0
1 + 2	200	0.5	0.5	0.0	0	0	0	1	0	0	0	0	0	0	0	0
Test item: 2500.0 µg / mL																
1	100				1	0	0	0	0	0	0	0	0	0	0	0
2	100				0	0	0	0	0	0	0	0	0	0	0	0
1 + 2	200	0.5	0.0	0.0	1	0	0	0	0	0	0	0	0	0	0	0
Test item: 5000.0 µg / mL																
1	100				0	0	0	0	0	0	0	0	0	0	0	0
2	100				0	0	0	0	0	1	0	1	0	0	0	0
1 + 2	200	1.0	1.0	0.5	0	0	0	0	0	1	0	1	0	0	0	0

* Inclusive cells carrying exchanges

Abbreviations

g = gap, ig = iso-gap (gaps are achromatic lesions of chromatid or chromosome type where no or only a minimal misalignment of chromosomal material is visible), b = break, ib = iso-break, f = fragment, if = iso-fragment, d = deletion, id = iso-deletion, ma = multiple aberration (= more than 4 events in one cell [excluding gaps]), ex = chromatid type exchange, cx = chromosome type exchange, cd = chromosomal disintegration (= pulverization)

Table 6: Structural chromosome aberrations Experiment I;
preparation interval 18 hrs with S9 mix: exposure period 4 hrs

Slide no.	Cells scored	% Aberrant cells			Aberrations											
		incl. gaps*	excl. gaps*	with ex-changes	Gaps		Chromatid type				Chromosome type				Other	
					g	ig	b	f	d	ex	ib	if	id	cx	ma	cd
With S9 mix																
Solvent control: Deionised water 10.0 %																
1	100				1	0	1	0	0	2	0	0	0	0	0	0
2	100				0	0	1	0	0	0	0	0	0	0	0	0
1 + 2	200	2.5	2.0	1.0	1	0	2	0	0	2	0	0	0	0	0	0
Positive control: CPA 1.4 µg / mL																
1	100				1	0	6	1	0	4	0	0	0	0	0	0
2	100				1	0	9	1	0	8	2	0	0	0	1	0
1 + 2	200	13.0	12.0	5.5	2	0	15	2	0	12	2	0	0	0	1	0
Test item: 1250.0 µg / mL																
1	100				0	0	0	0	0	0	0	0	0	0	0	0
2	100				1	0	0	0	0	0	0	0	0	0	0	0
1 + 2	200	0.5	0.0	0.0	1	0	0	0	0	0	0	0	0	0	0	0
Test item: 2500.0 µg / mL																
1	100				0	0	0	0	0	0	0	0	0	0	0	0
2	100				1	0	2	0	0	0	0	1	0	0	0	0
1 + 2	200	2.0	1.5	0.0	1	0	2	0	0	0	0	1	0	0	0	0
Test item: 5000.0 µg / mL																
1	100				0	0	1	0	0	0	0	0	0	0	0	0
2	100				0	0	0	0	0	0	0	0	0	0	0	0
1 + 2	200	0.5	0.5	0.0	0	0	1	0	0	0	0	0	0	0	0	0

* Inclusive cells carrying exchanges

Abbreviations

g = gap, ig = iso-gap (gaps are achromatic lesions of chromatid or chromosome type where no or only a minimal misalignment of chromosomal material is visible), b = break, ib = iso-break, f = fragment, if = iso-fragment, d = deletion, id = iso-deletion, ma = multiple aberration (= more than 4 events in one cell [excluding gaps]), ex = chromatid type exchange, cx = chromosome type exchange, cd = chromosomal disintegration (= pulverization)

12.5 Experiment II

Table 7: Number of polyploid cells and mitotic index;
preparation interval 18 hrs with and without S9 mix

Treatment group	Conc. per mL	S9 mix	Exposure period/ Recovery	Polyploid cells*				Mitotic indices**			
				Culture 1	Culture 2	Total	%	Absolute 1	Absolute 2	Mean	%***
Solv. control [#]	10.0 %	-	18 / - hrs	8	10	18	1.8	16.5	15.5	16.0	100.0
Pos. control ^{###}	500.0 µg	-	18 / - hrs	7	0	7	0.7	15.7	14.4	15.1	94.1
Test item	1250.0 µg	-	18 / - hrs	14	8	22	2.2	17.5	17.1	17.3	108.1
"	2500.0 µg	-	18 / - hrs	14	4	18	1.8	17.4	18.3	17.9	111.6
"	5000.0 µg	-	18 / - hrs	9	3	12	1.2	18.2	17.6	17.9	111.9
Solv. control [#]	10.0 %	+	4 / 14 hrs	10	11	21	2.1	17.9	17.7	17.8	100.0
Pos. control ^{###}	2.0 µg	+	4 / 14 hrs	11	6	17	1.7	16.5	16.4	16.5	92.4
Test item	1250.0 µg	+	4 / 14 hrs	11	5	16	1.6	17.0	16.1	16.6	93.0
"	2500.0 µg	+	4 / 14 hrs	13	5	18	1.8	13.9	17.3	15.6	87.6
"	5000.0 µg	+	4 / 14 hrs	8	17	25	2.5	15.1	17.6	16.4	91.9

* The number of polyploid cells was determined of each test group in a sample of 500 cells per culture

** The mitotic index was determined in a sample of 1000 cells per culture of each test group in %

*** For the positive control groups and the test item groups, the relative values of the mitotic index are related to the solvent controls

Deionised water

EMS

CPA

Table 8: Structural chromosome aberrations Experiment II;
preparation interval 18 hrs without S9 mix: exposure period 18 hrs

Slide no.	Cells scored	% Aberrant cells			Aberrations											
		incl. gaps*	excl. gaps*	with ex-changes	Gaps		Chromatid type				Chromosome type				Other	
					g	ig	b	f	d	ex	ib	if	id	cx	ma	cd
Without S9 mix																
Solvent control: Deionised water 10.0 %																
1	100				0	0	0	0	0	0	0	0	0	0	0	0
2	100				2	0	2	0	0	0	1	0	0	0	0	0
1 + 2	200	2.5	1.5	0.0	2	0	2	0	0	0	1	0	0	0	0	0
Positive control: EMS 500.0 µg / mL																
1	100				2	0	13	0	0	3	4	0	0	0	0	0
2	100				3	0	18	0	0	10	3	1	0	0	0	0
1 + 2	200	24.0	21.5	6.5	5	0	31	0	0	13	7	1	0	0	0	0
Test item: 1250.0 µg / mL																
1	100				0	0	1	0	0	0	0	0	0	0	0	0
2	100				0	0	2	0	0	0	0	0	0	0	0	0
1 + 2	200	1.5	1.5	0.0	0	0	3	0	0	0	0	0	0	0	0	0
Test item: 2500.0 µg / mL																
1	100				1	0	1	0	0	0	0	0	0	0	0	0
2	100				2	0	0	0	0	0	1	0	0	0	0	0
1 + 2	200	2.5	1.0	0.0	3	0	1	0	0	0	1	0	0	0	0	0
Test item: 5000.0 µg / mL																
1	100				0	0	2	0	0	0	1	0	0	0	0	0
2	100				0	0	1	0	0	0	0	0	0	0	0	0
1 + 2	200	1.5	1.5	0.0	0	0	3	0	0	0	1	0	0	0	0	0

* Inclusive cells carrying exchanges

Abbreviations

g = gap, ig = iso-gap (gaps are achromatic lesions of chromatid or chromosome type where no or only a minimal misalignment of chromosomal material is visible), b = break, ib = iso-break, f = fragment, if = iso-fragment, d = deletion, id = iso-deletion, ma = multiple aberration (= more than 4 events in one cell [excluding gaps]), ex = chromatid type exchange, cx = chromosome type exchange, cd = chromosomal disintegration (= pulverization)

Table 9: Structural chromosome aberrations Experiment II;
preparation interval 18 hrs with S9 mix: exposure period 4 hrs

Slide no.	Cells scored	% Aberrant cells			Aberrations											
		incl. gaps*	excl. gaps*	with ex-changes	Gaps		Chromatid type				Chromosome type				Other	
					g	ig	b	f	d	ex	ib	if	id	cx	ma	cd
With S9 mix																
Solvent control: Deionised water 10.0 %																
1	100				2	1	0	0	0	0	0	0	0	0	0	0
2	100				0	0	0	0	0	0	0	0	0	0	0	0
1 + 2	200	1.5	0.0	0.0	2	1	0	0	0	0	0	0	0	0	0	0
Positive control: CPA 2.0 µg / mL																
1	100				1	0	2	3	0	3	2	0	0	0	2	0
2	100				0	0	10	3	0	4	5	0	0	0	0	0
1 + 2	200	13.5	13.0	2.5	1	0	12	6	0	7	7	0	0	0	2	0
Test item: 1250.0 µg / mL																
1	100				0	0	0	0	0	0	0	0	0	0	0	0
2	100				0	0	2	0	0	0	0	0	0	0	0	0
1 + 2	200	1.0	1.0	0.0	0	0	2	0	0	0	0	0	0	0	0	0
Test item: 2500.0 µg / mL																
1	100				1	0	1	0	0	0	0	0	0	0	0	0
2	100				1	0	1	0	0	0	0	0	0	0	0	0
1 + 2	200	2.0	1.0	0.0	2	0	2	0	0	0	0	0	0	0	0	0
Test item: 5000.0 µg / mL																
1	100				2	0	1	0	0	0	1	0	0	0	0	0
2	100				0	0	0	0	0	1	1	0	0	0	0	0
1 + 2	200	3.0	2.0	0.5	2	0	1	0	0	1	2	0	0	0	0	0

* Inclusive cells carrying exchanges

Abbreviations

g = gap, ig = iso-gap (gaps are achromatic lesions of chromatid or chromosome type where no or only a minimal misalignment of chromosomal material is visible), b = break, ib = iso-break, f = fragment, if = iso-fragment, d = deletion, id = iso-deletion, ma = multiple aberration (= more than 4 events in one cell [excluding gaps]), ex = chromatid type exchange, cx = chromosome type exchange, cd = chromosomal disintegration (= pulverization)

12.6 Biometry

Statistical significance at the five per cent level ($p < 0.05$) was scored by means of the Fisher's exact test. Evaluation was performed only for cells carrying aberrations excluding gaps.

Table 10: Biometry of Experiment I

	Test group versus solvent control	Preparation interval	Exposure period	S9 mix	p-value
Test group	1250.0 µg/mL	18 hrs	4 hrs	-	0.250
"	2500.0 µg/mL	18 hrs	4 hrs	-	n.c.
"	5000.0 µg/mL	18 hrs	4 hrs	-	0.125
"	1250.0 µg/mL	18 hrs	4 hrs	+	n.c.
"	2500.0 µg/mL	18 hrs	4 hrs	+	n.c.
"	5000.0 µg/mL	18 hrs	4 hrs	+	n.c.
Positive control versus solvent control					
EMS	900.0 µg/mL	18 hrs	4 hrs	-	< 0.001 ^s
CPA	1.4 µg/mL	18 hrs	4 hrs	+	< 0.001 ^s

Table 11: Biometry of Experiment II

	Test group versus solvent control	Preparation interval	Exposure period	S9 mix	p-value
Test group	1250.0 µg/mL	18 hrs	18 hrs	-	n.c.
"	2500.0 µg/mL	18 hrs	18 hrs	-	n.c.
"	5000.0 µg/mL	18 hrs	18 hrs	-	n.c.
"	1250.0 µg/mL	18 hrs	4 hrs	+	0.125
"	2500.0 µg/mL	18 hrs	4 hrs	+	0.125
"	5000.0 µg/mL	18 hrs	4 hrs	+	0.031 ^s
Positive control versus solvent control					
EMS	500.0 µg/mL	18 hrs	18 hrs	-	< 0.001 ^s
CPA	2.0 µg/mL	18 hrs	4 hrs	+	< 0.001 ^s

n.c. Not calculated as the aberration rate is equal or lower than the corresponding control rate

^s Aberration rate is statistically significant higher than the control rate

13 ANNEX II

13.1 Chromosome Aberrations: Classification and Criteria

1. Gaps

Gaps are small areas of the chromosome, which are unstained. The chromatids remain aligned as normal and the gap does not extend along the chromatid for a distance greater than the width of a chromatid. If the gap occurs on one chromatid only it is a chromatid gap (g).

2. Chromatid Breaks

Chromatid breaks (b) vary in appearance. The chromatid may remain aligned but show a gap which is too large to classify as a gap. Alternatively, the chromatid may be broken so that the broken fragment is displaced. In some cases, the fragment is not seen at all. A chromatid fragment (f) should be scored if the chromosome of origin cannot be identified. In addition, deletions can occur as a result of a break. The missing terminal end of a chromatid in the assessed metaphase is classified as deletion (d).

3. Chromosome Breaks

Chromosome breaks (ib) are breaks in both chromatids of the chromosome. A fragment with two chromatids is formed and this may be displaced by varying degrees. Breaks are distinguished from gaps by the size of the unstained region. A chromosome break is scored if the fragment is associated with a chromosome from which it was probably derived. However, fragments are often seen in isolation and are then scored as chromatid fragments (if). In addition, isodeletions can occur as a result of an isobreak. The missing terminal end of a chromosome in the assessed metaphase is classified as isodeletion (id).

4. Exchanges

Exchanges are formed by faulty rejoining of broken chromosomes and may be of the chromosome or chromatid type. Chromatid exchanges (ex) have numerous different forms but are generally not further classified. Where multiple exchanges have occurred each exchange point is counted as one chromatid exchange. Chromosome exchanges (cx) generally appear as either a dicentric or a ring form, either of which can be associated with a fragment, which if possible should be scored as part of the exchange.

5. Multiple Aberrations

If many aberrations are present in one metaphase, the exact details may not be scorable. This is particularly the case when chromosome pulverisation (cd) occurs. If the number of aberrations is greater than 4 then the cell is classified as multiple aberrant (ma).

6. Chromosome Number

If the chromosome (centromere) number is 22 ± 1 then it is classified as a diploid cell and scored for aberrations. If less than 22 ± 1 chromosomes are counted then the cell is ignored under the assumption, that some chromosomes may have been lost for technical reasons. If greater than 22 ± 1 chromosomes are scored then the count is recorded and the cell classified as an aneuploid cell. If multiple copies of the haploid chromosome number (other than diploid) are scored then the count is recorded and the cell classified as polyploid. If the chromosomes are arranged in closely apposed pairs, i.e. 4 chromatids instead of 2, the cell is scored as endoreduplicated (e).

14 ANNEX III

14.1 Historical laboratory control data

14.1.1 Percentage of aberrant cells in Chinese hamster V79 cell cultures (2005 to 2006)

Without S9 mix										
		Aberrant cells (%)								
Test group Concentration	Cells scored	Including gaps			Excluding gaps			With exchanges		
		Range	Mean	Calculated range*	Range	Mean	Calculated range*	Range	Mean	Calculated range*
Negative control										
Culture medium MEM	17800	0.0-6.0	1.7	0.9-2.6	0.0-3.0	1.1	0.5-1.7	0.0-1.5	0.2	0.1-0.4
Aqueous solv. ** 10 % (v/v)	18000	0.0-4.5	2.0	1.1-2.8	0.0-3.5	1.4	0.7-2.1	0.0-1.5	0.2	0.1-0.4
Org. solvents*** 0.5 % (v/v)	32200	0.0-4.5	1.8	1.0-2.7	0.0-4.0	1.3	0.6-2.1	0.0-0.5	0.1	0.1-0.3
Total	68000	0.0-6.0	1.8	0.9-2.7	0.0-4.0	1.3	0.6-2.0	0.0-1.5	0.1	0.1-0.4
Positive control										
EMS 200-900 µg/mL	52400	8.0-70.0	19.6	12.0-27.3	7.5-68.0	18.7	11.0-26.3	0.0-35.0	7.3	3.2-11.3
With S9 mix										
		Aberrant cells (%)								
Test group Concentration	Cells scored	Including gaps			Excluding gaps			With exchanges		
		Range	Mean	Calculated range*	Range	Mean	Calculated range*	Range	Mean	Calculated range*
Negative control										
Culture medium MEM	12600	0.0-5.0	2.2	1.3-3.2	0.0-4.0	1.6	0.9-2.2	0.0-1.5	0.4	0.0-0.7
Aqueous solv. ** 10 % (v/v)	12800	0.0-5.0	2.2	1.2-3.1	0.0-3.5	1.5	0.7-2.3	0.0-1.5	0.3	0.0-0.6
Org. solvents*** 0.5 % (v/v)	24200	0.0-5.0	2.1	1.2-3.1	0.0-4.0	1.6	0.8-2.3	0.0-2.0	0.3	0.0-0.7
Total	49600	0.0-5.0	2.2	1.2-3.1	0.0-4.0	1.5	0.8-2.3	0.0-2.0	0.3	0.0-0.7
Positive control										
CPA 1.0-2.0 µg/mL	32800	7.5-100.0	14.1	9.4-18.7	6.5-100.0	13.2	8.7-17.7	0.0-24.0	3.9	2.0-5.8

* Mean ± standard deviation

** Aqueous solvents: deionised water and 0.9 % (w/v) saline

*** Organic solvents: acetone, DMSO, ethanol, and tetrahydrofurane

14.1.2 Percentage of polyploid cells in Chinese hamster V79 cell cultures (2005 to 2006)

Without S9 mix				
Polyploid cells (%)				
Test group Concentration	Cells scored	Range	Mean	Calculated range*
Negative control				
Culture medium MEM	17800	0.5-4.6	2.0	1.3-2.7
Aqueous solv. ** 10 % (v/v)	18000	0.6-4.4	2.0	1.4-2.6
Organic solv. *** 0.5 % (v/v)	32200	0.0-5.2	2.2	1.5-2.8
Total	68000	0.0-5.2	2.1	1.4-2.7
Positive control****				
EMS 200-900 µg/mL	52400	0.0-4.6	2.0	1.4-2.6
With S9 mix				
Polyploid cells (%)				
Test group Concentration	Cells scored	Range	Mean	Calculated range*
Negative control				
Culture medium MEM	12600	0.5-4.4	2.0	1.3-2.6
Aqueous solv. ** 10 % (v/v)	12800	0.6-3.3	1.9	1.3-2.5
Organic solv. *** 0.5 % (v/v)	24200	0.0-4.7	2.0	1.3-2.7
Total	49600	0.0-4.7	2.0	1.3-2.6
Positive control****				
CPA 1.0-2.0 µg/mL	38000	0.0-4.8	1.9	1.4-2.4

* Mean ± standard deviation

** Aqueous solvents: deionised water and 0.9 % (w/v) saline

*** Organic solvents: acetone, ethanol, DMSO, and tetrahydrofurane

**** Positive control only for induction of structural aberrations

Addendum to Annex 17 (90 days tox study)

AB Enzymes went back to Harlan Laboratories Ltd that conducted the 90 day oral toxicity study, expressing French ANSES concern and its request for further raw data on e.g. individual water consumption data, urinary ionograms or any other data that could substantiate this increase.

The report was reviewed by Dr Braun (study director), specifically the clinical biochemistry, the urinalysis and the histopathology. Harlan Laboratories' conclusions were the following:

- Variations of blood sodium are in the range of the control historical values

The control males had a mean sodium level of 143.4 mmol/l, which was nearly identical with the mean value of the historical control data (143.7 mmol/l).

Although the test item-treated males showed statistically significant increases in the sodium level, the historical control data revealed a 'normal' range for sodium from 138.5 to 149.2 mmol/l.

All females had slightly low sodium levels and although the high dose females had statistically significant differences they were well with the ranges of the historical control values.

- Studies and reports have been conducted using internationally agreed protocols as described in OECD Guideline 408

In compliance with EFSA and ANSES Guidance, the most up-to-date edition of the above mentioned Guidelines have been followed.

Although urinary ionograms are well suited for quantifying various fractions within the urine, these parameters, as well as water consumption, are not required by the regulatory guidelines and hence, one would be unlikely to include them in a standard study.

- These isolated findings have no impact on the overall meaning of the study

The urinalysis values that were analyzed did not show any abnormalities and the pathology was unremarkable.

The absence of any values that exceeded the ranges of the historical control values confirms that although these may actually be secondary effects of the test item administration, these isolated findings are not indicative of any adverse change and hence did not affect the NOEL or NOAEL.

Those conclusions were endorsed by the French ANSES, as shown in its opinion, dated 5 July 2013.

REPORT (PART I OF II)

Lyso-Phospholipase

90-Day Oral (Gavage) Toxicity Study in the Wistar Rat

Study Director:

Test Facility: Harlan Laboratories Ltd.
(former RCC Ltd)
Zelgliweg 1
4452 Itingen / Switzerland

Sponsor: AB Enzymes GmbH
Feldbergstrasse 78
64293 Darmstadt / Germany

Study Identification: Harlan Laboratories Study **B99180**

Version: Final

Study Completion Date: 29-May-2009

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SIGNATURES

Study Director:

Test Facility Management:

Study Scientist
Analytical Chemistry:

Study Scientist
Pathology:

GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE

Harlan Laboratories Study: B99180
Test Item: Lyso-Phospholipase
Study Director:
Study Title: 90-Day Oral (Gavage) Toxicity Study in the Wistar Rat

This study has been performed in compliance with the:

Swiss Ordinance relating to Good Laboratory Practice adopted May 18th, 2005 [RS 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted on November 26th, 1997 by decision of the OECD Council [C (97)186/Final].

These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF and METI).

There were no circumstances that may have affected the quality or integrity of the data.

Study Director:

QUALITY ASSURANCE GLP STATEMENT

Harlan Laboratories Ltd., Zelgliweg 1, 4452 Itingen / Switzerland

Harlan Laboratories Study: B99180
Test Item: Lyso-Phospholipase
Study Director:
Study Title: 90-Day Oral (Gavage) Toxicity Study in the Wistar Rat

The general facilities and activities are inspected at least once yearly and the results are reported to the responsible person and the management.

Study procedures were periodically inspected. The study plan and this report were audited by the quality assurance. The dates are given below.

Dates and Types of QA Inspections		Dates of Reports to the Study Director and Test Facility Management
04 Sep 2008	Study plan	04 Sep 2008
01 Oct 2008	Study-based (animal delivery, randomization)	01 Oct 2008
08 Oct 2008	Study-based (test item, dose preparation, treatment, body weights)	08 Oct 2008
12 Dec 2008	Process-based (work-up)	12 Dec 2008
06 Jan 2009	Study based (necropsy)	06 Jan 2009
16 Feb 2009	Analytical part report	16 Feb 2009
26 Mar 2009	Pathology part report	26 Mar 2009
25/26 Mar 2009	Report	25/26 Mar 2009

This statement also confirms that this final report reflects the raw data.

Quality Assurance:

PREFACE

General Information

Test Item:	Lyso-Phospholipase
Study Title:	90-Day Oral (Gavage) Toxicity Study in the Wistar Rat
Sponsor:	AB Enzymes GmbH Feldbergstrasse 78 D-64293 Darmstadt / Germany
Study Monitor:	
Test Facility:	Harlan Laboratories Ltd. Zelgliweg 1 4452 Itingen / Switzerland
QA:	Harlan Laboratories Ltd. Quality Assurance GLP Zelgliweg 1 4452 Itingen / Switzerland

Responsibilities

Study Director
(until 15-Mar-2009):
Study Director
(from 16-Mar-2009):
Deputy Study Director
(until 15-Mar-2009):
Deputy Study Director
(from 16-Mar-2009):
Planning Coordinator:
Laboratory/Technical Coordinator:
Necropsy / Histotechnology:

Responsible for:

Clinical Laboratory Investigations:

Study Scientists:

Study Part Analytical Chemistry:
Study Part Pathology:

Quality Assurance:

Head of QA:

Schedule

Experimental Starting Date:	01-Oct-2008
Delivery of Animals:	01-Oct-2008
Acclimatization:	01 to 07-Oct-2008
Administration / Treatment:	08-Oct-2008 to 05-Jan-2009 (allocation A females) 08-Oct-2008 to 06-Jan-2009 (allocation A males)
Termination (Necropsy):	06-Jan-2009 (allocation A females) 07-Jan-2009 (allocation A males)
Experimental Completion Date:	28-May-2009

Accreditation

“Harlan Laboratories Ltd.” is accredited as a test laboratory for analysis in the fields of clinical chemistry, hematology, blood-coagulation and urine diagnostics in accordance with the Standard ISO/IEC 17025 under accreditation number STS 085 by the Swiss Accreditation Service.

Data Requirements / Test Guidelines

This study followed the procedures indicated by the following internationally accepted guidelines and recommendations:

- "Repeated Dose 90-Day Oral Toxicity Study in Rodents", OECD Guidelines for the testing of Chemicals, Section 4, Health Effects, Number 408, 21 September 1998.
- Directive 96/54/EC, B. 26. "Subchronic Oral Toxicity", 30 September 1996, including Additional Testing for Neurotoxicity.

Animal Welfare

This study was performed in an AAALAC-accredited laboratory in accordance with the Swiss Animal Protection Law under license no. 35.

Archiving

Harlan Laboratories Ltd. (4452 Itingen / Switzerland) will retain the study plan, raw data, sample of test item, specimens (as long as the quality permits evaluation), and the final report of the present study for at least ten years.

No data will be discarded without the Sponsor's written consent.

Frozen samples will be discarded three months after the final report has been issued, transferred to a GLP archive at additional costs, or returned to the Sponsor.

1 SUMMARY

General

In this subchronic toxicity study, Lyso-Phospholipase was administered daily by oral gavage to SPF-bred Wistar rats of both sexes at dose levels of 100, 300 and 1000 mg/kg body weight/day for a period of 13 weeks. A control group was treated similarly with the vehicle, bidistilled water, only.

The groups comprised 10 animals per sex, which were sacrificed after 13 weeks of treatment.

Clinical signs, detailed behavioural observations, food consumption and body weights were recorded periodically during the acclimatization and treatment periods. Ophthalmoscopic examinations were performed during the acclimatization and at the end of the treatment period. Functional observational battery, locomotor activity and grip strength were performed during week 13.

At the end of the dosing period, blood samples were withdrawn for hematology and plasma chemistry analyses. Urine samples were collected for urinalyses. All animals were killed, necropsied and examined *post mortem*. Histological examinations were performed on organs and tissues from all control and high dose animals, and all gross lesions from all animals.

Mortality / Viability

All animals survived until scheduled necropsy.

Clinical Signs

No clinical signs of toxicological relevance were noted during daily observations in males and females at all dose levels.

Detailed Behavioural Observations

No clinical signs were recorded during the weekly detailed behavioral observations (weeks 1-12).

Functional Observational Battery

No clinical signs were recorded during the functional observational battery (week 13).

Grip Strength

No test item-related changes were noted in fore- and hind limb grip strength in male and female rats at any dose level.

Locomotor Activity

The mean locomotor activity of males and females was not affected by the treatment with the test item.

Food Consumption

A slight trend to reduced mean daily- and relative food consumption was noted in test item-treated animals of both sexes at all dose levels during the treatment period. Although these changes in mean daily- and relative food consumption were not accompanied by changes in body weight development of test item-treated animals, these findings were considered to be related to the treatment with the test item.

Body Weights

The mean body weight development in control and test item-treated animals of both sexes was comparable at any dose level during the treatment period.

Ophthalmoscopic Examinations

Typical background findings (corneal opacity, persistent hyaloid vessel in vitreous body, persistent pupillary membrane) were noted without relationship to dose or treatment.

Clinical Laboratory Investigations

Hematology

After the 13-week treatment period, no test item-related changes of toxicological relevance were noted in hematology parameters in rats of both sexes at any dose level.

Clinical Biochemistry

After the 13-week treatment period, no test item-related changes of toxicological relevance were noted in clinical biochemistry parameters in rats of both sexes at any dose level.

Urinalysis

After the 13-week treatment period, no test item-related changes of toxicological relevance were noted in the urinalysis in males and females at any dose level.

Organ Weights

There were no differences indicating an effect of the test item. A few statistically significant deviations in average organ weights at the end of the treatment period were considered to be incidental, reflecting the usual individual variability.

Macroscopic / Microscopic Findings

At necropsy, performed at the end of the treatment period, no test item-related macroscopic findings were recorded.

The test item, Lyso-Phospholipase produced no histological evidence of toxicological properties in the organs and tissues examined.

2 PURPOSE

The purpose of this study was to assess the toxicity of Lyso-Phospholipase when administered to Wistar rats by oral gavage for a period of at least 90 days.

This study should provide a rational basis for toxicological risk assessment in man.

3 MATERIALS AND METHODS

3.1 Test System

Animals:	Rat, HanRcc: WIST(SPF)
Rationale:	Recognized by international guidelines as a recommended test system.
Breeder:	Harlan Laboratories Ltd. Laboratory Animal Services Wölferstrasse 4 4414 Füllinsdorf / Switzerland
Number of Animals:	Group 1: 10 males and 10 females Group 2: 10 males and 10 females Group 3: 10 males and 10 females Group 4: 10 males and 10 females
Total Number of Animals Used:	40 males and 40 females
Total Number of Animals Ordered:	41 males and 41 females
Age (at Delivery):	Approximately 7 weeks
Body Weight Range (at Acclimatization):	Males: 182.0 to 203.9 g Females: 138.2 to 162.4 g
Identification:	Acclimatization: Cage card and tail mark (later ear tattoo) Treatment: Cage card and individual ear tattoo
Randomization:	Computer-generated random algorithm.
Acclimatization:	Under test conditions after health examination. Only animals without any visible signs of illness were used for the study.

3.2 Allocation

The group identification and animal numbers assigned to treatment are stated in the following table:

Allocation and Dose Levels mg/kg bw/day		Group 1 control*	Group 2	Group 3	Group 4
		0	100	300	1000
Males	A	1 - 10	11 - 20	21 - 30	31 - 40
Females	A	41 - 50	51 - 60	61 - 70	71 - 80

* Control animals were treated with the vehicle, bidistilled water, only
A Main study animals

3.3 Husbandry

Room Numbers, Itingen:

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Conditions:

Standard laboratory conditions. Air-conditioned with 10 - 15 air changes per hour, continuously monitored environmental conditions (temp. range: 22 ± 3 °C; relative humidity range: 30 - 70%). Values outside of these ranges occasionally occurred, usually following room cleaning, and are considered not to have any influence on the study. Therefore, these data are not reported but are retained at Harlan Laboratories Ltd.. There was 12-hour fluorescent light/12-hour dark cycle with music during the light period.

Accommodation:

In groups of five in Makrolon type-4 cages with wire mesh tops and sterilized standard softwood bedding ('Lignocel' Schill AG, 4132 Muttenz / Switzerland).

Diet:

Pelleted standard Kliba Nafag 3433 (batch no. 44/08) rat maintenance diet (Provimi Kliba SA, 4303 Kaiseraugst / Switzerland) was available *ad libitum*. The feed batch was analyzed for contaminants.

Results of representative analyses for contaminants are included in Appendix I on p. 317 .

Water:

Community tap-water from Itingen was available *ad libitum* in water bottles. Results of bacteriological assay, chemical and contaminant analyses of representative samples are included in Appendix II on p. 320 .

3.4 Test Item / Vehicle

Data as supplied by the Sponsor.

3.4.1 Test Item

Identification:	Lyso-Phospholipase
Description:	Solid
Batch Number:	LPL-LF 07102 A3
Purity:	Considered to be 100%
Dry Matter:	96.3%
Ash:	0.8%
Fat:	0.4%
Carbohydrates:	28.8%
Total Protein (according to Kjeldahl):	66.3% (= 663 mg/g substance)
Lyso-Phospholipase Protein:	44.22 mg/g substance (= 6.67% of total protein)
Expiry Date (Retest Date):	30-Nov-2009
Storage Conditions:	At room temperature (15-25 °C) away from moisture and away from direct sunlight.
Safety Precautions:	Routine hygienic procedures (gloves, goggles, face mask). May cause sensitization by inhalation and skin contact. Do not breathe dust. Do not breathe spray. Avoid contact with skin.

3.4.2 Vehicle and Control Item

Identification:	Bidistilled water
-----------------	-------------------

3.5 Dose Formulations

The dose formulations were prepared weekly.

Lyso-Phospholipase was weighed into a glass beaker on a tared Mettler balance and the vehicle, bidistilled water, was added to give the appropriate final concentration of the test item in the suspension. The mixtures were prepared using a magnetic stirrer.

Homogeneity of the test item in the vehicle was maintained during the daily administration period using a magnetic stirrer.

3.5.1 Stability and Storage of Dose Formulations

Stability of Dose Formulations: 7 days based upon the results of stability analyses performed during a non-GLP dose range-finding study (RCC study no. B99178).

Storage of Dose Formulations In the refrigerator (2-8 °C) in glass beakers.

3.5.2 Analysis of Dose Formulations

Dose levels were in terms of test item as supplied unless otherwise stated by the Sponsor.

- Concentration, homogeneity and stability of dose formulations were determined by the Study Scientist (or his staff) according a photometric assay using BCA Total Protein Determination (08 Oct 2008) and thereafter using colourimetric enzymatic assay for Lyso-Phospholipase provided by the Sponsor and previously adapted at the Harlan Laboratories Ltd. (non-GLP dose range-finding study, RCC study no. B99178). The assay was based on the determination of free fatty acids following hydrolysis of Lyso-Phosphatidylcholine by Lyso-Phospholipase. The free fatty acids were determined using a “Free Fatty Acids Half Micro Test” (Roche, Switzerland).

Concentration, homogeneity and stability of dose formulations were determined in samples taken after experimental start (see Table 1).

Table 1: Concentration, Homogeneity and Stability (after 4 Hours and 7 days)

After Experimental Start – 08-Oct-2008			
	Homogeneity / Concentration	Stability 1	Stability 2
Group 1	a b c	d (4 hr, RT)	e (7 days, 2-8 °C)
Groups 2 - 4	a b c	d (4 hr, RT)	e (7 days, 2-8 °C)

RT: Room temperature
a,b etc: Internal sample designations

The concentration of the dose formulations were determined in samples taken during week 6 and 13 of the treatment (see Tables 2 and 3).

Table 2: Concentration

During Week 6 – 12-Nov-2008			
	Concentration	Stability 1	Stability 2
Group 1	a	---	---
Groups 2 - 4	a	---	---

Table 3: Concentration

During Week 13 – 31-Dec-2008			
	Concentration	Stability 1	Stability 2
Group 1	a	---	---
Groups 2 - 4	a	---	---

The aliquots for analysis of dose formulations were delivered to Dr. P. Sagelsdorff. No samples were discarded without the study director's consent. A detailed description of the method and the results are summarized in a part report prepared by Dr. P. Sagelsdorff and attached to the report in Appendix III on p. 324).

3.6 Treatment

Method:	Oral, by gavage
Rationale for Method:	Administration by gavage is a common and accepted route of exposure for studies of this type.
Frequency of Administration:	Daily, at approximately 24 hour intervals.
Dose Concentrations:	Group 1: 0 mg/kg/day Group 2: 100 mg/kg/day Group 3: 300 mg/kg/day Group 4: 1000 mg/kg/day
Rationale for Dose Level Selection:	The dose levels were selected based on a previous 14-day dose range-finding oral (gavage) toxicity study in Wistar rats, RCC Study Number B99178.
Dose Volume:	10 mL/kg body weight
Duration of Acclimatization Period:	7 days
Duration of Treatment Period:	90 days (allocation A females) 91 days (allocation A males)

3.7 Phase Designation

Phase 1: Acclimatization period
Phase 2: Treatment period

3.8 Activities and Observations

The following observations were recorded as follows:

3.8.1 Viability / Mortality

Observations for viability / mortality were recorded twice daily.

3.8.2 Clinical Signs

All animals were observed for clinical signs once during the acclimatization, twice daily on treatment days 1-3 and once daily thereafter.

3.8.3 Detailed Behavioral Observations

All animals were observed in their home cages, outside their home cages in a standard arena and in the hand. These observations were performed once before commencement of administration and once weekly (weeks 1 to 12) thereafter.

SUMMARY OF PARAMETERS (MINIMUM REQUIREMENT FOR EACH ANIMAL) OBSERVATIONS: DAILY CAGE-SIDE (D), PRETEST (P), WEEKLY (W), FOB (F)

	SCORE	PARAMETER	D	P	W	F
				-1	1-12	13
APPEARANCE	1-3	Piloerection	X	X	X	X
	1-3	Salivation	X	X	X	X
	1	Hunched posture	X	X	X	X
MOTOR	1-3	Ataxia	X	X	X	X
	1-3	Tremor/twitching	X	X	X	X
	1	Prostration	X	X	X	X
	1	Circling		X	X	X
	1-3	Spasm		X	X	X
BEHAVIOR	1-3	Hyperactivity	X	X	X	X
	1-3	Somnolence	X	X	X	X
	1-3	Increased exploration		X	X	X
	1-3	Reduced grooming		X	X	X
	1-3	Vocalisation		X	X	X
RESPIRATION	1	Dyspnea	X	X	X	X
	1	Tachypnea	X	X	X	X
	1	Bradypnea	X	X	X	X
REFLEXES	1	Blink		X	X	X
	1	Pinna		X	X	X
	1	Iridic light reflex		X	X	X
	1	Push-off (hind leg)		X	X	X
	1	Pain response		X	X	X
	1	Startle/hearing		X	X	X
	1	Righting reflex		X	X	X
MISCELLANEOUS	1-3	Lacrimation		X	X	X
	1	Limbs cyanotic		X	X	X
	1	Mydriasis		X	X	X
	1	Miosis		X	X	X
	1	Exophthalmos		X	X	X
	1-3	Reduced muscle tone		X	X	X

NB: Findings that were detected during daily observation of the standard parameters were tracked throughout the study for onset in other animals and progression/regression in the afflicted animal, and are listed in the tables. Parameters marked with 'X' were specifically observed for presence or absence.

3.8.6 Body Weights

Body weights were recorded weekly during acclimatization and treatment periods and before necropsy, using an on-line electronic recording system consisting of a Mettler balance connected to the Harlan Laboratories computer.

3.8.7 Ophthalmoscopic Examinations

Acclimatization: Once in all animals

During Week 12 (Treatment): In control and high-dose animals. The intermediate dose groups were not examined at Week 12 as no test item-related changes were seen in the animals of the high-dose groups.

The ophthalmoscopic examinations of both eyes of all animals were performed after the application of a mydriatic solution (Ciba Vision AG, 3172 Niederwangen / Switzerland) using a Miroflex 2 Ophthalmoscope (Eisenhut Vet. AG, 4123 Allschwil / Switzerland). A description of any abnormality was recorded. For unilateral findings unless otherwise indicated in the tables, the contralateral eye was without abnormalities.

3.9 Clinical Laboratory Investigations

Blood and Urine Sampling:

After 13 Weeks: 06-Jan-2009 (allocation A females)
07-Jan-2009 (allocation A males)

Blood samples were drawn from the retro-orbital plexus from all animals under light isoflurane anesthesia. The animals were fasted in metabolism cages for approximately 18 hours before blood sampling but allowed access to water *ad libitum*. The samples were collected early in the working day to reduce biological variation caused by circadian rhythms. Blood samples were drawn from the retro-orbital plexus using a micro-hematocrit glass capillary tube.

Urine was collected during the 18 hours fasting period into a specimen vial, using a metabolism cage.

In the summary and individual tables the names of some parameters have been abbreviated.

Detailed methodology, abbreviations and general remarks are described in Appendix IV on p. [339](#).

Clinical laboratory data are expressed, with a few exceptions, in general accordance with the International System of Units (SI).

3.9.1 Hematology

The following hematology parameters were determined:

Complete Blood Cell Count

Erythrocyte count	Differential leukocyte count:
Hemoglobin	Neutrophils
Hematocrit	Eosinophils
Mean corpuscular volume	Basophils
Red cell volume distribution width	Lymphocytes
Mean corpuscular hemoglobin	Monocytes
Mean corpuscular hemoglobin concentration	Large unstained cells
Hemoglobin concentration distribution width	Platelet count
Reticulocyte count	
Reticulocyte maturity index (low, medium, high fluorescence)	
Leukocyte count, total	

Hemoglobin Derivatives

Methemoglobin	Heinz bodies (slides prepared but not evaluated)
---------------	--

Coagulation

Prothrombin time (= Thromboplastin time)	Activated partial Thromboplastin time
--	---------------------------------------

3.9.2 Clinical Biochemistry

The following clinical biochemistry parameters were determined:

Glucose	Gamma-glutamyl-transferase
Urea	Creatine kinase
Creatinine	Sodium
Bilirubin, total	Potassium
Cholesterol, total	Chloride
Triglycerides	Calcium
Phospholipids	Phosphorus
Aspartate aminotransferase	Protein, total
Alanine aminotransferase	Albumin

Lactate dehydrogenase	Globulin
Glutamate dehydrogenase	Albumin/Globulin ratio
Alkaline phosphatase	

3.9.3 Urinalysis

The following urine parameters were determined:

Physical Examination

Urine volume (18 hour)	Color
Specific gravity (relative density)	Appearance

Chemical Examination

pH value	Urobilinogen
Nitrite	Bilirubin
Protein	Erythrocytes
Glucose	Leukocytes
Ketones	

3.10 Pathology

3.10.1 Necropsy

All animals were weighed and necropsied. Descriptions of all macroscopic abnormalities were recorded. All animals surviving to the end of the observation period were anesthetized by intraperitoneal injection of pentobarbitone and killed by exsanguination.

Sacrifice:

After 13 Weeks:	06-Jan-2009 (allocation A females)
	07-Jan-2009 (allocation A males)

Samples of the following tissues and organs were collected from all animals at necropsy and fixed in neutral phosphate buffered 4% formaldehyde solution except for eyes with optic nerve and hardierian gland which were fixed in Davidson's solution or epididymides and testes which were fixed in Bouin's solution:

Tissues / Organs	Weight	Collect	Examine
Adrenal glands	X	X	X
Aorta		X	X
Bone (sternum, femur including joint)		X	X
Bone marrow (femur)		X	X
Brain - including section of medulla/pons, cerebral and cerebellar cortex	X	X	X
Cecum		X	X
Colon		X	X
Duodenum		X	X
Epididymides (fixed in Bouin's solution)	X	X	X
Esophagus		X	X
Eyes w/optic nerve (fixed in Davidson's solution)		X	X
Harderian gland (fixed in Davidson's solution)		X	X
Heart including auricles	X	X	X
Ileum, with Peyer's patches		X	X
Jejunum with Peyer's patches		X	X
Kidneys	X	X	X
Larynx		X	X
Lacrimal gland, exorbital		X	X
Liver	X	X	X
Lungs, filled w/formalin at necropsy		X	X
Lymph nodes – mesenteric and mandibular		X	X
Mammary gland area		X	X
Nasal cavity		X	X
Ovaries	X	X	X
Pancreas		X	X
Pharynx		X	X
Pituitary gland		X	X
Prostate gland incl. coagulating glands		X	X
Rectum		X	X
Salivary glands - mandibular, sublingual		X	X
Sciatic nerve		X	X
Seminal vesicles		X	X
Skeletal muscle		X	X

Tissues / Organs	Weight	Collect	Examine
Skin		X	X
Spinal cord - cervical, midthoracic, lumbar		X	X
Spleen	X	X	X
Stomach		X	X
Testes (fixed in Bouin's solution)	X	X	X
Thymus	X	X	X
Thyroid (incl. parathyroid gland, if possible)		X	X
Tongue		X	X
Trachea		X	X
Urinary bladder, filled w/formalin at necropsy		X	X
Uterus with cervix as appropriate	X	X	X
Vagina		X	X
All gross lesions		X	X

3.10.2 Organ Weights

The organs from all animals listed in the table in Section 3.10.1 were weighed before fixation and recorded on the scheduled dates of necropsy. Relative organ weights were calculated on the basis of the body weight and brain weight.

The terminal body weight was recorded immediately prior to necropsy and the organ to terminal body weight ratios as well as organ to brain weight ratios were determined.

3.10.3 Histotechnique

All organ and tissue samples, as defined under Histopathology (see Section 3.10.4), were processed, embedded and cut at an approximate thickness of 2 to 4 micrometers and stained with hematoxylin and eosin.

3.10.4 Histopathology

Slides of all organs and tissues listed in the table in Section 3.10.1, which were collected at scheduled sacrifices from all animals of the control and high-dose groups and all gross lesions from all animals were examined by the study pathologist.

A description of all abnormalities is included in the pathology part report (see Appendix V on p. 352). Attempts were made to correlate gross observations with microscopic findings.

A peer review of findings was performed. The findings of the study pathologist and the peer reviewing pathologist compared favorably.

3.11 Data Compilation

The study data were sorted and presented using the ToxControl LIMS computer system. All electronically recorded data are conserved on a magnetic medium.

Individual values were rounded before printing. All derived values that appear in the tables represent the rounded results of calculations that used the exact raw data value.

Locomotor activity was recorded on-line, and the results were printed and transcribed into the computer system for compilation and analysis.

Grip strength data were recorded on data sheets and transcribed into the computer system for compilation and analysis.

3.12 Statistical Analysis

The following statistical methods were used to analyze grip strength, locomotor activity, body weight, ophthalmoscopic examinations, clinical laboratory data, organ weights and ratios as well as macroscopic findings:

- The Dunnett-test [see References] (many to one t-test) based on a pooled variance estimate was applied if the variables could be assumed to follow a normal distribution for the comparison of the treated groups and the control groups for each sex.
- The Steel-test [see References] (many-one rank test) was applied instead of the Dunnett-test when the data could not be assumed to follow a normal distribution.
- Fisher's exact-test [see References].

4 RESULTS

4.1 Analysis of Dose Formulations

(See Appendix III on p. 324)

The dose formulations were in the range of 90.3 to 119% of the nominal concentration and homogenous distribution was confirmed by a CV of $\leq 6.29\%$.

Lyso-Phospholipase in the dose formulations was found to be stable as the recoveries after storage for 4 hours at room temperature and for 7 days at 4°C were within 82.3 and 106% of the initial concentrations.

4.2 Observations

4.2.1 Viability / Mortality

(See Individual Tables on p. 132)

All animals survived until scheduled necropsy.

4.2.2 Clinical Signs

(See Summary Tables on p. 50 , Individual Tables on p. 141)

No clinical signs of toxicological relevance were noted during daily observations in males and females at all dose levels.

Kinked tail, transient hair loss and scabs were noted in isolated rats without dose dependence and were therefore considered to be of no toxicological relevance.

4.2.3 Detailed Behavioural Observations

(See Summary Tables on p. 59 , Individual Tables on p. 150)

No clinical signs were recorded during the weekly detailed behavioral observations (weeks 1-12).

4.2.4 Functional Observational Battery

No clinical signs were recorded during the functional observational battery (week 13).

Grip Strength

(See Summary Tables on p. 68 , Individual Tables on p. 159)

No test item-related changes were noted in fore- and hind limb grip strength in male rats at any dose level.

Statistically significant reductions in the mean fore limb grip strength were noted in females at all dose levels. A reduced mean hind limb grip strength was recorded in females treated with 300 mg/kg/day ($p < 0.05$). As no dose relationship could be established and as these changes were only observed in females, these findings were considered to be of no toxicological relevance.

Locomotor Activity

(See Summary Tables on p. 71 , Individual Tables on p. 168)

Males treated with 1000 mg/kg/day presented an elevated locomotor activity during the 20-30 minutes measurement interval ($p < 0.05$). This finding was considered to be fortuitous.

The mean locomotor activity of females was not affected by the treatment with the test item.

4.2.5 Food Consumption

(See Figures on p. 37 , Summary Tables on p. 76 , Individual Tables on p. 177)

No statistical analysis was performed on the mean daily- and relative food consumption due to the low number of cages ($n=2$).

A slight trend to reduced mean daily food consumption was noted in test item-treated males at all dose levels from days 15-22 onwards (except on days 29-43 in males treated with 100 mg/kg/day). A slight trend to reduced mean daily food consumption was noted in test item-treated females at all dose levels from days 36-43 onwards.

Reduced relative food consumption was recorded as follows:

- In males treated with 100 mg/kg/day from days 43-50 onwards (from days 29-36 onwards in females),
- In males treated with 300 mg/kg/day from days 50-57 onwards (from days 29-36 onwards in females),
- In males treated with 1000 mg/kg/day from days 15-22 onwards (from days 36-43 onwards in females).

Although these changes in mean daily- and relative food consumption were not accompanied by changes in body weight development of test item-treated animals, these findings were considered to be related to the treatment with the test item.

4.2.6 Body Weights

(See Figures on p. 43 , Summary Tables on p. 86 , Individual Tables on p. 195)

The mean body weight development in control and test item-treated animals of both sexes was comparable at any dose level during the treatment period.

4.2.7 Ophthalmoscopic Examinations

(See Summary Tables on p. 96 , Individual Tables on p. 213)

Typical background findings (corneal opacity, persistent hyaloid vessel in vitreous body, persistent pupillary membrane) were noted without relationship to dose or treatment.

4.3 Clinical Laboratory Investigations

4.3.1 Hematology

(See Summary Tables on p. 101 , Individual Tables on p. 230)

After the 13-week treatment period, no test item-related changes of toxicological relevance were noted in hematology parameters in rats of both sexes at any dose level.

An increased prothrombin time was recorded in females treated with 100 mg/kg/day ($p < 0.05$), which value remained within the range of the historical control data. This finding was considered to be incidental.

4.3.2 Clinical Biochemistry

(See Summary Tables on p. 107 , Individual Tables on p. 247)

After the 13-week treatment period, the following changes in clinical biochemistry parameters were noted:

- Increased cholesterol in male rats treated with 1000 mg/kg/day ($p < 0.05$),
- Dose-related increases in sodium in males (all $p < 0.01$) and increased sodium in females at 1000 mg/kg/day ($p < 0.01$). Elevations in sodium concentrations in Group 4 females are mainly due to low sodium concentrations recorded in control females,
- Increased chloride in male rats treated with 1000 mg/kg/day ($p < 0.01$),

- Increased calcium in males at all dose levels ($p < 0.01$ at 100 mg/kg/day and 1000 mg/kg/day and $p < 0.05$ at 300 mg/kg/day) and in females treated with 100 mg/kg/day ($p < 0.01$),
- Increased urea in females treated with 1000 mg/kg/day ($p < 0.01$),
- Increased total bilirubin in females treated with 1000 mg/kg/day ($p < 0.05$).

As the values of all previously-mentioned parameters remained within the range of the historical control data and as these changes had no histopathological correlate, these findings were considered to be of no toxicological relevance.

Increased chloride concentrations were noted in females treated with 1000 mg/kg/day ($p < 0.05$), which values were below the range of the historical control data. This change is mainly due to low sodium concentrations recorded in control females.

4.3.3 Urinalysis

(See Summary Tables on p. 112 , Individual Tables on p. 264)

After the 13-week treatment period, no test item-related changes of toxicological relevance were noted in the urinalysis in males and females at any dose level.

At the end of the treatment period, female rats treated with 1000 mg/kg/day had elevated urinary bilirubin ($p < 0.05$), which values remained within the range of the historical control data. This finding was considered to be of no toxicological relevance.

4.4 Pathology

4.4.1 Organ Weights

(See Summary Tables on p. 115 , Individual Tables on p. 273)

Males treated with 1000 mg/kg/day had decreased mean absolute heart weight ($p < 0.05$). This change may be due to lower body weights recorded in males treated with 1000 mg/kg/day when compared to control males.

Statistically significant decreases in mean absolute kidney weights were recorded in females at all dose levels ($p < 0.05$ at 100 mg/kg/day and 300 mg/kg/day and $p < 0.01$ at 1000 mg/kg/day). Decreased kidney-to-body weight ratios were noted in females treated either with 100 mg/kg/day ($p < 0.05$) or with 1000 mg/kg/day ($p < 0.05$). Dose-related decreases in kidney-to-brain weight ratios were noted in females (all $p < 0.01$) when compared to control females. As these changes had no microscopical correlate, these findings were considered to be of no toxicological relevance.

Decreased mean absolute and relative ovaries weight was recorded in females treated with 300 mg/kg/day (all $p < 0.05$). Decreased uterus-to-brain weight ratio was noted in females treated with 100 mg/kg/day ($p < 0.05$). As these changes had no microscopical correlate, these findings were considered to be of no toxicological relevance.

4.4.2 Macroscopic Findings

(See Summary Tables on p. 128 , Individual Tables on p. 298)

At the end of the treatment period, no test item-related gross lesions were observed. The macroscopic findings recorded were considered to be within the range of normal background lesions, which may be seen in rats of this strain and age in oral toxicity studies and were considered to be incidental, reflecting the usual variability.

4.4.3 Microscopic Findings

(See Appendix V on p. 352)

The test item Lyso-Phospholipase produced no histological evidence of toxicological properties in the organs and tissues examined. All findings recorded were within the range of normal background lesions, which may be recorded in animals of this strain and age.

5 DISCUSSION AND CONCLUSION

Oral administration of Lyso-Phospholipase to Wistar rats at doses of 100, 300 and 1000 mg/kg/day for at least 13 weeks resulted in no premature death, no clinical signs of adverse nature during daily observations, detailed behavioural observations and during the functional observational battery, no effects on fore- or hind limb grip strength, no effects on locomotor activity, no effects on body weight development, no test item-related changes observed during the ophthalmoscopic examinations, no effects on hematology, clinical biochemistry or urinalysis parameters, no effects on organ weight, no test item-related macroscopic findings of toxicological relevance. The test item, Lyso-Phospholipase produced no histological evidence of toxicological properties in the organs and tissues examined.

Insofar as the marginally reduced mean daily absolute and relative food consumption values noted in rats of both sexes were not accompanied by concomitant changes in mean body weight, and no other findings of toxicological relevance were noted, these differences were considered to be unrelated to the test item.

Therefore, the no-observed effect level (NOEL) and the no-observed-adverse-effect level (NOAEL) were considered to be above 1000 mg/kg/day, the highest dose level used in this study.

6 REFERENCES

1. C.W. Dunnett:
A Multiple Comparison Procedure for Comparing Several Treatments with a Control, J. Amer. Stat. Assoc. 50, 1096-1121 (1955).
2. R.G. Miller:
Simultaneous Statistical Inference, Springer Verlag, New York (1981).
3. R.A. Fisher:
Statistical Methods for Research Workers, Oliver and Boyd, Edinburgh (1950).

7 FIGURES

FOOD CONSUMPTION (G/ANIMAL/DAY) - GRAPHICS

Data excluded from Summary Report

Not Reported

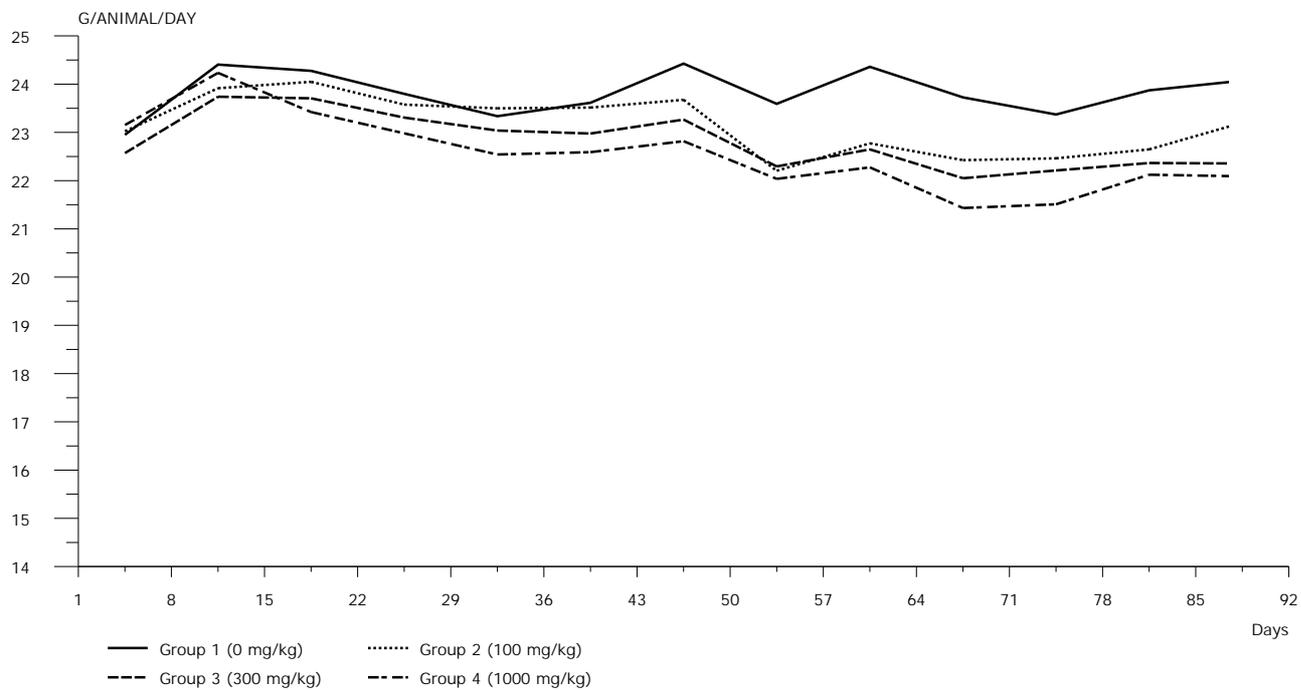
All Study Phases

Cage 17 Male Group 10 Reserve Removed

Cage 18 Female Group 10 Reserve Removed

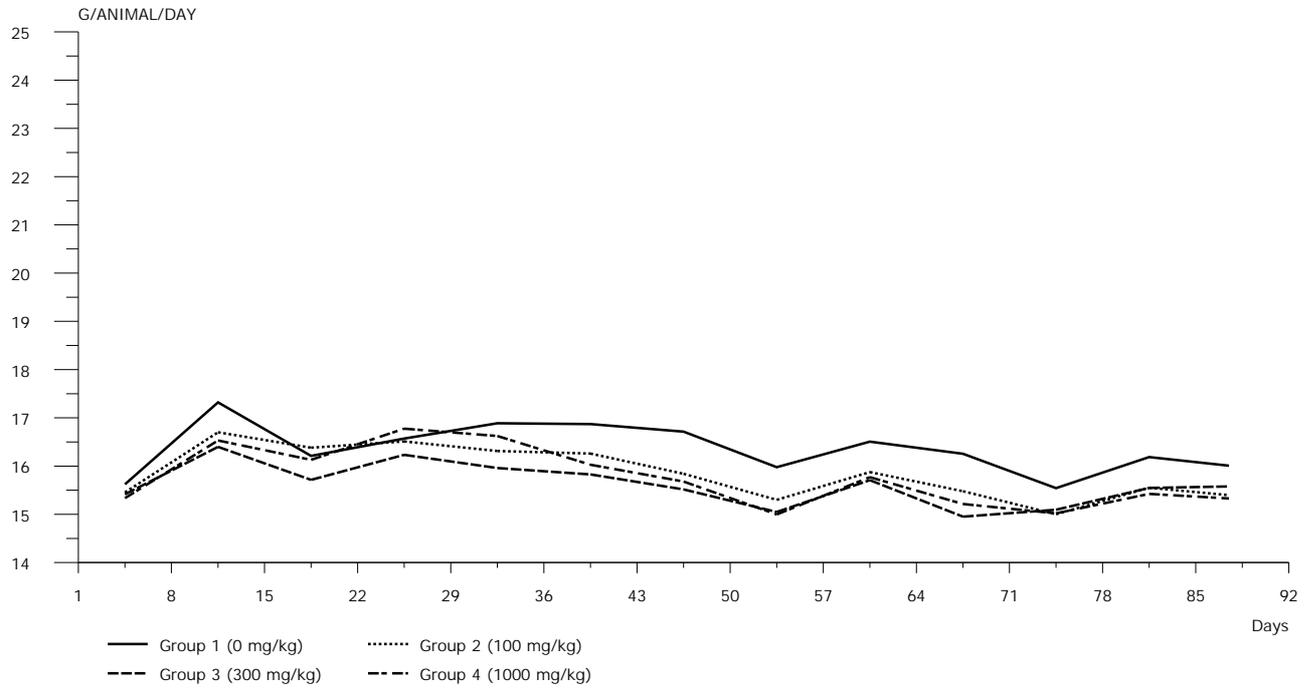
FOOD CONSUMPTION (G/ANIMAL/DAY) - GRAPHICS
MALES

TREATMENT



**FOOD CONSUMPTION (G/ANIMAL/DAY) - GRAPHICS
FEMALES**

TREATMENT



RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) - GRAPHICS

Data excluded from Summary Report

Not Reported

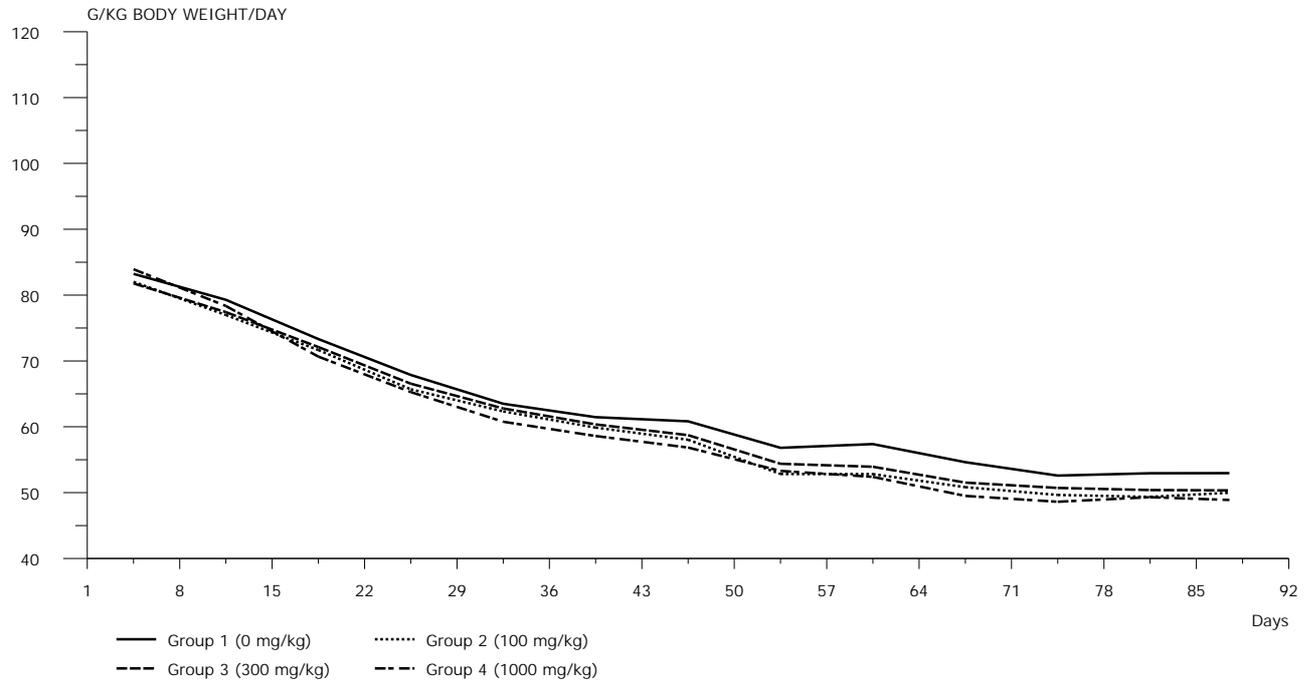
All Study Phases

Cage 17 Male Group 10 Reserve Removed

Cage 18 Female Group 10 Reserve Removed

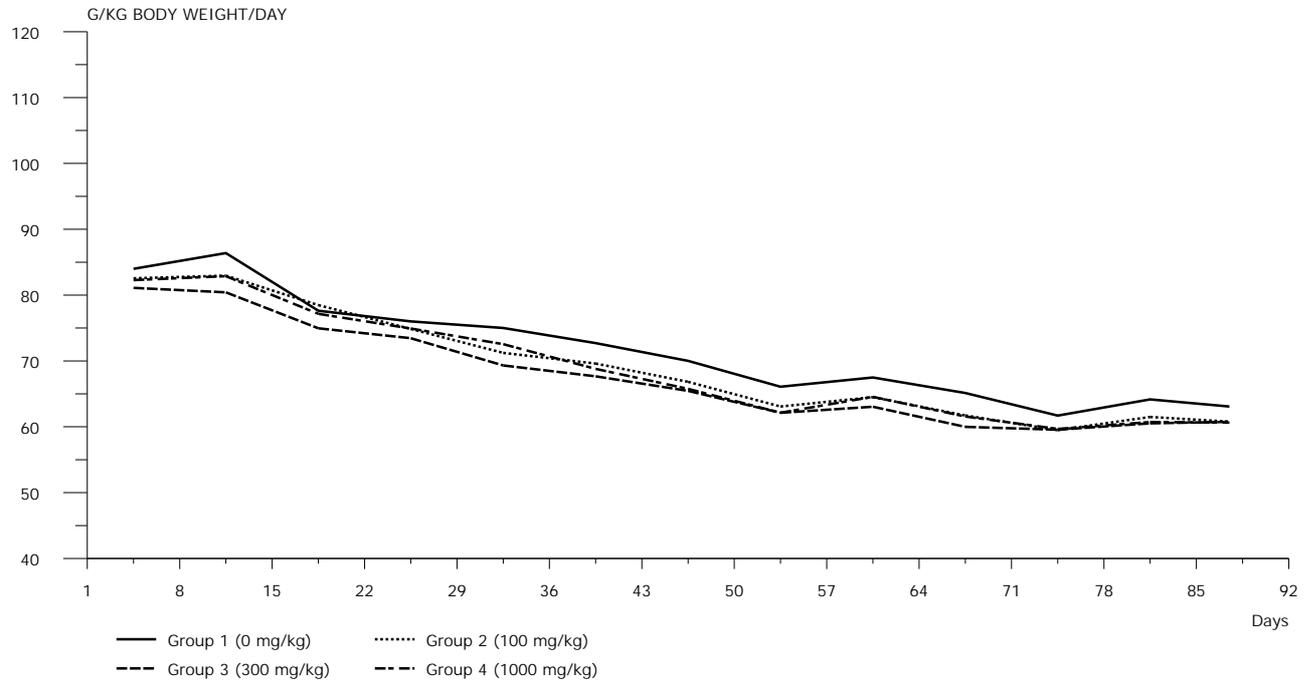
**RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) - GRAPHICS
MALES**

TREATMENT



**RELATIVE FOOD CONSUMPTION (G/KG BODY WEIGHT/DAY) - GRAPHICS
FEMALES**

TREATMENT



BODY WEIGHTS (G) - GRAPHICS

Data excluded from Summary Report

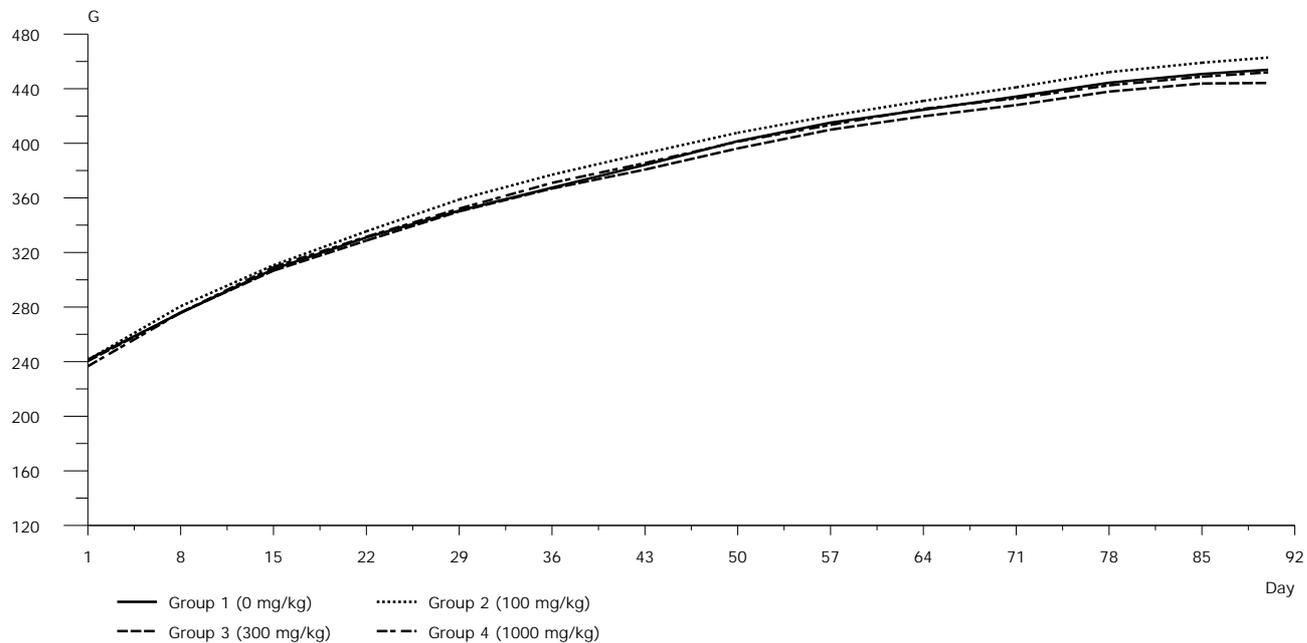
Not Reported

All Study Phases

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

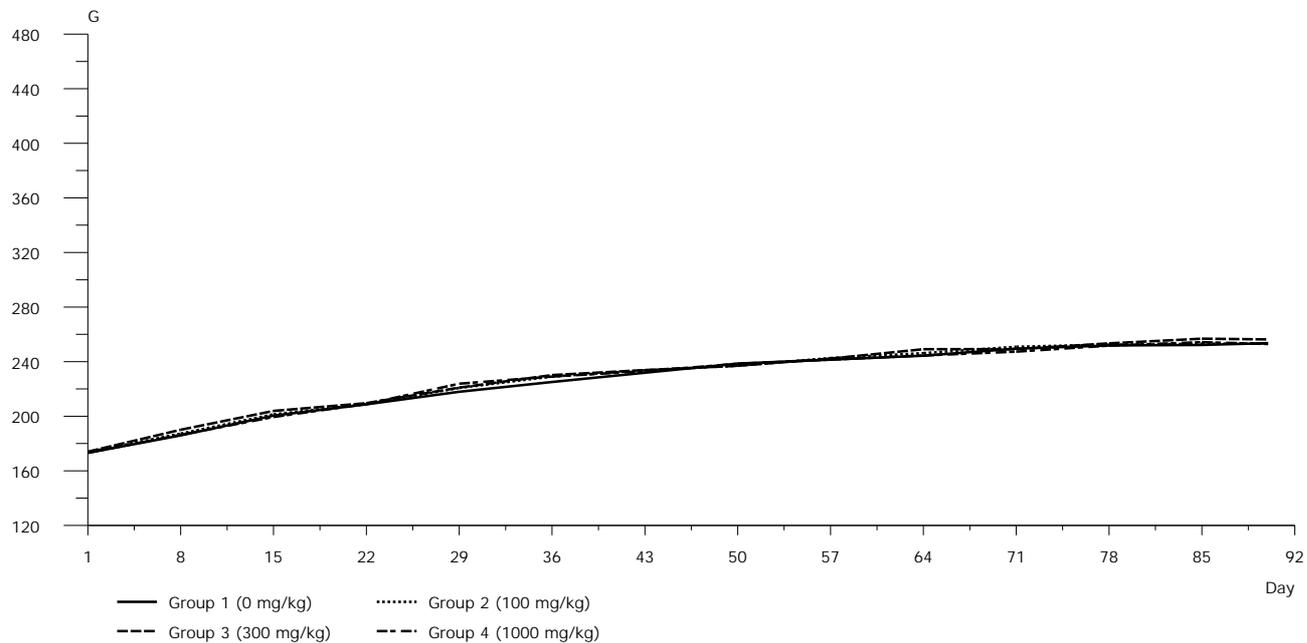
BODY WEIGHTS (G) - GRAPHICS
MALES

TREATMENT



**BODY WEIGHTS (G) - GRAPHICS
FEMALES**

TREATMENT



BODY WEIGHT GAIN (%) - GRAPHICS

Data excluded from Summary Report

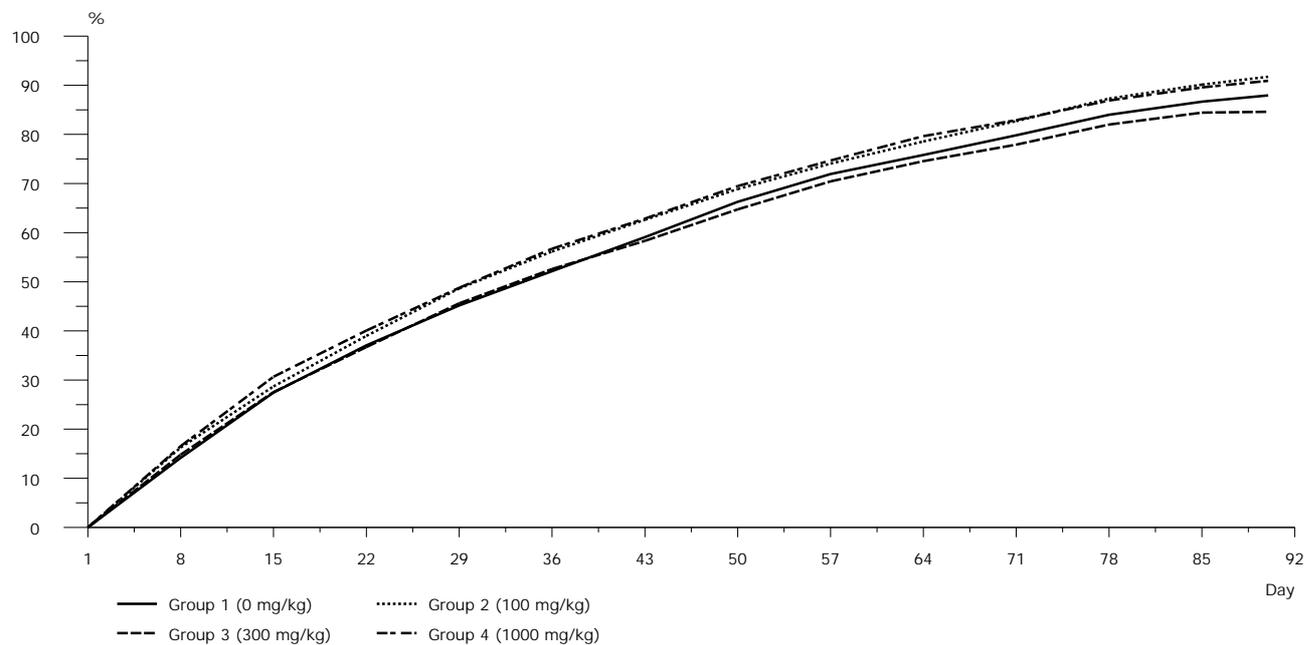
Not Reported

All Study Phases

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

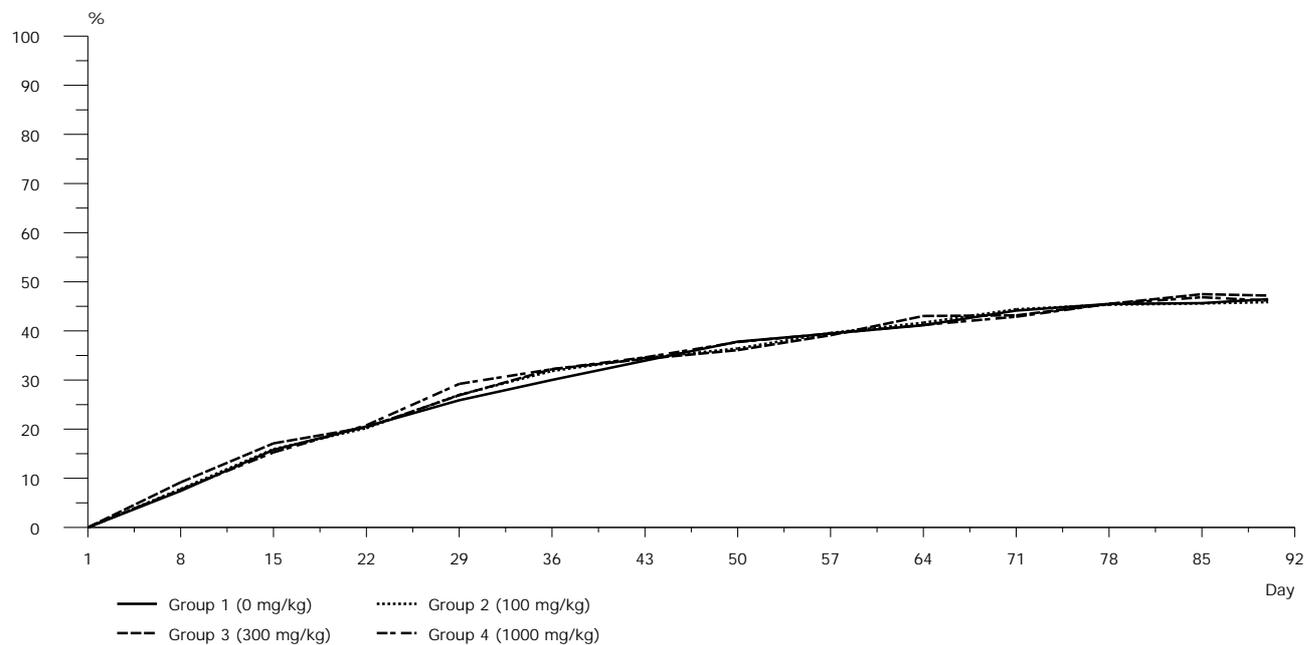
BODY WEIGHT GAIN (%) - GRAPHICS
MALES

TREATMENT



**BODY WEIGHT GAIN (%) - GRAPHICS
FEMALES**

TREATMENT



8 SUMMARY TABLES

CLINICAL SIGNS - SUMMARY

Affected animals as percentage to observed animals

0 0%
< between 1% and 9%
1 between 10% and 19%
2 between 20% and 29%
... ...
9 between 90% and 99%
A 100%

Data excluded from Summary Report

Not Reported

All Study Phases

Animal 81 Male Group 10 Reserve Removed
Animal 82 Female Group 10 Reserve Removed

Incomplete Recordings

Selection of Findings

All findings reported

CLINICAL SIGNS - SUMMARY
MALES

ACCLIMATIZATION

Weeks / Days

1

-----7

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

CLINICAL SIGNS - SUMMARY

MALES

TREATMENT

Weeks / Days

1 2 3 4 5 6
1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7

Group 1 (0 mg/kg)

DESCRIPTIVES

- KINKED (3)

TAIL APEX

G11111111111111
%11111111111111

No further abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

APPEARANCE

- HAIR LOSS (3)

HEAD

G11111111111111
%11111111111111

- SCABS (3)

HEAD

G1111.....
%1111.....

No further abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

CLINICAL SIGNS - SUMMARY

MALES

TREATMENT

Weeks / Days

13 14

1 2 3 4 5 6 7 -

Group 1 (0 mg/kg)

DESCRIPTIVES

- KINKED (3)

TAIL APEX G 1 1 1 1 1 1 1

 % 1 1 1 1 1 1 1

No further abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

DESCRIPTIVES

- KINKED (3)

TAIL APEX G 1 1 1 1 1 1 1

 % 1 1 1 1 1 1 1

No further abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

CLINICAL SIGNS - SUMMARY
FEMALES

ACCLIMATIZATION

Weeks / Days

1

-----7

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

CLINICAL SIGNS - SUMMARY
FEMALES

TREATMENT

Weeks / Days

1 2 3 4 5 6
1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

APPEARANCE

- HAIR LOSS (3)

NECK (CERVICAL)

G1111111111
%1111111111

No further abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

**CLINICAL SIGNS - SUMMARY
FEMALES**

TREATMENT

	Weeks / Days																																									
	7							8							9							10							11							12						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

APPEARANCE

- HAIR LOSS (3)

NECK (CERVICAL)	G 11 111111111111111111111111111111
	% 11 111111111111111111111111111111
POSTERIOR DORSUM	G 2222222222222222222222222222
	% 111111111111111111111111111111
LEFT FLANK	G 122222222222222222222222222222
	% 111111111111111111111111111111
RIGHT FLANK	G 122222222222222222222222222222
	% 111111111111111111111111111111

No further abnormality recorded.

Group 3 (300 mg/kg)

APPEARANCE

- HAIR LOSS (3)

NECK (CERVICAL)	G	11
	%	11

No further abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

CLINICAL SIGNS - SUMMARY
FEMALES

TREATMENT

Weeks / Days
13 14
1 2 3 4 5 6 7 -

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

APPEARANCE

- HAIR LOSS (3)

NECK (CERVICAL)	G	1 1 1 1 1 1
	%	1 1 1 1 1 1
POSTERIOR DORSUM	G	2 2 2 2 1 2
	%	1 1 1 1 1 1
LEFT FLANK	G	2 2
	%	1 1
RIGHT FLANK	G	2 2
	%	1 1

No further abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

DETAILED BEHAVIORAL OBSERVATIONS - SUMMARY

Affected animals as percentage to observed animals

0 0%
< between 1% and 9%
1 between 10% and 19%
2 between 20% and 29%
... ...
9 between 90% and 99%
A 100%

Data excluded from Summary Report

Not Reported

All Study Phases

Animal 81 Male Group 10 Reserve Removed
Animal 82 Female Group 10 Reserve Removed

Incomplete Recordings

Selection of Findings

All findings reported

**DETAILED BEHAVIORAL OBSERVATIONS - SUMMARY
MALES**

ACCLIMATIZATION

Weeks / Days

1

--3----

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

**DETAILED BEHAVIORAL OBSERVATIONS - SUMMARY
MALES**

TREATMENT

Weeks / Days

1 2 3 4 5 6
--3-----3-----6---3-----3-----3-----

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

**DETAILED BEHAVIORAL OBSERVATIONS - SUMMARY
MALES**

TREATMENT

Weeks / Days

7 8 9 10 11 12
--3-----3-----3-----3-----3-----3-----

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

**DETAILED BEHAVIORAL OBSERVATIONS - SUMMARY
MALES**

TREATMENT

Weeks / Days
13 14
-- 3 -- 6 --

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

**DETAILED BEHAVIORAL OBSERVATIONS - SUMMARY
FEMALES**

ACCLIMATIZATION

Weeks / Days

1

--3----

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

**DETAILED BEHAVIORAL OBSERVATIONS - SUMMARY
FEMALES**

TREATMENT

Weeks / Days

1 2 3 4 5 6
--3-----3-----6---3-----3-----3-----

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

**DETAILED BEHAVIORAL OBSERVATIONS - SUMMARY
FEMALES**

TREATMENT

Weeks / Days

7 8 9 10 11 12
--3-----3-----3-----3-----3-----3-----

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

**DETAILED BEHAVIORAL OBSERVATIONS - SUMMARY
FEMALES**

TREATMENT

Weeks / Days	
13	14
--3--	6--

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

G : Rounded group means of grades of affected animals
% : Affected animals as percentage to observed animals (See explanation on cover page)

GRIP STRENGTH - SUMMARY

Data excluded from Summary Report

Not Reported

All Measurements

Animal 81 Male Group 10 Reserve Removed

Animal 82 Female Group 10 Reserve Removed

Reported Parameter

Parameter Statistical Testing

AT WEEK 13

Grip Fore GRIP FORELIMB DUNNETT

Grip Hind GRIP HINDLIMB DUNNETT

AT WEEK 13

Grip Fore GRIP FORELIMB DUNNETT

Grip Hind GRIP HINDLIMB DUNNETT

Statistical Methods

DUNNETT DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not significant (-)

**GRIP STRENGTH - SUMMARY
AT WEEK 13
FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
GRIP STRENGTH					

Grip Fore	MEAN	1.49	1.30 **	1.36 *	1.32 **
KILOGRAM	ST.DEV.	0.15	0.06	0.09	0.08
	MINIMUM	1.28	1.18	1.19	1.21
	MAXIMUM	1.71	1.37	1.47	1.41
	N	10	10	10	10
Grip Hind	MEAN	0.87	0.85 -	0.79 *	0.82 -
KILOGRAM	ST.DEV.	0.05	0.07	0.09	0.05
	MINIMUM	0.81	0.69	0.62	0.74
	MAXIMUM	0.96	0.93	0.97	0.88
	N	10	10	10	10

*/**/- : Significant at 5% (*), 1% (**), or not significant (-)

**GRIP STRENGTH - SUMMARY
AT WEEK 13
MALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
GRIP STRENGTH					

Grip Fore	MEAN	1.65	1.71 -	1.69 -	1.68 -
KILOGRAM	ST.DEV.	0.11	0.09	0.07	0.06
	MINIMUM	1.52	1.60	1.63	1.57
	MAXIMUM	1.84	1.86	1.86	1.74
	N	10	10	10	10
Grip Hind	MEAN	1.15	1.18 -	1.17 -	1.19 -
KILOGRAM	ST.DEV.	0.08	0.07	0.08	0.04
	MINIMUM	1.02	1.04	1.02	1.09
	MAXIMUM	1.27	1.27	1.26	1.25
	N	10	10	10	10

*/**/- : Significant at 5% (*), 1% (**), or not significant (-)

LOCOMOTOR ACTIVITY - SUMMARY

Data excluded from Summary Report

Not Reported

All Measurements

Animal 81 Male Group 10 Reserve Removed

Animal 82 Female Group 10 Reserve Removed

Reported Parameter

Parameter Statistical Testing

AT WEEK 13

0-10 MIN	LOCOMOTOR ACTIVITY	DUNNETT
10-20 MIN	LOCOMOTOR ACTIVITY	DUNNETT
20-30 MIN	LOCOMOTOR ACTIVITY	DUNNETT
30-40 MIN	LOCOMOTOR ACTIVITY	DUNNETT
40-50 MIN	LOCOMOTOR ACTIVITY	DUNNETT
50-60 MIN	LOCOMOTOR ACTIVITY	DUNNETT
Total	LOCOMOTOR ACTIVITY	DUNNETT

AT WEEK 13

0-10 MIN	LOCOMOTOR ACTIVITY	DUNNETT
10-20 MIN	LOCOMOTOR ACTIVITY	DUNNETT
20-30 MIN	LOCOMOTOR ACTIVITY	DUNNETT
30-40 MIN	LOCOMOTOR ACTIVITY	DUNNETT
40-50 MIN	LOCOMOTOR ACTIVITY	DUNNETT
50-60 MIN	LOCOMOTOR ACTIVITY	DUNNETT
Total	LOCOMOTOR ACTIVITY	DUNNETT

Statistical Methods

DUNNETT DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not significant (-)

**LOCOMOTOR ACTIVITY - SUMMARY
AT WEEK 13
FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
LOCOMOTOR ACTIVITY					

0-10 MIN	MEAN	449	534 -	480 -	539 -
	ST.DEV.	98	145	133	144
	MINIMUM	298	303	253	337
	MAXIMUM	591	678	648	772
	N	10	10	10	10
10-20 MIN	MEAN	251	306 -	230 -	309 -
	ST.DEV.	72	120	74	83
	MINIMUM	115	97	103	129
	MAXIMUM	360	465	312	415
	N	10	10	10	10
20-30 MIN	MEAN	199	263 -	170 -	215 -
	ST.DEV.	107	93	124	125
	MINIMUM	9	145	17	12
	MAXIMUM	431	434	402	431
	N	10	10	10	10
30-40 MIN	MEAN	214	233 -	189 -	132 -
	ST.DEV.	114	106	126	85
	MINIMUM	77	48	6	18
	MAXIMUM	418	388	403	293
	N	10	10	10	10
40-50 MIN	MEAN	110	158 -	92 -	55 -
	ST.DEV.	96	106	98	84
	MINIMUM	0	0	0	0
	MAXIMUM	282	300	282	255
	N	10	10	10	10
50-60 MIN	MEAN	59	100 -	27 -	77 -
	ST.DEV.	59	112	32	121
	MINIMUM	2	0	0	0
	MAXIMUM	162	333	111	345
	N	10	10	10	10

*/**/- : Significant at 5% (*), 1% (**), or not significant (-)

LOCOMOTOR ACTIVITY - SUMMARY
AT WEEK 13
FEMALES

	Group 1	Group 2	Group 3	Group 4	
	0 mg/kg	100 mg/kg	300 mg/kg	1000 mg/kg	
<hr/>					
LOCOMOTOR ACTIVITY					

Total	MEAN	1282	1593 -	1188 -	1327 -
	ST.DEV.	296	510	352	401
	MINIMUM	681	728	671	813
	MAXIMUM	1574	2304	1784	2000
	N	10	10	10	10

*/**/- : Significant at 5% (*), 1% (**), or not significant (-)

LOCOMOTOR ACTIVITY - SUMMARY
AT WEEK 13
MALES

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
LOCOMOTOR ACTIVITY					

0-10 MIN	MEAN	452	496 -	456 -	491 -
	ST.DEV.	66	90	159	118
	MINIMUM	346	349	229	332
	MAXIMUM	527	613	820	671
	N	10	10	10	10
10-20 MIN	MEAN	271	266 -	259 -	310 -
	ST.DEV.	58	69	123	125
	MINIMUM	147	149	45	150
	MAXIMUM	330	373	407	508
	N	10	10	10	10
20-30 MIN	MEAN	178	178 -	184 -	261 *
	ST.DEV.	51	103	79	61
	MINIMUM	71	0	84	181
	MAXIMUM	238	338	317	374
	N	10	10	10	10
30-40 MIN	MEAN	147	121 -	131 -	157 -
	ST.DEV.	73	79	122	80
	MINIMUM	27	0	2	55
	MAXIMUM	278	258	369	302
	N	10	10	10	10
40-50 MIN	MEAN	103	133 -	88 -	106 -
	ST.DEV.	76	66	82	140
	MINIMUM	1	73	8	0
	MAXIMUM	243	267	265	392
	N	10	10	10	10
50-60 MIN	MEAN	94	126 -	74 -	54 -
	ST.DEV.	48	123	74	100
	MINIMUM	1	14	6	0
	MAXIMUM	143	361	213	330
	N	10	10	10	10

*/**/- : Significant at 5% (*), 1% (**), or not significant (-)

LOCOMOTOR ACTIVITY - SUMMARY
AT WEEK 13
MALES

	Group 1	Group 2	Group 3	Group 4	
	0 mg/kg	100 mg/kg	300 mg/kg	1000 mg/kg	
<hr/>					
LOCOMOTOR ACTIVITY					

Total	MEAN	1244	1320 -	1192 -	1378 -
	ST.DEV.	165	292	395	393
	MINIMUM	957	715	549	785
	MAXIMUM	1549	1723	1832	1998
	N	10	10	10	10

*/**/- : Significant at 5% (*), 1% (**), or not significant (-)

FOOD CONSUMPTION (G/ANIMAL/DAY) - SUMMARY

Data excluded from Summary Report

Not Reported

All Study Phases

Cage 17 Male Group 10 Reserve Removed

Cage 18 Female Group 10 Reserve Removed

**FOOD CONSUMPTION (G/ANIMAL/DAY) - SUMMARY
MALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
ACCLIMATIZATION					
Days 1-8	MEAN	20.9	20.6	20.4	20.9
	ST.DEV.	0.4	0.9	0.9	0.4
	N	2	2	2	2
TREATMENT					
Days 1-8	MEAN	23.0	23.0	22.6	23.2
	ST.DEV.	0.0	1.0	0.8	0.5
	N	2	2	2	2
Days 8-15	MEAN	24.4	23.9	23.7	24.2
	ST.DEV.	0.1	1.2	0.7	0.2
	N	2	2	2	2
Days 15-22	MEAN	24.3	24.0	23.7	23.4
	ST.DEV.	0.0	1.2	0.8	0.1
	N	2	2	2	2
Days 22-29	MEAN	23.8	23.6	23.3	23.0
	ST.DEV.	0.2	1.1	0.9	0.1
	N	2	2	2	2
Days 29-36	MEAN	23.3	23.5	23.0	22.5
	ST.DEV.	0.5	0.9	0.4	0.1
	N	2	2	2	2
Days 36-43	MEAN	23.6	23.5	23.0	22.6
	ST.DEV.	0.2	1.3	0.1	0.0
	N	2	2	2	2
Days 43-50	MEAN	24.4	23.7	23.3	22.8
	ST.DEV.	0.5	1.7	0.2	0.5
	N	2	2	2	2
Days 50-57	MEAN	23.6	22.2	22.3	22.0
	ST.DEV.	0.8	1.4	0.0	0.0
	N	2	2	2	2
Days 57-64	MEAN	24.4	22.8	22.6	22.3
	ST.DEV.	0.6	1.4	0.6	0.0
	N	2	2	2	2
Days 64-71	MEAN	23.7	22.4	22.1	21.4
	ST.DEV.	0.6	1.4	0.7	0.0
	N	2	2	2	2

**FOOD CONSUMPTION (G/ANIMAL/DAY) - SUMMARY
MALES**

		Group 1	Group 2	Group 3	Group 4
		0 mg/kg	100 mg/kg	300 mg/kg	1000 mg/kg
TREATMENT					
Days 71-78	MEAN	23.4	22.5	22.2	21.5
	ST.DEV.	0.6	1.7	0.8	0.1
	N	2	2	2	2
Days 78-85	MEAN	23.9	22.6	22.4	22.1
	ST.DEV.	0.5	1.2	0.7	0.1
	N	2	2	2	2
Days 85-90	MEAN	24.0	23.1	22.4	22.1
	ST.DEV.	0.6	0.9	0.4	0.3
	N	2	2	2	2
MEAN OF MEANS Over TREATMENT		23.8	23.1	22.8	22.6

**FOOD CONSUMPTION (G/ANIMAL/DAY) - SUMMARY
FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
ACCLIMATIZATION					
Days 1-8	MEAN	15.0	14.9	14.5	15.0
	ST.DEV.	0.2	0.3	0.2	0.3
	N	2	2	2	2
TREATMENT					
Days 1-8	MEAN	15.6	15.5	15.4	15.3
	ST.DEV.	0.6	0.2	0.6	0.4
	N	2	2	2	2
Days 8-15	MEAN	17.3	16.7	16.4	16.5
	ST.DEV.	0.7	0.0	0.6	0.2
	N	2	2	2	2
Days 15-22	MEAN	16.2	16.4	15.7	16.1
	ST.DEV.	1.3	0.1	0.5	0.3
	N	2	2	2	2
Days 22-29	MEAN	16.6	16.5	16.2	16.8
	ST.DEV.	0.8	0.0	0.7	0.7
	N	2	2	2	2
Days 29-36	MEAN	16.9	16.3	16.0	16.6
	ST.DEV.	0.6	0.2	0.6	0.9
	N	2	2	2	2
Days 36-43	MEAN	16.9	16.3	15.8	16.0
	ST.DEV.	1.2	0.2	0.7	0.2
	N	2	2	2	2
Days 43-50	MEAN	16.7	15.8	15.5	15.7
	ST.DEV.	1.3	0.3	0.7	0.2
	N	2	2	2	2
Days 50-57	MEAN	16.0	15.3	15.0	15.0
	ST.DEV.	1.5	0.2	0.6	0.1
	N	2	2	2	2
Days 57-64	MEAN	16.5	15.9	15.7	15.8
	ST.DEV.	1.4	0.2	0.7	0.0
	N	2	2	2	2
Days 64-71	MEAN	16.3	15.5	15.0	15.2
	ST.DEV.	1.0	0.1	0.5	0.5
	N	2	2	2	2

**FOOD CONSUMPTION (G/ANIMAL/DAY) - SUMMARY
FEMALES**

		Group 1	Group 2	Group 3	Group 4
		0 mg/kg	100 mg/kg	300 mg/kg	1000 mg/kg
TREATMENT					
Days 71-78	MEAN	15.5	15.0	15.1	15.0
	ST.DEV.	0.9	0.4	0.7	0.4
	N	2	2	2	2
Days 78-85	MEAN	16.2	15.6	15.5	15.4
	ST.DEV.	1.0	0.1	0.5	0.5
	N	2	2	2	2
Days 85-90	MEAN	16.0	15.4	15.6	15.3
	ST.DEV.	1.3	0.2	0.9	0.7
	N	2	2	2	2
MEAN OF MEANS Over TREATMENT		16.4	15.9	15.6	15.8

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

Data excluded from Summary Report

Not Reported

All Study Phases

Cage 17 Male Group 10 Reserve Removed

Cage 18 Female Group 10 Reserve Removed

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

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
ACCLIMATIZATION					
Days 1-8	MEAN	108.2	107.6	104.7	110.6
	ST.DEV.	3.0	4.9	2.0	2.0
	N	2	2	2	2
TREATMENT					
Days 1-8	MEAN	83.2	82.0	81.8	83.9
	ST.DEV.	0.0	0.6	0.6	0.3
	N	2	2	2	2
Days 8-15	MEAN	79.3	77.0	77.4	78.4
	ST.DEV.	0.2	0.8	0.2	0.7
	N	2	2	2	2
Days 15-22	MEAN	73.3	71.7	72.1	70.7
	ST.DEV.	0.1	0.2	0.4	1.0
	N	2	2	2	2
Days 22-29	MEAN	67.9	65.7	66.6	65.3
	ST.DEV.	0.9	0.2	0.9	1.5
	N	2	2	2	2
Days 29-36	MEAN	63.5	62.3	62.8	60.8
	ST.DEV.	1.0	0.4	0.2	1.2
	N	2	2	2	2
Days 36-43	MEAN	61.5	59.9	60.4	58.6
	ST.DEV.	0.1	0.2	1.0	1.1
	N	2	2	2	2
Days 43-50	MEAN	60.8	58.0	58.7	56.9
	ST.DEV.	0.3	1.3	2.0	0.3
	N	2	2	2	2
Days 50-57	MEAN	56.8	52.8	54.4	53.3
	ST.DEV.	0.9	0.6	1.1	0.8
	N	2	2	2	2
Days 57-64	MEAN	57.4	52.8	53.9	52.4
	ST.DEV.	0.5	0.5	0.2	1.1
	N	2	2	2	2
Days 64-71	MEAN	54.6	50.8	51.5	49.5
	ST.DEV.	0.6	0.5	0.2	1.1
	N	2	2	2	2

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

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
TREATMENT					
Days 71-78	MEAN	52.6	49.7	50.7	48.6
	ST.DEV.	0.4	0.8	0.4	1.2
	N	2	2	2	2
Days 78-85	MEAN	53.0	49.4	50.4	49.3
	ST.DEV.	0.2	0.4	0.1	1.3
	N	2	2	2	2
Days 85-90	MEAN	53.0	50.0	50.3	48.9
	ST.DEV.	0.3	1.0	0.8	0.4
	N	2	2	2	2
MEAN OF MEANS Over TREATMENT		62.8	60.2	60.9	59.7

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

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
ACCLIMATIZATION					
Days 1-8	MEAN	98.7	98.2	96.1	99.7
	ST.DEV.	0.1	6.8	1.4	1.3
	N	2	2	2	2
TREATMENT					
Days 1-8	MEAN	84.0	82.5	81.1	82.3
	ST.DEV.	2.0	3.2	0.1	3.3
	N	2	2	2	2
Days 8-15	MEAN	86.4	83.0	80.4	82.9
	ST.DEV.	1.3	2.6	0.5	0.4
	N	2	2	2	2
Days 15-22	MEAN	77.6	78.5	75.0	77.2
	ST.DEV.	2.6	3.0	0.4	0.5
	N	2	2	2	2
Days 22-29	MEAN	76.0	74.9	73.5	74.9
	ST.DEV.	0.9	3.0	1.2	0.4
	N	2	2	2	2
Days 29-36	MEAN	75.0	71.2	69.3	72.6
	ST.DEV.	1.2	2.2	0.7	1.4
	N	2	2	2	2
Days 36-43	MEAN	72.7	69.6	67.7	68.8
	ST.DEV.	2.5	1.4	1.5	2.4
	N	2	2	2	2
Days 43-50	MEAN	70.0	66.8	65.5	65.8
	ST.DEV.	2.0	0.6	0.9	0.6
	N	2	2	2	2
Days 50-57	MEAN	66.1	63.1	62.1	62.1
	ST.DEV.	2.9	1.6	0.3	1.8
	N	2	2	2	2
Days 57-64	MEAN	67.5	64.5	63.0	64.5
	ST.DEV.	3.1	2.2	0.9	2.6
	N	2	2	2	2
Days 64-71	MEAN	65.1	61.7	60.0	61.6
	ST.DEV.	1.0	2.2	1.7	3.6
	N	2	2	2	2

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

		Group 1	Group 2	Group 3	Group 4
		0 mg/kg	100 mg/kg	300 mg/kg	1000 mg/kg
TREATMENT					
Days 71-78	MEAN	61.7	59.5	59.6	59.7
	ST.DEV.	0.2	3.7	0.5	2.6
	N	2	2	2	2
Days 78-85	MEAN	64.2	61.5	60.5	60.7
	ST.DEV.	0.4	2.3	0.3	3.7
	N	2	2	2	2
Days 85-90	MEAN	63.1	60.8	60.8	60.6
	ST.DEV.	1.5	1.5	1.6	3.9
	N	2	2	2	2
MEAN OF MEANS Over TREATMENT		71.5	69.0	67.6	68.7

BODY WEIGHTS (G) - SUMMARY

Data excluded from Summary Report

Not Reported

All Study Phases

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

BODY WEIGHTS (G) - SUMMARY
MALES

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
ACCLIMATIZATION					
Day 1	MEAN	193.3	191.8 -	194.6 -	189.2 -
	ST.DEV.	3.6	7.8	5.6	6.5
	N	10	10	10	10
TREATMENT					
Day 1	MEAN	241.5	241.4 -	240.4 -	236.7 -
	ST.DEV.	4.3	10.4	10.7	7.1
	N	10	10	10	10
Day 8	MEAN	275.7	280.7 -	276.0 -	275.9 -
	ST.DEV.	4.7	13.9	15.0	11.4
	N	10	10	10	10
Day 15	MEAN	307.8	310.6 -	306.7 -	309.3 -
	ST.DEV.	5.8	15.8	18.9	12.8
	N	10	10	10	10
Day 22	MEAN	331.0	335.5 -	328.7 -	331.5 -
	ST.DEV.	6.7	20.2	22.2	14.8
	N	10	10	10	10
Day 29	MEAN	350.6	358.9 -	350.1 -	352.2 -
	ST.DEV.	9.5	22.0	26.3	17.8
	N	10	10	10	10
Day 36	MEAN	367.5	377.0 -	366.9 -	371.0 -
	ST.DEV.	11.5	23.3	30.6	19.5
	N	10	10	10	10
Day 43	MEAN	384.2	392.6 -	380.8 -	385.5 -
	ST.DEV.	10.7	26.2	30.9	20.9
	N	10	10	10	10
Day 50	MEAN	401.5	407.7 -	396.3 -	401.2 -
	ST.DEV.	11.7	27.8	35.4	23.4
	N	10	10	10	10
Day 57	MEAN	415.2	420.2 -	410.0 -	413.5 -
	ST.DEV.	12.4	28.2	37.7	23.8
	N	10	10	10	10
Day 64	MEAN	424.6	431.1 -	419.9 -	425.3 -
	ST.DEV.	13.3	29.7	39.2	25.4
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not sig. (-)

BODY WEIGHTS (G) - SUMMARY
MALES

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
TREATMENT					
Day 71	MEAN	434.3	441.0 -	428.0 -	433.0 -
	ST.DEV.	13.1	28.8	41.2	26.7
	N	10	10	10	10
Day 78	MEAN	444.4	452.2 -	437.9 -	442.5 -
	ST.DEV.	11.9	30.0	42.6	27.3
	N	10	10	10	10
Day 85	MEAN	450.8	459.0 -	443.8 -	448.8 -
	ST.DEV.	13.5	31.7	45.3	26.4
	N	10	10	10	10
Day 90	MEAN	453.9	462.9 -	444.2 -	452.0 -
	ST.DEV.	14.3	31.7	45.2	28.4
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not sig. (-)

**BODY WEIGHTS (G) - SUMMARY
FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
ACCLIMATIZATION					
Day 1	MEAN	151.8	151.9 -	151.0 -	150.6 -
	ST.DEV.	3.4	7.9	6.5	7.6
	N	10	10	10	10
TREATMENT					
Day 1	MEAN	173.2	173.7 -	174.1 -	173.2 -
	ST.DEV.	6.6	8.7	6.7	11.0
	N	10	10	10	10
Day 8	MEAN	186.0	187.3 -	190.1 -	186.5 -
	ST.DEV.	6.8	9.8	9.1	10.6
	N	10	10	10	10
Day 15	MEAN	200.5	201.4 -	203.9 -	199.5 -
	ST.DEV.	7.8	10.8	10.7	10.6
	N	10	10	10	10
Day 22	MEAN	208.7	208.9 -	209.6 -	209.0 -
	ST.DEV.	9.4	13.5	11.8	11.2
	N	10	10	10	10
Day 29	MEAN	218.0	220.8 -	220.9 -	223.9 -
	ST.DEV.	9.9	15.5	11.5	15.5
	N	10	10	10	10
Day 36	MEAN	225.1	229.1 -	230.2 -	229.1 -
	ST.DEV.	9.9	14.8	11.9	15.9
	N	10	10	10	10
Day 43	MEAN	231.9	233.7 -	233.8 -	233.1 -
	ST.DEV.	9.2	13.2	12.4	13.3
	N	10	10	10	10
Day 50	MEAN	238.6	237.1 -	237.0 -	238.4 -
	ST.DEV.	11.0	14.7	14.1	13.7
	N	10	10	10	10
Day 57	MEAN	241.5	242.7 -	242.3 -	241.5 -
	ST.DEV.	13.0	16.1	14.0	14.8
	N	10	10	10	10
Day 64	MEAN	244.4	246.2 -	249.1 -	244.5 -
	ST.DEV.	12.4	16.1	14.4	14.8
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not sig. (-)

**BODY WEIGHTS (G) - SUMMARY
FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
TREATMENT					
Day 71	MEAN	249.5	250.9 -	249.2 -	247.3 -
	ST.DEV.	11.3	14.6	14.0	13.0
	N	10	10	10	10
Day 78	MEAN	251.9	252.5 -	253.4 -	251.8 -
	ST.DEV.	13.0	13.7	16.8	12.6
	N	10	10	10	10
Day 85	MEAN	252.2	253.1 -	256.8 -	254.2 -
	ST.DEV.	14.3	17.7	15.4	14.6
	N	10	10	10	10
Day 90	MEAN	253.6	253.4 -	256.3 -	253.0 -
	ST.DEV.	14.2	15.8	16.5	12.7
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not sig. (-)

BODY WEIGHT GAIN (%) - SUMMARY

Data excluded from Summary Report

Not Reported

All Study Phases

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

**BODY WEIGHT GAIN (%) - SUMMARY
MALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
ACCLIMATIZATION					
Day 1	MEAN	0	0	0	0
	ST.DEV.	0	0	0	0
	N	10	10	10	10
TREATMENT					
Day 1	MEAN	0	0	0	0
	ST.DEV.	0	0	0	0
	N	10	10	10	10
Day 8	MEAN	14	16 -	15 -	17 *
	ST.DEV.	2	2	2	2
	N	10	10	10	10
Day 15	MEAN	27	29 -	28 -	31 -
	ST.DEV.	2	3	4	3
	N	10	10	10	10
Day 22	MEAN	37	39 -	37 -	40 -
	ST.DEV.	3	5	6	4
	N	10	10	10	10
Day 29	MEAN	45	49 -	46 -	49 -
	ST.DEV.	4	5	8	5
	N	10	10	10	10
Day 36	MEAN	52	56 -	53 -	57 -
	ST.DEV.	5	6	9	6
	N	10	10	10	10
Day 43	MEAN	59	63 -	58 -	63 -
	ST.DEV.	5	7	9	6
	N	10	10	10	10
Day 50	MEAN	66	69 -	65 -	69 -
	ST.DEV.	5	7	11	7
	N	10	10	10	10
Day 57	MEAN	72	74 -	70 -	75 -
	ST.DEV.	6	8	12	7
	N	10	10	10	10
Day 64	MEAN	76	79 -	75 -	80 -
	ST.DEV.	6	8	12	8
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**), or not sig. (-)

**BODY WEIGHT GAIN (%) - SUMMARY
MALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
TREATMENT					
Day 71	MEAN	80	83 -	78 -	83 -
	ST.DEV.	6	8	13	8
	N	10	10	10	10
Day 78	MEAN	84	87 -	82 -	87 -
	ST.DEV.	6	8	13	8
	N	10	10	10	10
Day 85	MEAN	87	90 -	84 -	90 -
	ST.DEV.	6	9	14	8
	N	10	10	10	10
Day 90	MEAN	88	92 -	85 -	91 -
	ST.DEV.	6	9	14	8
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not sig. (-)

**BODY WEIGHT GAIN (%) - SUMMARY
FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
ACCLIMATIZATION					
Day 1	MEAN	0	0	0	0
	ST.DEV.	0	0	0	0
	N	10	10	10	10
TREATMENT					
Day 1	MEAN	0	0	0	0
	ST.DEV.	0	0	0	0
	N	10	10	10	10
Day 8	MEAN	7	8 -	9 -	8 -
	ST.DEV.	2	2	2	2
	N	10	10	10	10
Day 15	MEAN	16	16 -	17 -	15 -
	ST.DEV.	3	3	3	4
	N	10	10	10	10
Day 22	MEAN	21	20 -	20 -	21 -
	ST.DEV.	4	3	3	3
	N	10	10	10	10
Day 29	MEAN	26	27 -	27 -	29 -
	ST.DEV.	3	4	3	2
	N	10	10	10	10
Day 36	MEAN	30	32 -	32 -	32 -
	ST.DEV.	4	5	3	3
	N	10	10	10	10
Day 43	MEAN	34	34 -	34 -	35 -
	ST.DEV.	4	3	4	3
	N	10	10	10	10
Day 50	MEAN	38	36 -	36 -	38 -
	ST.DEV.	5	5	5	3
	N	10	10	10	10
Day 57	MEAN	39	40 -	39 -	39 -
	ST.DEV.	5	4	4	3
	N	10	10	10	10
Day 64	MEAN	41	42 -	43 -	41 -
	ST.DEV.	5	5	4	3
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**), or not sig. (-)

**BODY WEIGHT GAIN (%) - SUMMARY
 FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
TREATMENT					
Day 71	MEAN	44	44 -	43 -	43 -
	ST.DEV.	6	3	5	4
	N	10	10	10	10
Day 78	MEAN	45	45 -	46 -	46 -
	ST.DEV.	7	4	6	4
	N	10	10	10	10
Day 85	MEAN	46	46 -	47 -	47 -
	ST.DEV.	6	5	5	3
	N	10	10	10	10
Day 90	MEAN	46	46 -	47 -	46 -
	ST.DEV.	7	5	6	4
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not sig. (-)

OPHTHALMOSCOPIC EXAMINATIONS - SUMMARY

Data excluded from Summary Report

Not Reported

All Study Phases

Animal 81 Male Group 10 Reserve Removed

Animal 82 Female Group 10 Reserve Removed

Reported Grades

No grade conversion defined

**OPHTHALMOSCOPIC EXAMINATIONS - SUMMARY
ACCLIMATIZATION, Day 6, OPTHALMOSCOPY
MALES**

	Group 1 0 mg/kg		Group 2 100 mg/kg		Group 3 300 mg/kg		Group 4 1000 mg/kg	
Animals observed	10		10		10		10	
	Mean	%	Mean	%	Mean	%	Mean	%
Unscheduled Findings								
CORNEA								
- CORNEAL OPACITY (3)								
LEFT EYE	1.0	10%	1.0	30% -	1.0	20% -	1.0	10% -
RIGHT EYE	1.0	30%	1.3	30% -	1.0	20% -	1.0	40% -
LENS								
- PERSISTENT PUPIL MEMBRANE (1)								
LEFT EYE	1.0	20%	-	0% -	-	0% -	-	0% -
RIGHT EYE	1.0	20%	-	0% -	-	0% -	1.0	10% -
VITREOUS BODY								
- PERSISTENT HYALOID VESSEL (1)								
LEFT EYE	1.0	50%	1.0	20% -	1.0	60% -	1.0	40% -
RIGHT EYE	1.0	60%	1.0	40% -	1.0	60% -	1.0	50% -

% : Percentage of affected animals

*/**/- : Fisher's Exact Test significant at 5% (*), 1% (**), or not significant (-)

**OPHTHALMOSCOPIC EXAMINATIONS - SUMMARY
ACCLIMATIZATION, Day 6, OPTHALMOSCOPY
FEMALES**

	Group 1 0 mg/kg		Group 2 100 mg/kg		Group 3 300 mg/kg		Group 4 1000 mg/kg	
Animals observed	10		10		10		10	
	Mean	%	Mean	%	Mean	%	Mean	%
Unscheduled Findings								
CORNEA								
- CORNEAL OPACITY (3)								
LEFT EYE	1.5	20%	-	0% -	2.0	10% -	-	0% -
RIGHT EYE	1.0	30%	1.0	10% -	1.0	40% -	1.0	10% -
LENS								
- PERSISTENT PUPIL MEMBRANE (1)								
RIGHT EYE	-	0%	-	0% -	-	0% -	1.0	10% -
VITREOUS BODY								
- HEMORRHAGE IN VITREOUS (3)								
RIGHT EYE	-	0%	1.0	10% -	-	0% -	-	0% -
- PERSISTENT HYALOID VESSEL (1)								
LEFT EYE	1.0	30%	1.0	50% -	1.0	40% -	1.0	40% -
RIGHT EYE	1.0	50%	1.0	40% -	1.0	50% -	1.0	30% -

% : Percentage of affected animals

*/**/- : Fisher's Exact Test significant at 5% (*), 1% (**), or not significant (-)

OPHTHALMOSCOPIC EXAMINATIONS - SUMMARY
TREATMENT, Day 84, OPTHALMOSCOPY
MALES

	Group 1		Group 2	Group 3	Group 4	
	0 mg/kg		100 mg/kg	300 mg/kg	1000 mg/kg	
Animals observed	10		0	0	10	
	Mean	%			Mean	%
Unscheduled Findings						
CORNEA						
- CORNEAL OPACITY (3)						
LEFT EYE	1.0	10%	-	-	1.0	10%
RIGHT EYE	1.0	10%	-	-	1.0	40%
LENS						
- PERSISTENT PUPIL MEMBRANE (1)						
LEFT EYE	1.0	20%	-	-	-	0%
RIGHT EYE	1.0	20%	-	-	1.0	10%
VITREOUS BODY						
- PERSISTENT HYALOID VESSEL (1)						
LEFT EYE	-	0%	-	-	1.0	10%
RIGHT EYE	1.0	30%	-	-	1.0	10%

% : Percentage of affected animals

*/**/- : Fisher's Exact Test significant at 5% (*), 1% (**), or not significant (-)

OPHTHALMOSCOPIC EXAMINATIONS - SUMMARY
TREATMENT, Day 84, OPTHALMOSCOPY
FEMALES

	Group 1		Group 2	Group 3	Group 4	
	0 mg/kg		100 mg/kg	300 mg/kg	1000 mg/kg	
Animals observed	10		0	0	10	
	Mean	%			Mean	%
Unscheduled Findings						
CORNEA						
- CORNEAL OPACITY (3)						
LEFT EYE	1.0	30%	-	-	-	0% -
RIGHT EYE	1.0	40%	-	-	1.0	10% -
LENS						
- PERSISTENT PUPIL MEMBRANE (1)						
RIGHT EYE	-	0%	-	-	1.0	10% -
VITREOUS BODY						
- PERSISTENT HYALOID VESSEL (1)						
LEFT EYE	1.0	20%	-	-	1.0	10% -
RIGHT EYE	1.0	20%	-	-	1.0	10% -

% : Percentage of affected animals

*/**/- : Fisher's Exact Test significant at 5% (*), 1% (**), or not significant (-)

Hematology - SUMMARY

Data excluded from Summary Report

Not Reported

All Measurements

Animal 81 Male Group 10 Reserve Removed
Animal 82 Female Group 10 Reserve Removed

Reported Parameter

Parameter

Statistical Testing

After 13 Weeks

RBC	ERYTHROCYTES (RBC)	DUNNETT
HB	HEMOGLOBIN (HB)	DUNNETT
HCT	HEMATOCRIT (HCT)	DUNNETT
MCV	MEAN CORPUSCULAR VOLUME (MCV)	DUNNETT
RDW	RED CELL VOL. DISTR. WIDTH (RDW)	DUNNETT
MCH	MEAN CORPUSCULAR HEMOGLOBIN (MCH)	DUNNETT
MCHC	MEAN CORPUSCULAR HEMOGLOBIN CONC. (MCHC)	DUNNETT
HDW	HEMOGLOBIN CONC. DISTR. WIDTH	DUNNETT
RETI	RETICULOCYTE (REL)	STEEL
RETI	RETICULOCYTE (ABS)	DUNNETT
L RETI	MATURITY INDEX (L-RETI)	STEEL
M RETI	MATURITY INDEX (M-RETI)	STEEL
H RETI	MATURITY INDEX (H-RETI)	STEEL
WBC	LEUKOCYTES, TOTAL (WBC)	DUNNETT
NEUT	NEUTROPHILS (NEUT)	STEEL
EOS	EOSINOPHILS (EOS)	STEEL
BASO	BASOPHILS (BASO)	STEEL
LYMPH	LYMPHOCYTES (LYMPH)	STEEL
MONO	MONOCYTES (MONO)	STEEL
LUC	LARGE UNSTAINED CELLS (LUC)	STEEL
NEUT	NEUTROPHILS (NEUT)	DUNNETT
EOS	EOSINOPHILS (EOS)	DUNNETT
BASO	BASOPHILS (BASO)	DUNNETT
LYMPH	LYMPHOCYTES (LYMPH)	DUNNETT
MONO	MONOCYTES (MONO)	DUNNETT
LUC	LARGE UNSTAINED CELLS (LUC)	DUNNETT
PLATELETS	THROMBOCYTES (PLATELETS)	DUNNETT
MET-HB	METHEMOGLOBIN (MET-HB)	STEEL
PT	PROTHROMBIN TIME (PT)	STEEL
PTT	PARTIAL THROMBOPLASTIN TIME (PTT)	STEEL

Statistical Methods

DUNNETT DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not significant (-)

Hematology - SUMMARY

Statistical Methods

STEEL STEEL-Test sig. at 5% (*), 1% (**) or not significant (-)

Hematology - SUMMARY
MALES

GENERAL							
	RBC	HB	HCT	MCV	RDW	MCH	MCHC
	T/l	mmol/l	rel. l	fl	rel. l	fmol	mmol/l
After 13 Weeks							
Group 1	8.64	9.5	0.43	49.4	0.137	1.09	22.15
Group 2	8.65 -	9.4 -	0.43 -	49.3 -	0.140 -	1.09 -	22.11 -
Group 3	8.75 -	9.6 -	0.43 -	49.9 -	0.148 -	1.10 -	22.12 -
Group 4	8.56 -	9.5 -	0.43 -	50.4 -	0.150 -	1.11 -	22.00 -

GENERAL	RETICULOCYTE COUNT					GENERAL	
HDW	RETI	RETI	L RETI	M RETI	H RETI	WBC	
mmol/l	rel. l	G/l	rel. l	rel. l	rel. l	G/l	
After 13 Weeks							
Group 1	1.70	0.018	157	0.546	0.368	0.080	5.44
Group 2	1.80 -	0.020 -	164 -	0.559 -	0.357 -	0.087 -	5.13 -
Group 3	1.71 -	0.019 -	175 -	0.538 -	0.374 -	0.085 -	5.02 -
Group 4	1.61 -	0.020 -	162 -	0.530 -	0.372 -	0.093 -	5.24 -

DIFF.WBC COUNT (REL)						
NEUT	EOS	BASO	LYMPH	MONO	LUC	
rel. l	rel. l	rel. l	rel. l	rel. l	rel. l	
After 13 Weeks						
Group 1	0.235	0.015	0.007	0.717	0.026	0.005
Group 2	0.238 -	0.013 -	0.006 -	0.721 -	0.020 -	0.005 -
Group 3	0.239 -	0.017 -	0.006 -	0.724 -	0.021 -	0.005 -
Group 4	0.212 -	0.013 -	0.005 -	0.732 -	0.024 -	0.004 -

*/**/- : Significant at 5% (*), 1% (**), or not significant (-)

Hematology - SUMMARY
MALES

	DIFF.WBC COUNT (ABS)						GENERAL
	NEUT	EOS	BASO	LYMPH	MONO	LUC	PLATELETS
	G/1	G/1	G/1	G/1	G/1	G/1	G/1
After 13 Weeks							
Group 1	1.32	0.08	0.04	3.83	0.13	0.03	946
Group 2	1.22 -	0.07 -	0.04 -	3.66 -	0.11 -	0.03 -	944 -
Group 3	1.24 -	0.09 -	0.03 -	3.53 -	0.11 -	0.02 -	944 -
Group 4	1.12 -	0.08 -	0.03 -	3.87 -	0.11 -	0.03 -	953 -

	GENERAL	COAGULATION	
	MET-HB	PT	PTT
	rel. 1	rel. 1	sec
After 13 Weeks			
Group 1	0.010	0.82	23.5
Group 2	0.010 -	0.82 -	22.9 -
Group 3	0.009 -	0.82 -	25.0 -
Group 4	0.009 -	0.87 -	25.3 -

*/**/- : Significant at 5% (*), 1% (**) or not significant (-)

Hematology - SUMMARY
FEMALES

GENERAL							
	RBC	HB	HCT	MCV	RDW	MCH	MCHC
	T/l	mmol/l	rel. l	fl	rel. l	fmol	mmol/l
After 13 Weeks							
Group 1	7.59	9.1	0.40	52.4	0.142	1.20	22.94
Group 2	7.65 -	9.3 -	0.40 -	52.9 -	0.140 -	1.22 -	22.99 -
Group 3	7.50 -	9.0 -	0.39 -	51.9 -	0.139 -	1.20 -	23.03 -
Group 4	7.49 -	9.0 -	0.39 -	52.6 -	0.132 -	1.21 -	22.96 -

GENERAL		RETICULOCYTE COUNT				GENERAL	
	HDW	RETI	RETI	L RETI	M RETI	H RETI	WBC
	mmol/l	rel. l	G/l	rel. l	rel. l	rel. l	G/l
After 13 Weeks							
Group 1	1.56	0.024	175	0.607	0.339	0.043	2.66
Group 2	1.50 -	0.022 -	159 -	0.690 -	0.278 -	0.035 -	2.39 -
Group 3	1.54 -	0.022 -	162 -	0.663 -	0.303 -	0.039 -	2.66 -
Group 4	1.45 -	0.023 -	187 -	0.612 -	0.353 -	0.040 -	2.63 -

DIFF.WBC COUNT (REL)						
	NEUT	EOS	BASO	LYMPH	MONO	LUC
	rel. l					
After 13 Weeks						
Group 1	0.210	0.026	0.007	0.729	0.021	0.009
Group 2	0.190 -	0.024 -	0.006 -	0.759 -	0.017 -	0.008 -
Group 3	0.228 -	0.017 -	0.010 -	0.716 -	0.017 -	0.006 -
Group 4	0.204 -	0.024 -	0.007 -	0.722 -	0.021 -	0.011 -

*/**/- : Significant at 5% (*), 1% (**), or not significant (-)

Hematology - SUMMARY
FEMALES

	DIFF.WBC COUNT (ABS)						GENERAL
	NEUT	EOS	BASO	LYMPH	MONO	LUC	PLATELETS
	G/1	G/1	G/1	G/1	G/1	G/1	G/1
After 13 Weeks							
Group 1	0.57	0.07	0.02	1.93	0.05	0.02	1102
Group 2	0.45 -	0.06 -	0.02 -	1.80 -	0.05 -	0.02 -	974 -
Group 3	0.61 -	0.06 -	0.02 -	1.90 -	0.05 -	0.02 -	1001 -
Group 4	0.58 -	0.07 -	0.02 -	1.88 -	0.05 -	0.03 -	997 -

	GENERAL	COAGULATION	
	MET-HB	PT	PTT
	rel. 1	rel. 1	sec
After 13 Weeks			
Group 1	0.010	0.80	35.0
Group 2	0.010 -	0.88 *	31.8 -
Group 3	0.009 -	0.84 -	31.6 -
Group 4	0.009 -	0.84 -	34.9 -

*/**/- : Significant at 5% (*), 1% (**), or not significant (-)

Biochemistry - SUMMARY

Data excluded from Summary Report

Not Reported

All Measurements

Animal 81 Male Group 10 Reserve Removed
Animal 82 Female Group 10 Reserve Removed

Reported Parameter

Parameter Statistical Testing

After 13 Weeks

GLUCOSE	GLUCOSE	DUNNETT
UREA	UREA	DUNNETT
CREAT	CREATININE	DUNNETT
BILI-T	BILIRUBIN, TOTAL	STEEL
CHOLEST	CHOLESTEROL, TOTAL	DUNNETT
TRIGLY	TRIGLYCERIDES	DUNNETT
PHOS-LIP	PHOSPHOLIPIDS	DUNNETT
ASAT	ASPARTATE AMINOTRANSFERASE (ASAT)	DUNNETT
ALAT	ALANINE AMINOTRANSFERASE (ALAT)	DUNNETT
LDH	LACTATE DEHYDROGENASE (LDH)	DUNNETT
GLDH	GLUTAMATE-DEHYDROGENASE (GLDH)	DUNNETT
ALP	ALKALINE PHOSPHATASE (ALP)	DUNNETT
GGT	GAMMA-GLUTAMYLTRANSFERASE (GGT)	STEEL
CK	CREATINE KINASE (CK)	DUNNETT
SODIUM	SODIUM	DUNNETT
POTASSIUM	POTASSIUM	DUNNETT
CHLORIDE	CHLORIDE	DUNNETT
CALCIUM	CALCIUM	DUNNETT
PHOSPHORUS	PHOSPHORUS	DUNNETT
PROTEIN	PROTEIN, TOTAL	DUNNETT
ALBUMIN	ALBUMIN	DUNNETT
GLOBULIN	GLOBULIN	DUNNETT
A/G RATIO	A/G RATIO	STEEL

Statistical Methods

DUNNETT DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not significant (-)
STEEL STEEL-Test sig. at 5% (*), 1% (**) or not significant (-)

Biochemistry - SUMMARY
MALES

GENERAL							
	GLUCOSE	UREA	CREAT	BILI-T	CHOLEST	TRIGLY	PHOS-LIP
	mmol/l	mmol/l	µmol/l	µmol/l	mmol/l	mmol/l	mmol/l
After 13 Weeks							
Group 1	6.51	5.68	29.2	1.90	1.66	0.47	1.44
Group 2	6.12 -	5.66 -	29.2 -	1.95 -	1.87 -	0.37 -	1.54 -
Group 3	6.43 -	5.37 -	29.3 -	2.05 -	1.56 -	0.36 -	1.40 -
Group 4	6.27 -	5.43 -	28.0 -	2.30 -	2.04 *	0.38 -	1.61 -

GENERAL							
	ASAT	ALAT	LDH	GLDH	ALP	GGT	CK
	U/l	U/l	U/l	U/l	U/l	U/l	U/l
After 13 Weeks							
Group 1	89.6	36.8	110.1	7.4	50.7	0.0	115.9
Group 2	91.7 -	34.8 -	115.5 -	6.7 -	48.2 -	0.0 -	134.9 -
Group 3	82.6 -	35.2 -	102.7 -	6.8 -	53.5 -	0.0 -	120.1 -
Group 4	82.1 -	33.9 -	129.5 -	6.4 -	54.0 -	0.0 -	235.1 -

GENERAL							
	SODIUM	POTASSIUM	CHLORIDE	CALCIUM	PHOSPHORUS	PROTEIN	ALBUMIN
	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	g/l	g/l
After 13 Weeks							
Group 1	143.4	3.58	103.0	2.65	1.67	71.34	43.52
Group 2	144.6 **	3.57 -	103.5 -	2.74 **	1.73 -	72.74 -	44.80 -
Group 3	145.8 **	3.56 -	104.0 -	2.72 *	1.74 -	73.86 -	45.70 -
Group 4	146.7 **	3.68 -	105.0 **	2.74 **	1.71 -	73.15 -	43.18 -

*/**/- : Significant at 5% (*), 1% (**) or not significant (-)

Biochemistry - SUMMARY
MALES

GENERAL

.....
GLOBULIN A/G RATIO
g/l

After 13 Weeks

Group 1	27.82	1.50
Group 2	27.94 -	1.60 -
Group 3	28.16 -	1.50 -
Group 4	29.97 -	1.45 -

*/**/- : Significant at 5% (*), 1% (**) or not significant (-)

Biochemistry - SUMMARY
FEMALES

GENERAL							
	GLUCOSE	UREA	CREAT	BILI-T	CHOLEST	TRIGLY	PHOS-LIP
	mmol/l	mmol/l	µmol/l	µmol/l	mmol/l	mmol/l	mmol/l
After 13 Weeks							
Group 1	5.01	6.15	29.4	2.00	1.34	0.28	1.51
Group 2	4.86 -	7.29 -	31.5 -	2.20 -	1.64 -	0.26 -	1.75 -
Group 3	5.24 -	7.20 -	31.9 -	2.25 -	1.67 -	0.24 -	1.81 -
Group 4	4.94 -	7.63 **	34.3 -	2.90 *	1.49 -	0.27 -	1.63 -

GENERAL							
	ASAT	ALAT	LDH	GLDH	ALP	GGT	CK
	U/l	U/l	U/l	U/l	U/l	U/l	U/l
After 13 Weeks							
Group 1	78.1	31.9	115.9	6.7	22.6	0.0	140.5
Group 2	83.3 -	32.4 -	110.7 -	7.9 -	25.3 -	0.0 -	116.7 -
Group 3	76.9 -	28.7 -	139.4 -	4.8 -	25.0 -	0.0 -	250.6 -
Group 4	73.9 -	29.5 -	124.2 -	10.4 -	22.2 -	0.0 -	124.7 -

GENERAL							
	SODIUM	POTASSIUM	CHLORIDE	CALCIUM	PHOSPHORUS	PROTEIN	ALBUMIN
	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	g/l	g/l
After 13 Weeks							
Group 1	136.1	3.17	97.5	2.62	1.13	74.30	48.15
Group 2	136.8 -	3.15 -	97.4 -	2.72 **	1.30 -	76.42 -	50.64 -
Group 3	136.8 -	3.06 -	98.1 -	2.66 -	1.18 -	76.12 -	50.27 -
Group 4	138.6 **	3.01 -	99.6 *	2.66 -	1.18 -	74.64 -	49.37 -

*/**/- : Significant at 5% (*), 1% (**) or not significant (-)

Biochemistry - SUMMARY
FEMALES

GENERAL

.....
GLOBULIN A/G RATIO
g/l

After 13 Weeks

Group 1	26.15	1.87
Group 2	25.78 -	1.92 -
Group 3	25.85 -	1.99 -
Group 4	25.28 -	1.94 -

*/**/- : Significant at 5% (*), 1% (**) or not significant (-)

Urinalysis - SUMMARY

Data excluded from Summary Report

Not Reported

All Measurements

Animal 81 Male Group 10 Reserve Removed

Animal 82 Female Group 10 Reserve Removed

Reported Parameter

Parameter Statistical Testing

After 13 Weeks

VOLUME/18h	VOLUME/18h	STEEL
REL DENS	RELATIVE DENSITY	STEEL
pH	pH	STEEL
NITRITE	NITRITE	
PROTEIN	PROTEIN	STEEL
GLUCOSE	GLUCOSE	STEEL
KETONES	KETONES	STEEL
UROBILI	UROBILINOGEN	STEEL
BILIRUBIN	BILIRUBIN	STEEL
ERY	ERYTHROCYTES	STEEL
LEU	LEUCOCYTES	STEEL

Statistical Methods

STEEL STEEL-Test sig. at 5% (*), 1% (**) or not significant (-)

Urinalysis - SUMMARY
MALES

GENERAL							
	VOLUME/18h	REL DENS	pH	NITRITE	PROTEIN	GLUCOSE	KETONES
	ml	rel. 1		SCORE 0/1	g/l	mmol/l	mmol/l
After 13 Weeks							
Group 1	4.7	1.047	6.8	1	0.25	0	1.0
Group 2	6.3 -	1.042 -	7.0 -	1	0.25 -	0 -	1.5 -
Group 3	5.7 -	1.043 -	6.8 -	1	0.25 -	0 -	0.5 -
Group 4	6.2 -	1.044 -	7.0 -	0	0.25 -	0 -	1.0 -

GENERAL				
	UROBILI	BILIRUBIN	ERY	LEU
	µmol/l	µmol/l	per µl	per µl
After 13 Weeks				
Group 1	0	0	10	25
Group 2	0 -	0 -	25 -	25 -
Group 3	0 -	0 -	10 -	25 -
Group 4	0 -	0 -	10 -	25 -

*/**/- : Significant at 5% (*), 1% (**), or not significant (-)

Urinalysis - SUMMARY
FEMALES

GENERAL							
	VOLUME/18h	REL DENS	pH	NITRITE	PROTEIN	GLUCOSE	KETONES
	ml	rel. 1		SCORE 0/1	g/l	mmol/l	mmol/l
After 13 Weeks							
Group 1	6.5	1.037	6.0	0	0.25	0	0.0
Group 2	5.7 -	1.039 -	6.0 -	1	0.25 -	0 -	0.0 -
Group 3	6.3 -	1.036 -	6.0 -	1	0.13 -	0 -	0.0 -
Group 4	4.3 -	1.041 -	6.0 -	1	0.25 -	0 -	0.5 -

GENERAL				
	UROBILI	BILIRUBIN	ERY	LEU
	µmol/l	µmol/l	per µl	per µl
After 13 Weeks				
Group 1	0	0	0	0
Group 2	0 -	0 -	0 -	0 -
Group 3	0 -	0 -	0 -	0 -
Group 4	0 -	9 *	0 -	0 -

*/**/- : Significant at 5% (*), 1% (**), or not significant (-)

ORGAN WEIGHTS (GRAM) - SUMMARY

Exclusions from Summary

Not Reported

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

Selection of Organs

All organs reported

**ORGAN WEIGHTS (GRAM) - SUMMARY
AFTER WEEK 13 OF TREATMENT
MALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
BODY W.	MEAN	436.1	447.2 -	425.2 -	429.1 -
	ST.DEV.	13.2	34.2	43.8	28.9
	MINIMUM	409.9	406.5	352.0	372.7
	MAXIMUM	450.5	512.4	504.4	483.2
	N	10	10	10	10
BRAIN	MEAN	2.11	2.08 -	2.12 -	2.08 -
	ST.DEV.	0.06	0.05	0.10	0.08
	MINIMUM	2.01	1.97	1.94	1.98
	MAXIMUM	2.20	2.13	2.23	2.20
	N	10	10	10	10
HEART	MEAN	1.15	1.13 -	1.08 -	1.00 *
	ST.DEV.	0.13	0.18	0.11	0.08
	MINIMUM	1.00	0.96	0.89	0.90
	MAXIMUM	1.46	1.62	1.30	1.15
	N	10	10	10	10
LIVER	MEAN	11.22	11.06 -	10.75 -	10.59 -
	ST.DEV.	1.09	1.72	1.24	0.78
	MINIMUM	9.91	9.60	8.55	9.24
	MAXIMUM	13.55	15.22	13.29	11.64
	N	10	10	10	10
THYMUS	MEAN	0.297	0.267 -	0.301 -	0.325 -
	ST.DEV.	0.073	0.029	0.091	0.067
	MINIMUM	0.159	0.237	0.212	0.224
	MAXIMUM	0.402	0.320	0.492	0.423
	N	10	10	10	10
KIDNEYS	MEAN	2.29	2.18 -	2.10 -	2.10 -
	ST.DEV.	0.23	0.20	0.21	0.16
	MINIMUM	1.99	1.82	1.68	1.87
	MAXIMUM	2.65	2.45	2.41	2.39
	N	10	10	10	10
ADRENALS	MEAN	0.060	0.060 -	0.062 -	0.062 -
	ST.DEV.	0.007	0.005	0.010	0.008
	MINIMUM	0.046	0.055	0.047	0.051
	MAXIMUM	0.069	0.072	0.079	0.072
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**), or not sig. (-)

**ORGAN WEIGHTS (GRAM) - SUMMARY
AFTER WEEK 13 OF TREATMENT
MALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
SPLEEN	MEAN	0.73	0.69 -	0.72 -	0.70 -
	ST.DEV.	0.11	0.06	0.12	0.13
	MINIMUM	0.62	0.60	0.56	0.56
	MAXIMUM	0.90	0.75	0.89	0.94
	N	10	10	10	10
TESTES	MEAN	3.85	3.91 -	3.82 -	3.61 -
	ST.DEV.	0.31	0.27	0.32	0.36
	MINIMUM	3.27	3.36	3.21	3.02
	MAXIMUM	4.26	4.39	4.28	4.14
	N	10	10	10	10
EPIDIDYDYMID	MEAN	1.552	1.487 -	1.466 -	1.421 -
	ST.DEV.	0.168	0.142	0.108	0.080
	MINIMUM	1.339	1.315	1.301	1.321
	MAXIMUM	1.853	1.731	1.649	1.555
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not sig. (-)

**ORGAN/BODY WEIGHT RATIOS (%) - SUMMARY
AFTER WEEK 13 OF TREATMENT
MALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
BODY W.	MEAN	436.1	447.2 -	425.2 -	429.1 -
	ST.DEV.	13.2	34.2	43.8	28.9
	MINIMUM	409.9	406.5	352.0	372.7
	MAXIMUM	450.5	512.4	504.4	483.2
	N	10	10	10	10
BRAIN	MEAN	0.49	0.47 -	0.50 -	0.49 -
	ST.DEV.	0.01	0.03	0.04	0.04
	MINIMUM	0.47	0.41	0.44	0.44
	MAXIMUM	0.50	0.50	0.57	0.56
	N	10	10	10	10
HEART	MEAN	0.26	0.26 -	0.25 -	0.23 -
	ST.DEV.	0.02	0.05	0.02	0.01
	MINIMUM	0.24	0.23	0.23	0.21
	MAXIMUM	0.32	0.39	0.30	0.25
	N	10	10	10	10
LIVER	MEAN	2.58	2.46 -	2.53 -	2.47 -
	ST.DEV.	0.25	0.22	0.12	0.18
	MINIMUM	2.20	2.21	2.27	2.18
	MAXIMUM	3.06	2.97	2.71	2.74
	N	10	10	10	10
THYMUS	MEAN	0.068	0.060 -	0.071 -	0.076 -
	ST.DEV.	0.017	0.006	0.019	0.018
	MINIMUM	0.039	0.052	0.046	0.052
	MAXIMUM	0.096	0.071	0.106	0.109
	N	10	10	10	10
KIDNEYS	MEAN	0.53	0.49 -	0.50 -	0.49 -
	ST.DEV.	0.04	0.04	0.06	0.03
	MINIMUM	0.47	0.43	0.43	0.43
	MAXIMUM	0.59	0.56	0.61	0.53
	N	10	10	10	10
ADRENALS	MEAN	0.014	0.013 -	0.015 -	0.015 -
	ST.DEV.	0.002	0.002	0.002	0.002
	MINIMUM	0.010	0.011	0.011	0.012
	MAXIMUM	0.016	0.017	0.017	0.017
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**), or not sig. (-)

**ORGAN/BODY WEIGHT RATIOS (%) - SUMMARY
AFTER WEEK 13 OF TREATMENT
MALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
SPLEEN	MEAN	0.17	0.15 -	0.17 -	0.16 -
	ST.DEV.	0.02	0.01	0.02	0.03
	MINIMUM	0.14	0.13	0.14	0.13
	MAXIMUM	0.20	0.18	0.20	0.22
	N	10	10	10	10
TESTES	MEAN	0.89	0.88 -	0.90 -	0.84 -
	ST.DEV.	0.07	0.05	0.09	0.08
	MINIMUM	0.73	0.82	0.73	0.68
	MAXIMUM	0.96	0.95	1.02	0.95
	N	10	10	10	10
EPIDIDYMIUM	MEAN	0.356	0.333 -	0.347 -	0.332 -
	ST.DEV.	0.034	0.027	0.033	0.023
	MINIMUM	0.297	0.293	0.289	0.304
	MAXIMUM	0.414	0.388	0.384	0.379
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**), or not sig. (-)

**ORGAN/BRAIN WEIGHT RATIOS (%) - SUMMARY
AFTER WEEK 13 OF TREATMENT
MALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
BRAIN	MEAN	2.11	2.08 -	2.12 -	2.08 -
	ST.DEV.	0.06	0.05	0.10	0.08
	MINIMUM	2.01	1.97	1.94	1.98
	MAXIMUM	2.20	2.13	2.23	2.20
	N	10	10	10	10
HEART	MEAN	54.61	54.43 -	50.76 -	48.09 -
	ST.DEV.	5.45	9.43	4.60	4.00
	MINIMUM	47.39	48.73	44.06	43.06
	MAXIMUM	66.36	80.20	58.30	53.55
	N	10	10	10	10
LIVER	MEAN	532.12	530.73 -	507.67 -	509.06 -
	ST.DEV.	55.30	80.62	50.35	45.43
	MINIMUM	450.45	458.10	423.27	442.11
	MAXIMUM	651.44	731.73	601.36	584.92
	N	10	10	10	10
THYMUS	MEAN	14.010	12.832 -	14.129 -	15.562 -
	ST.DEV.	3.262	1.265	3.790	2.895
	MINIMUM	7.833	11.127	10.341	11.256
	MAXIMUM	19.052	15.166	22.063	19.583
	N	10	10	10	10
KIDNEYS	MEAN	108.69	104.81 -	99.19 -	100.97 -
	ST.DEV.	11.28	8.96	9.24	8.79
	MINIMUM	95.45	90.10	83.17	85.00
	MAXIMUM	124.04	117.79	115.12	114.07
	N	10	10	10	10
ADRENALS	MEAN	2.862	2.882 -	2.940 -	2.957 -
	ST.DEV.	0.376	0.263	0.395	0.429
	MINIMUM	2.130	2.582	2.327	2.440
	MAXIMUM	3.317	3.512	3.575	3.618
	N	10	10	10	10
SPLEEN	MEAN	34.68	33.04 -	33.97 -	33.35 -
	ST.DEV.	5.55	2.70	4.86	5.42
	MINIMUM	28.64	28.17	28.87	28.00
	MAXIMUM	42.79	35.58	43.20	43.72
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**), or not sig. (-)

**ORGAN/BRAIN WEIGHT RATIOS (%) - SUMMARY
AFTER WEEK 13 OF TREATMENT
MALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
TESTES	MEAN	182.60	187.43 -	180.57 -	173.56 -
	ST.DEV.	17.69	11.45	14.54	16.50
	MINIMUM	148.64	170.56	155.83	145.89
	MAXIMUM	204.98	211.06	198.56	191.96
	N	10	10	10	10
EPIDIDYDYMID	MEAN	73.557	71.352 -	69.396 -	68.294 -
	ST.DEV.	8.147	6.255	5.967	4.891
	MINIMUM	60.864	62.322	59.955	63.206
	MAXIMUM	86.589	83.221	78.900	78.535
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not sig. (-)

**ORGAN WEIGHTS (GRAM) - SUMMARY
AFTER WEEK 13 OF TREATMENT
FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
BODY W.	MEAN	242.9	243.1 -	243.3 -	236.8 -
	ST.DEV.	13.1	14.7	15.2	12.4
	MINIMUM	229.9	222.9	211.4	217.9
	MAXIMUM	262.0	265.1	264.1	256.1
	N	10	10	10	10
BRAIN	MEAN	1.93	1.96 -	1.99 -	1.94 -
	ST.DEV.	0.08	0.06	0.05	0.06
	MINIMUM	1.81	1.87	1.86	1.86
	MAXIMUM	2.06	2.07	2.05	2.06
	N	10	10	10	10
HEART	MEAN	0.75	0.71 -	0.75 -	0.71 -
	ST.DEV.	0.04	0.03	0.07	0.06
	MINIMUM	0.66	0.66	0.61	0.60
	MAXIMUM	0.82	0.75	0.84	0.80
	N	10	10	10	10
LIVER	MEAN	6.60	6.83 -	6.90 -	6.22 -
	ST.DEV.	0.62	0.78	0.86	0.63
	MINIMUM	5.88	5.68	5.14	5.15
	MAXIMUM	7.90	8.10	8.04	7.30
	N	10	10	10	10
THYMUS	MEAN	0.289	0.257 -	0.290 -	0.256 -
	ST.DEV.	0.049	0.040	0.041	0.081
	MINIMUM	0.222	0.186	0.253	0.065
	MAXIMUM	0.364	0.319	0.388	0.349
	N	10	10	10	10
KIDNEYS	MEAN	1.54	1.41 *	1.42 *	1.35 **
	ST.DEV.	0.13	0.07	0.13	0.09
	MINIMUM	1.31	1.30	1.17	1.22
	MAXIMUM	1.73	1.53	1.61	1.49
	N	10	10	10	10
ADRENALS	MEAN	0.077	0.071 -	0.073 -	0.076 -
	ST.DEV.	0.009	0.010	0.008	0.009
	MINIMUM	0.062	0.055	0.058	0.063
	MAXIMUM	0.089	0.090	0.087	0.086
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not sig. (-)

**ORGAN WEIGHTS (GRAM) - SUMMARY
AFTER WEEK 13 OF TREATMENT
FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
SPLEEN	MEAN	0.54	0.53 -	0.53 -	0.51 -
	ST.DEV.	0.11	0.07	0.06	0.09
	MINIMUM	0.40	0.41	0.43	0.39
	MAXIMUM	0.76	0.65	0.61	0.73
	N	10	10	10	10
OVARIES	MEAN	0.116	0.113 -	0.097 *	0.109 -
	ST.DEV.	0.023	0.008	0.013	0.017
	MINIMUM	0.067	0.101	0.075	0.092
	MAXIMUM	0.154	0.123	0.117	0.144
	N	10	10	10	10
UTERUS	MEAN	1.14	0.83 -	0.90 -	0.93 -
	ST.DEV.	0.48	0.15	0.18	0.20
	MINIMUM	0.67	0.67	0.73	0.69
	MAXIMUM	2.31	1.11	1.31	1.34
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**), or not sig. (-)

**ORGAN/BODY WEIGHT RATIOS (%) - SUMMARY
AFTER WEEK 13 OF TREATMENT
FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
BODY W.	MEAN	242.9	243.1 -	243.3 -	236.8 -
	ST.DEV.	13.1	14.7	15.2	12.4
	MINIMUM	229.9	222.9	211.4	217.9
	MAXIMUM	262.0	265.1	264.1	256.1
	N	10	10	10	10
BRAIN	MEAN	0.80	0.81 -	0.82 -	0.82 -
	ST.DEV.	0.06	0.05	0.06	0.04
	MINIMUM	0.69	0.74	0.74	0.74
	MAXIMUM	0.89	0.90	0.94	0.87
	N	10	10	10	10
HEART	MEAN	0.31	0.29 -	0.31 -	0.30 -
	ST.DEV.	0.02	0.02	0.02	0.03
	MINIMUM	0.28	0.28	0.28	0.23
	MAXIMUM	0.34	0.33	0.35	0.33
	N	10	10	10	10
LIVER	MEAN	2.72	2.80 -	2.83 -	2.63 -
	ST.DEV.	0.20	0.22	0.28	0.25
	MINIMUM	2.52	2.43	2.43	2.02
	MAXIMUM	3.12	3.09	3.34	2.85
	N	10	10	10	10
THYMUS	MEAN	0.119	0.106 -	0.119 -	0.109 -
	ST.DEV.	0.018	0.014	0.017	0.034
	MINIMUM	0.085	0.080	0.103	0.025
	MAXIMUM	0.143	0.128	0.164	0.149
	N	10	10	10	10
KIDNEYS	MEAN	0.63	0.58 *	0.58 -	0.57 *
	ST.DEV.	0.04	0.04	0.06	0.04
	MINIMUM	0.57	0.52	0.49	0.49
	MAXIMUM	0.71	0.65	0.66	0.62
	N	10	10	10	10
ADRENALS	MEAN	0.032	0.029 -	0.030 -	0.032 -
	ST.DEV.	0.003	0.004	0.004	0.004
	MINIMUM	0.026	0.024	0.023	0.025
	MAXIMUM	0.036	0.034	0.036	0.037
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**), or not sig. (-)

**ORGAN/BODY WEIGHT RATIOS (%) - SUMMARY
AFTER WEEK 13 OF TREATMENT
FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
SPLEEN	MEAN	0.22	0.22 -	0.22 -	0.22 -
	ST.DEV.	0.04	0.02	0.03	0.04
	MINIMUM	0.17	0.18	0.18	0.17
	MAXIMUM	0.30	0.26	0.27	0.31
	N	10	10	10	10
OVARIES	MEAN	0.048	0.046 -	0.040 *	0.046 -
	ST.DEV.	0.009	0.004	0.005	0.008
	MINIMUM	0.029	0.040	0.032	0.036
	MAXIMUM	0.061	0.052	0.049	0.061
	N	10	10	10	10
UTERUS	MEAN	0.47	0.34 -	0.37 -	0.39 -
	ST.DEV.	0.21	0.07	0.08	0.09
	MINIMUM	0.29	0.25	0.28	0.27
	MAXIMUM	1.00	0.47	0.53	0.59
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not sig. (-)

**ORGAN/BRAIN WEIGHT RATIOS (%) - SUMMARY
AFTER WEEK 13 OF TREATMENT
FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
BRAIN	MEAN	1.93	1.96 -	1.99 -	1.94 -
	ST.DEV.	0.08	0.06	0.05	0.06
	MINIMUM	1.81	1.87	1.86	1.86
	MAXIMUM	2.06	2.07	2.05	2.06
	N	10	10	10	10
HEART	MEAN	38.77	36.28 -	37.73 -	36.47 -
	ST.DEV.	2.80	1.80	3.34	3.04
	MINIMUM	34.74	33.33	30.81	31.58
	MAXIMUM	43.09	38.30	41.38	42.47
	N	10	10	10	10
LIVER	MEAN	342.06	348.35 -	346.50 -	320.97 -
	ST.DEV.	32.46	44.50	40.68	29.16
	MINIMUM	306.25	278.43	259.60	271.05
	MAXIMUM	405.13	415.38	396.06	368.69
	N	10	10	10	10
THYMUS	MEAN	14.975	13.143 -	14.547 -	13.188 -
	ST.DEV.	2.357	2.270	1.897	4.115
	MINIMUM	11.408	9.118	12.808	3.421
	MAXIMUM	18.667	16.359	19.208	18.083
	N	10	10	10	10
KIDNEYS	MEAN	79.75	71.56 **	71.13 **	69.71 **
	ST.DEV.	7.34	3.55	6.83	3.60
	MINIMUM	68.95	66.67	59.69	63.87
	MAXIMUM	87.85	78.46	79.31	75.25
	N	10	10	10	10
ADRENALS	MEAN	3.997	3.616 -	3.638 -	3.898 -
	ST.DEV.	0.485	0.470	0.318	0.426
	MINIMUM	3.100	2.696	3.118	3.298
	MAXIMUM	4.615	4.348	4.286	4.456
	N	10	10	10	10
SPLEEN	MEAN	27.88	27.29 -	26.69 -	26.21 -
	ST.DEV.	6.00	4.15	3.65	4.91
	MINIMUM	20.83	20.10	21.29	20.10
	MAXIMUM	40.64	34.76	32.80	37.82
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not sig. (-)

**ORGAN/BRAIN WEIGHT RATIOS (%) - SUMMARY
AFTER WEEK 13 OF TREATMENT
FEMALES**

		Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
OVARIES	MEAN	6.037	5.751 -	4.852 *	5.635 -
	ST.DEV.	1.308	0.554	0.658	0.956
	MINIMUM	3.526	5.000	3.827	4.798
	MAXIMUM	8.235	6.471	5.850	7.742
	N	10	10	10	10
UTERUS	MEAN	58.66	42.60 *	45.21 -	47.87 -
	ST.DEV.	23.72	8.35	9.10	10.69
	MINIMUM	36.81	34.36	36.10	34.85
	MAXIMUM	115.50	57.51	66.50	69.79
	N	10	10	10	10

*/**/- : DUNNETT-Test based on pooled variance sig. at 5% (*), 1% (**) or not sig. (-)

MACROSCOPICAL FINDINGS - SUMMARY
ALL NECROPSIES

Not Reported

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

MACROSCOPICAL FINDINGS - SUMMARY

ALL NECROPSIES

MALES

	Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
ANIMALS EXAMINED	10	10	10	10
ANIMALS COMPLETED	10	10	10	10
ANIMALS WITHOUT FINDINGS	8	6	7	7
ANIMALS AFFECTED				
LUNGS				
- FOCUS/FOCI	0%	0% -	0% -	10% -
STOMACH				
- FOCUS/FOCI	10%	10% -	10% -	0% -
KIDNEYS				
- PELVIC DILATION	0%	0% -	0% -	10% -
THYMUS				
- FOCUS/FOCI	10%	30% -	0% -	10% -
MANDIBULAR L.NODE				
- FOCUS/FOCI	0%	0% -	10% -	0% -
SKIN				
- KINKED TAIL	0%	0% -	10% -	0% -

*/**/- : Fisher's Exact Test significant at 5% (*), 1% (**) or not significant (-)

MACROSCOPICAL FINDINGS - SUMMARY
ALL NECROPSIES
FEMALES

	Group 1 0 mg/kg	Group 2 100 mg/kg	Group 3 300 mg/kg	Group 4 1000 mg/kg
ANIMALS EXAMINED	10	10	10	10
ANIMALS COMPLETED	10	10	10	10
ANIMALS WITHOUT FINDINGS	8	7	9	6
ANIMALS AFFECTED				
STOMACH				
- FOCUS/FOCI	0%	0% -	0% -	10% -
LIVER				
- DISCOLORATION	0%	0% -	0% -	10% -
KIDNEYS				
- PELVIC DILATION	0%	0% -	0% -	10% -
- REDUCED IN SIZE	0%	10% -	0% -	0% -
- DISCOLORATION	0%	10% -	0% -	0% -
OVARIES				
- FOCUS/FOCI	0%	0% -	10% -	0% -
UTERUS				
- DILATION	10%	0% -	0% -	0% -
SPLEEN				
- ECTOPIC SPLENIC TISSUE	0%	10% -	0% -	0% -
MANDIBULAR L.NODE				
- FOCUS/FOCI	0%	10% -	0% -	0% -
- DISCOLORATION	10%	0% -	0% -	0% -
SKIN				
- ALOPECIA	0%	10% -	0% -	0% -
BODY CAVITIES				
- NODULE(S)	0%	0% -	0% -	10% -

*/**/- : Fisher's Exact Test significant at 5% (*), 1% (**) or not significant (-)

9 INDIVIDUAL TABLES

MORTALITY DATA
ALL NECROPSIES

Animal(s) without death date / death status

Not Reported

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

MORTALITY DATA
ALL NECROPSIES
MALES

Group 1 (0 mg/kg)

ACCLIMATIZATION (Days 1 to 7)

No mortality data recorded

TREATMENT (Days 1 to 92)

ANIMAL	DEATH DATE	DAY	P	K	S	O	COMMENT
1	07-JAN-09	92	X				
2	07-JAN-09	92	X				
3	07-JAN-09	92	X				
4	07-JAN-09	92	X				
5	07-JAN-09	92	X				
6	07-JAN-09	92	X				
7	07-JAN-09	92	X				
8	07-JAN-09	92	X				
9	07-JAN-09	92	X				
10	07-JAN-09	92	X				
Total:			10	0	0	0	

P = PLANNED NECROPSY , K = KILLED IN EXTR. , S = SPONTAN. DEATH , O = OTHER

MORTALITY DATA
ALL NECROPSIES
MALES

Group 2 (100 mg/kg)

ACCLIMATIZATION (Days 1 to 7)

No mortality data recorded

TREATMENT (Days 1 to 92)

ANIMAL	DEATH DATE	DAY	P	K	S	O	COMMENT
11	07-JAN-09	92	X				
12	07-JAN-09	92	X				
13	07-JAN-09	92	X				
14	07-JAN-09	92	X				
15	07-JAN-09	92	X				
16	07-JAN-09	92	X				
17	07-JAN-09	92	X				
18	07-JAN-09	92	X				
19	07-JAN-09	92	X				
20	07-JAN-09	92	X				
Total:			10	0	0	0	

P = PLANNED NECROPSY , K = KILLED IN EXTR. , S = SPONTAN. DEATH , O = OTHER

MORTALITY DATA
ALL NECROPSIES
MALES

Group 3 (300 mg/kg)

ACCLIMATIZATION (Days 1 to 7)

No mortality data recorded

TREATMENT (Days 1 to 92)

ANIMAL	DEATH DATE	DAY	P	K	S	O	COMMENT
21	07-JAN-09	92	X				
22	07-JAN-09	92	X				
23	07-JAN-09	92	X				
24	07-JAN-09	92	X				
25	07-JAN-09	92	X				
26	07-JAN-09	92	X				
27	07-JAN-09	92	X				
28	07-JAN-09	92	X				
29	07-JAN-09	92	X				
30	07-JAN-09	92	X				
Total:			10	0	0	0	

P = PLANNED NECROPSY , K = KILLED IN EXTR. , S = SPONTAN. DEATH , O = OTHER

MORTALITY DATA
ALL NECROPSIES
MALES

Group 4 (1000 mg/kg)

ACCLIMATIZATION (Days 1 to 7)

No mortality data recorded

TREATMENT (Days 1 to 92)

ANIMAL	DEATH DATE	DAY	P	K	S	O	COMMENT
31	07-JAN-09	92	X				
32	07-JAN-09	92	X				
33	07-JAN-09	92	X				
34	07-JAN-09	92	X				
35	07-JAN-09	92	X				
36	07-JAN-09	92	X				
37	07-JAN-09	92	X				
38	07-JAN-09	92	X				
39	07-JAN-09	92	X				
40	07-JAN-09	92	X				
Total:			10	0	0	0	

P = PLANNED NECROPSY , K = KILLED IN EXTR. , S = SPONTAN. DEATH , O = OTHER

**MORTALITY DATA
ALL NECROPSIES
FEMALES**

Group 1 (0 mg/kg)

ACCLIMATIZATION (Days 1 to 7)

No mortality data recorded

TREATMENT (Days 1 to 92)

ANIMAL	DEATH DATE	DAY	P	K	S	O	COMMENT
41	06-JAN-09	91	X				
42	06-JAN-09	91	X				
43	06-JAN-09	91	X				
44	06-JAN-09	91	X				
45	06-JAN-09	91	X				
46	06-JAN-09	91	X				
47	06-JAN-09	91	X				
48	06-JAN-09	91	X				
49	06-JAN-09	91	X				
50	06-JAN-09	91	X				
Total:			10	0	0	0	

P = PLANNED NECROPSY , K = KILLED IN EXTR. , S = SPONTAN. DEATH , O = OTHER

**MORTALITY DATA
ALL NECROPSIES
FEMALES**

Group 2 (100 mg/kg)

ACCLIMATIZATION (Days 1 to 7)

No mortality data recorded

TREATMENT (Days 1 to 92)

ANIMAL	DEATH DATE	DAY	P	K	S	O	COMMENT
51	06-JAN-09	91	X				
52	06-JAN-09	91	X				
53	06-JAN-09	91	X				
54	06-JAN-09	91	X				
55	06-JAN-09	91	X				
56	06-JAN-09	91	X				
57	06-JAN-09	91	X				
58	06-JAN-09	91	X				
59	06-JAN-09	91	X				
60	06-JAN-09	91	X				
Total:			10	0	0	0	

P = PLANNED NECROPSY , K = KILLED IN EXTR. , S = SPONTAN. DEATH , O = OTHER

**MORTALITY DATA
ALL NECROPSIES
FEMALES**

Group 3 (300 mg/kg)

ACCLIMATIZATION (Days 1 to 7)

No mortality data recorded

TREATMENT (Days 1 to 92)

ANIMAL	DEATH DATE	DAY	P	K	S	O	COMMENT
61	06-JAN-09	91	X				
62	06-JAN-09	91	X				
63	06-JAN-09	91	X				
64	06-JAN-09	91	X				
65	06-JAN-09	91	X				
66	06-JAN-09	91	X				
67	06-JAN-09	91	X				
68	06-JAN-09	91	X				
69	06-JAN-09	91	X				
70	06-JAN-09	91	X				
Total:			10	0	0	0	

P = PLANNED NECROPSY , K = KILLED IN EXTR. , S = SPONTAN. DEATH , O = OTHER

**MORTALITY DATA
ALL NECROPSIES
FEMALES**

Group 4 (1000 mg/kg)

ACCLIMATIZATION (Days 1 to 7)

No mortality data recorded

TREATMENT (Days 1 to 92)

ANIMAL	DEATH DATE	DAY	P	K	S	O	COMMENT
71	06-JAN-09	91	X				
72	06-JAN-09	91	X				
73	06-JAN-09	91	X				
74	06-JAN-09	91	X				
75	06-JAN-09	91	X				
76	06-JAN-09	91	X				
77	06-JAN-09	91	X				
78	06-JAN-09	91	X				
79	06-JAN-09	91	X				
80	06-JAN-09	91	X				
Total:			10	0	0	0	

P = PLANNED NECROPSY , K = KILLED IN EXTR. , S = SPONTAN. DEATH , O = OTHER

CLINICAL SIGNS

Comments

Data excluded from Summary Report

Not Reported

All Study Phases

Animal 81 Male Group 10 Reserve Removed

Animal 82 Female Group 10 Reserve Removed

Incomplete Recordings

Selection of Findings

All findings reported

CLINICAL SIGNS

MALES

ACCLIMATIZATION

Weeks / Days

1

-----7

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

CLINICAL SIGNS

MALES

TREATMENT

Weeks / Days

1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7
1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7

Group 1 (0 mg/kg)

Animal 10

DESCRIPTIVES

- KINKED (3)

TAIL APEX11111111111111

No further abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

Animal 36

APPEARANCE

- HAIR LOSS (3)

HEAD11111111111111

- SCABS (3)

HEAD1111.....

No further abnormality recorded.

CLINICAL SIGNS

MALES

TREATMENT

Weeks / Days

1 3 1 4

1 2 3 4 5 6 7 -

Group 1 (0 mg/kg)

Animal 10

DESCRIPTIVES

- KINKED (3)

TAIL APEX 1 1 1 1 1 1 1

No further abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

Animal 21

DESCRIPTIVES

- KINKED (3)

TAIL APEX 1 1 1 1 1 1 1

No further abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

CLINICAL SIGNS
FEMALES

ACCLIMATIZATION

Weeks / Days

1

-----7

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

CLINICAL SIGNS

FEMALES

TREATMENT

Weeks / Days

1 3 1 4

1 2 3 4 5 6 7 -

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

Animal 51

APPEARANCE

- HAIR LOSS (3)

POSTERIOR DORSUM 2 2 2 2 1 2

LEFT FLANK 2 2

RIGHT FLANK 2 2

Animal 54

APPEARANCE

- HAIR LOSS (3)

NECK (CERVICAL) 1 1 1 1 1 1

No further abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

DETAILED BEHAVIORAL OBSERVATIONS

Comments

Data excluded from Summary Report

Not Reported

All Study Phases

Animal 81 Male Group 10 Reserve Removed

Animal 82 Female Group 10 Reserve Removed

Incomplete Recordings

Selection of Findings

All findings reported

DETAILED BEHAVIORAL OBSERVATIONS
MALES

ACCLIMATIZATION

Weeks / Days

1

-- 3 ----

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

**DETAILED BEHAVIORAL OBSERVATIONS
MALES**

TREATMENT

Weeks / Days

1 2 3 4 5 6
-- 3 ----- 3 ----- 6 ----- 3 ----- 3 ----- 3 -----

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

DETAILED BEHAVIORAL OBSERVATIONS
MALES

TREATMENT

Weeks / Days

7 8 9 10 11 12
-- 3 ----- 3 ----- 3 ----- 3 ----- 3 ----- 3 -----

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

DETAILED BEHAVIORAL OBSERVATIONS
MALES

TREATMENT

Weeks / Days	
1 3	1 4
-- 3 --	6 --

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

**DETAILED BEHAVIORAL OBSERVATIONS
FEMALES**

ACCLIMATIZATION

Weeks / Days

1

-- 3 ----

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

**DETAILED BEHAVIORAL OBSERVATIONS
FEMALES**

TREATMENT

Weeks / Days

1 2 3 4 5 6
-- 3 ----- 3 ----- 6 --- 3 ----- 3 ----- 3 -----

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

**DETAILED BEHAVIORAL OBSERVATIONS
FEMALES**

TREATMENT

Weeks / Days

7 8 9 10 11 12
-- 3 ----- 3 ----- 3 ----- 3 ----- 3 ----- 3 -----

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

**DETAILED BEHAVIORAL OBSERVATIONS
FEMALES**

TREATMENT

Weeks / Days	
1 3	1 4
-- 3 --	6 --

Group 1 (0 mg/kg)

No abnormality recorded.

Group 2 (100 mg/kg)

No abnormality recorded.

Group 3 (300 mg/kg)

No abnormality recorded.

Group 4 (1000 mg/kg)

No abnormality recorded.

GRIP STRENGTH

Comments

Data excluded from Summary Report

Not Reported

All Measurements

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

Reported Parameter

AT WEEK 13

Grip Fore	GRIP FORELIMB
Grip Hind	GRIP HINDLIMB

AT WEEK 13

Grip Fore	GRIP FORELIMB
Grip Hind	GRIP HINDLIMB

**GRIP STRENGTH
AT WEEK 13
FEMALES**

Group 1 (0 mg/kg)

	GRIP STRENGTH	
	Grip Fore	Grip Hind
	KILOGRAM	KILOGRAM
41	1.28	0.88
42	1.31	0.84
43	1.33	0.94
44	1.61	0.87
45	1.39	0.82
46	1.55	0.81
47	1.59	0.96
48	1.61	0.84
49	1.53	0.91
50	1.71	0.87

**GRIP STRENGTH
AT WEEK 13
FEMALES**

Group 2 (100 mg/kg)

	GRIP STRENGTH	
	Grip Fore	Grip Hind
	KILOGRAM	KILOGRAM
51	1.36	0.84
52	1.33	0.69
53	1.23	0.83
54	1.21	0.93
55	1.33	0.79
56	1.32	0.91
57	1.37	0.85
58	1.31	0.93
59	1.31	0.84
60	1.18	0.84

**GRIP STRENGTH
AT WEEK 13
FEMALES**

Group 3 (300 mg/kg)

	GRIP STRENGTH	
	Grip Fore	Grip Hind
	KILOGRAM	KILOGRAM
61	1.35	0.84
62	1.28	0.80
63	1.44	0.75
64	1.42	0.97
65	1.34	0.72
66	1.47	0.81
67	1.33	0.73
68	1.46	0.76
69	1.19	0.62
70	1.30	0.87

**GRIP STRENGTH
AT WEEK 13
FEMALES**

Group 4 (1000 mg/kg)

	GRIP STRENGTH	
	Grip Fore	Grip Hind
	KILOGRAM	KILOGRAM
71	1.39	0.74
72	1.36	0.87
73	1.25	0.82
74	1.37	0.86
75	1.37	0.87
76	1.22	0.83
77	1.39	0.74
78	1.21	0.85
79	1.26	0.78
80	1.41	0.88

**GRIP STRENGTH
AT WEEK 13
MALES**

Group 1 (0 mg/kg)

	GRIP STRENGTH	
	Grip Fore	Grip Hind
	KILOGRAM	KILOGRAM
1	1.52	1.14
2	1.59	1.02
3	1.70	1.15
4	1.65	1.26
5	1.84	1.18
6	1.57	1.18
7	1.53	1.04
8	1.68	1.15
9	1.60	1.11
10	1.79	1.27

**GRIP STRENGTH
AT WEEK 13
MALES**

Group 2 (100 mg/kg)

	GRIP STRENGTH	
	Grip Fore	Grip Hind
	KILOGRAM	KILOGRAM
11	1.71	1.19
12	1.62	1.17
13	1.71	1.18
14	1.83	1.24
15	1.61	1.11
16	1.72	1.24
17	1.60	1.04
18	1.70	1.16
19	1.74	1.21
20	1.86	1.27

**GRIP STRENGTH
AT WEEK 13
MALES**

Group 3 (300 mg/kg)

	GRIP STRENGTH	
	Grip Fore	Grip Hind
	KILOGRAM	KILOGRAM
21	1.67	1.17
22	1.63	1.08
23	1.74	1.22
24	1.65	1.02
25	1.67	1.22
26	1.64	1.26
27	1.67	1.13
28	1.72	1.25
29	1.71	1.19
30	1.86	1.20

**GRIP STRENGTH
AT WEEK 13
MALES**

Group 4 (1000 mg/kg)

	GRIP STRENGTH	
	Grip Fore	Grip Hind
	KILOGRAM	KILOGRAM
31	1.61	1.21
32	1.69	1.19
33	1.73	1.17
34	1.74	1.22
35	1.65	1.19
36	1.69	1.09
37	1.73	1.25
38	1.73	1.19
39	1.57	1.21
40	1.67	1.22

LOCOMOTOR ACTIVITY

Comments

Data excluded from Summary Report

Not Reported

All Measurements

Animal 81 Male Group 10 Reserve Removed
Animal 82 Female Group 10 Reserve Removed

Reported Parameter

AT WEEK 13

0-10 MIN LOCOMOTOR ACTIVITY
10-20 MIN LOCOMOTOR ACTIVITY
20-30 MIN LOCOMOTOR ACTIVITY
30-40 MIN LOCOMOTOR ACTIVITY
40-50 MIN LOCOMOTOR ACTIVITY
50-60 MIN LOCOMOTOR ACTIVITY
Total LOCOMOTOR ACTIVITY

AT WEEK 13

0-10 MIN LOCOMOTOR ACTIVITY
10-20 MIN LOCOMOTOR ACTIVITY
20-30 MIN LOCOMOTOR ACTIVITY
30-40 MIN LOCOMOTOR ACTIVITY
40-50 MIN LOCOMOTOR ACTIVITY
50-60 MIN LOCOMOTOR ACTIVITY
Total LOCOMOTOR ACTIVITY

**LOCOMOTOR ACTIVITY
AT WEEK 13
FEMALES**

Group 1 (0 mg/kg)

	LOCOMOTOR ACTIVITY						
	0-10 MIN	10-20 MIN	20-30 MIN	30-40 MIN	40-50 MIN	50-60 MIN	Total
41	578	360	431	77	0	17	1463
42	395	241	167	418	282	71	1574
43	369	115	9	164	1	23	681
44	411	232	148	131	183	98	1203
45	591	215	225	172	79	2	1284
46	518	213	198	321	117	12	1379
47	516	297	259	164	44	150	1430
48	298	206	178	101	52	19	854
49	453	308	139	346	112	38	1396
50	364	327	233	242	232	162	1560

**LOCOMOTOR ACTIVITY
AT WEEK 13
FEMALES**

Group 2 (100 mg/kg)

	LOCOMOTOR ACTIVITY						
	0-10 MIN	10-20 MIN	20-30 MIN	30-40 MIN	40-50 MIN	50-60 MIN	Total
51	423	251	170	155	63	0	1062
52	664	335	154	150	148	87	1538
53	610	255	247	150	216	333	1811
54	355	206	239	236	105	51	1192
55	438	338	306	298	300	1	1681
56	678	430	353	358	219	248	2286
57	303	232	145	48	0	0	728
58	526	453	269	295	204	136	1883
59	670	97	315	247	29	89	1447
60	674	465	434	388	292	51	2304

**LOCOMOTOR ACTIVITY
AT WEEK 13
FEMALES**

Group 3 (300 mg/kg)

	LOCOMOTOR ACTIVITY						
	0-10 MIN	10-20 MIN	20-30 MIN	30-40 MIN	40-50 MIN	50-60 MIN	Total
61	513	312	209	267	30	15	1346
62	427	157	148	20	8	13	773
63	253	144	28	96	138	12	671
64	388	103	17	403	0	22	933
65	648	203	22	6	282	111	1272
66	481	267	153	188	5	26	1120
67	579	276	223	193	228	39	1538
68	316	241	217	173	58	2	1007
69	634	286	402	328	108	26	1784
70	565	308	282	215	64	0	1434

**LOCOMOTOR ACTIVITY
AT WEEK 13
FEMALES**

Group 4 (1000 mg/kg)

	LOCOMOTOR ACTIVITY						
	0-10 MIN	10-20 MIN	20-30 MIN	30-40 MIN	40-50 MIN	50-60 MIN	Total
71	440	317	307	78	4	120	1266
72	337	129	143	133	71	0	813
73	490	322	149	119	3	9	1092
74	592	379	342	48	2	26	1389
75	637	415	431	172	0	345	2000
76	772	389	246	240	255	18	1920
77	442	309	248	140	5	0	1144
78	371	238	96	77	4	239	1025
79	687	321	178	293	138	2	1619
80	621	273	12	18	64	10	998

**LOCOMOTOR ACTIVITY
AT WEEK 13
MALES**

Group 1 (0 mg/kg)

	LOCOMOTOR ACTIVITY						
	0-10 MIN	10-20 MIN	20-30 MIN	30-40 MIN	40-50 MIN	50-60 MIN	Total
1	402	147	71	101	118	118	957
2	463	255	183	73	98	143	1215
3	350	275	173	199	108	100	1205
4	346	200	238	151	194	133	1262
5	464	303	173	27	4	109	1080
6	460	330	234	181	133	96	1434
7	470	281	207	278	68	1	1305
8	515	287	127	197	1	90	1217
9	527	328	216	105	243	130	1549
10	521	305	154	159	64	15	1218

**LOCOMOTOR ACTIVITY
AT WEEK 13
MALES**

Group 2 (100 mg/kg)

	LOCOMOTOR ACTIVITY						Total
	0-10 MIN	10-20 MIN	20-30 MIN	30-40 MIN	40-50 MIN	50-60 MIN	
11	399	184	270	102	267	68	1290
12	471	226	0	0	187	361	1245
13	349	149	42	0	130	45	715
14	613	313	204	149	76	14	1369
15	612	296	338	258	198	21	1723
16	599	342	228	109	83	333	1694
17	456	259	107	121	73	57	1073
18	449	258	202	110	99	138	1256
19	518	373	165	169	147	98	1470
20	492	262	220	192	73	128	1367

**LOCOMOTOR ACTIVITY
AT WEEK 13
MALES**

Group 3 (300 mg/kg)

	LOCOMOTOR ACTIVITY						
	0-10 MIN	10-20 MIN	20-30 MIN	30-40 MIN	40-50 MIN	50-60 MIN	Total
21	473	366	280	98	54	35	1306
22	229	45	149	42	78	6	549
23	413	269	84	8	36	24	834
24	451	56	317	285	36	10	1155
25	820	407	175	369	26	35	1832
26	498	252	130	2	8	112	1002
27	557	369	252	117	198	184	1677
28	329	276	213	200	265	213	1496
29	348	233	96	147	70	36	930
30	441	319	141	40	105	88	1134

**LOCOMOTOR ACTIVITY
AT WEEK 13
MALES**

Group 4 (1000 mg/kg)

	LOCOMOTOR ACTIVITY						
	0-10 MIN	10-20 MIN	20-30 MIN	30-40 MIN	40-50 MIN	50-60 MIN	Total
31	412	319	181	278	313	83	1586
32	332	247	257	140	47	8	1031
33	423	214	281	105	11	0	1034
34	570	508	374	206	10	330	1998
35	495	230	193	127	62	10	1117
36	671	442	290	99	0	8	1510
37	619	484	299	140	4	9	1555
38	339	150	183	55	52	6	785
39	456	233	282	115	164	37	1287
40	589	271	270	302	392	48	1872

FOOD CONSUMPTION (G/ANIMAL/DAY)

Comments

Data excluded from Summary Report

Not Reported

All Study Phases

Cage 17	Male	Group 10	Reserve Removed
Cage 18	Female	Group 10	Reserve Removed

FOOD CONSUMPTION (G/ANIMAL/DAY)
MALES

Group 1 (0 mg/kg)

CAGE	1	2
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ACCLIMATIZATION

Days 1-8	21.2	20.6
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CAGE	1	2
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TREATMENT

Days 1-8	23.0	22.9
8-15	24.5	24.4
15-22	24.3	24.3
22-29	23.7	23.9
29-36	23.7	23.0
36-43	23.8	23.4
43-50	24.8	24.0
50-57	24.2	23.0
57-64	24.8	23.9
64-71	24.2	23.3
71-78	23.8	23.0
78-85	24.3	23.5
85-90	24.4	23.6

FOOD CONSUMPTION (G/ANIMAL/DAY)
MALES

Group 2 (100 mg/kg)

CAGE	3	4
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ACCLIMATIZATION

Days 1-8	20.0	21.3
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CAGE	3	4
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TREATMENT

Days 1-8	22.3	23.7
8-15	23.1	24.8
15-22	23.2	24.9
22-29	22.8	24.3
29-36	22.9	24.1
36-43	22.6	24.4
43-50	22.5	24.9
50-57	21.2	23.2
57-64	21.8	23.8
64-71	21.4	23.4
71-78	21.2	23.7
78-85	21.8	23.5
85-90	22.5	23.8

FOOD CONSUMPTION (G/ANIMAL/DAY)
MALES

Group 4 (1000 mg/kg)

CAGE	7	8
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ACCLIMATIZATION

Days 1-8	21.2	20.6
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CAGE	7	8
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TREATMENT

Days 1-8	23.5	22.8
8-15	24.4	24.1
15-22	23.5	23.4
22-29	22.9	23.1
29-36	22.5	22.6
36-43	22.6	22.6
43-50	23.1	22.5
50-57	22.0	22.0
57-64	22.2	22.3
64-71	21.4	21.4
71-78	21.4	21.6
78-85	22.1	22.2
85-90	22.3	21.9

FOOD CONSUMPTION (G/ANIMAL/DAY)
FEMALES

Group 1 (0 mg/kg)

CAGE	9	10
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ACCLIMATIZATION

Days 1-8	14.8	15.1
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CAGE	9	10
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TREATMENT

Days 1-8	15.2	16.0
8-15	16.8	17.8
15-22	15.3	17.1
22-29	16.0	17.2
29-36	16.4	17.3
36-43	16.0	17.8
43-50	15.8	17.6
50-57	14.9	17.0
57-64	15.5	17.5
64-71	15.6	16.9
71-78	14.9	16.2
78-85	15.5	16.9
85-90	15.1	16.9

FOOD CONSUMPTION (G/ANIMAL/DAY)
FEMALES

Group 2 (100 mg/kg)

CAGE	11	12
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ACCLIMATIZATION

Days 1-8	15.1	14.7
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CAGE	11	12
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TREATMENT

Days 1-8	15.6	15.3
8-15	16.7	16.7
15-22	16.3	16.4
22-29	16.5	16.5
29-36	16.5	16.1
36-43	16.1	16.4
43-50	15.6	16.1
50-57	15.2	15.4
57-64	16.0	15.7
64-71	15.5	15.4
71-78	15.3	14.7
78-85	15.6	15.5
85-90	15.3	15.5

FOOD CONSUMPTION (G/ANIMAL/DAY)
FEMALES

Group 3 (300 mg/kg)

CAGE	13	14
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ACCLIMATIZATION

Days 1-8	14.4	14.6
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CAGE	13	14
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TREATMENT

Days 1-8	15.0	15.8
8-15	16.0	16.8
15-22	15.3	16.1
22-29	15.7	16.8
29-36	15.5	16.4
36-43	15.3	16.3
43-50	15.0	16.0
50-57	14.6	15.5
57-64	15.2	16.2
64-71	14.6	15.3
71-78	14.6	15.6
78-85	15.2	15.9
85-90	14.9	16.2

FOOD CONSUMPTION (G/ANIMAL/DAY)
FEMALES

Group 4 (1000 mg/kg)

CAGE	15	16
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ACCLIMATIZATION

Days 1-8	15.2	14.8
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CAGE	15	16
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TREATMENT

Days 1-8	15.1	15.6
8-15	16.4	16.6
15-22	16.3	15.9
22-29	17.2	16.3
29-36	17.3	16.0
36-43	15.9	16.2
43-50	15.8	15.5
50-57	15.1	14.9
57-64	15.8	15.7
64-71	14.8	15.6
71-78	14.8	15.3
78-85	15.1	15.8
85-90	14.8	15.8

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

Comments

Data excluded from Summary Report

Not Reported

All Study Phases

Cage 17	Male	Group 10	Reserve Removed
Cage 18	Female	Group 10	Reserve Removed

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

Group 1 (0 mg/kg)

CAGE	1	2
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ACCLIMATIZATION

Days 1-8	110.3	106.1
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CAGE	1	2
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TREATMENT

Days 1-8	83.2	83.2
8-15	79.5	79.1
15-22	73.3	73.4
22-29	67.2	68.5
29-36	64.2	62.8
36-43	61.4	61.6
43-50	61.0	60.6
50-57	57.5	56.2
57-64	57.7	57.0
64-71	55.0	54.2
71-78	52.9	52.3
78-85	53.1	52.8
85-90	53.2	52.8

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

Group 2 (100 mg/kg)

CAGE	11	12
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ACCLIMATIZATION

Days 1-8	103.0	93.5
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CAGE	11	12
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TREATMENT

Days 1-8	84.8	80.3
8-15	84.8	81.1
15-22	80.6	76.3
22-29	77.0	72.7
29-36	72.7	69.7
36-43	70.6	68.7
43-50	67.2	66.4
50-57	64.2	62.0
57-64	66.1	62.9
64-71	63.3	60.2
71-78	62.1	56.8
78-85	63.1	59.8
85-90	61.9	59.7

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

Group 4 (1000 mg/kg)

CAGE	15	16
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ACCLIMATIZATION

Days 1-8	100.6	98.8
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CAGE	15	16
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TREATMENT

Days 1-8	80.0	84.6
8-15	82.6	83.1
15-22	77.5	76.8
22-29	75.2	74.6
29-36	73.5	71.6
36-43	67.1	70.5
43-50	65.3	66.2
50-57	60.8	63.4
57-64	62.7	66.4
64-71	59.1	64.1
71-78	57.9	61.5
78-85	58.1	63.4
85-90	57.9	63.4

BODY WEIGHTS (G)

Comments

Data excluded from Summary Report

Not Reported

All Study Phases

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

BODY WEIGHTS (G)

MALES

Group 1 (0 mg/kg)

Animal	1	2	3	4	5	6	7
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ACCLIMATIZATION

Day	1	188.8	196.0	186.6	194.4	196.3	195.5	190.7
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Animal	1	2	3	4	5	6	7
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TREATMENT

Day	1	239.3	247.2	231.8	243.1	241.9	245.7	239.4
	8	275.7	284.8	271.9	271.6	276.1	280.0	274.2
	15	303.3	320.0	305.1	305.8	304.6	314.3	303.8
	22	328.1	341.9	329.2	328.6	328.2	339.6	325.3
	29	342.9	366.5	357.2	351.2	344.5	360.2	341.9
	36	359.3	384.3	373.5	373.8	355.2	378.1	362.1
	43	379.0	395.9	394.6	394.1	373.8	393.6	379.6
	50	398.8	416.2	409.2	414.4	393.7	410.6	391.5
	57	417.4	429.1	421.9	429.0	406.3	423.2	410.0
	64	428.4	439.8	429.4	440.1	412.3	428.9	421.0
	71	436.0	446.9	433.7	453.6	425.5	439.2	436.6
	78	449.9	454.1	445.1	458.9	438.3	450.1	450.9
	85	459.0	463.3	450.5	464.9	447.2	458.3	456.5
	90	463.1	464.6	451.9	467.0	452.9	463.1	458.4

Animal	8	9	10
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ACCLIMATIZATION

Day	1	192.5	194.2	197.6
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Animal	8	9	10
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TREATMENT

Day	1	242.1	240.6	244.3
	8	278.8	268.3	276.0
	15	312.8	305.1	303.2
	22	339.4	323.3	326.7
	29	359.4	340.4	342.3
	36	378.9	351.4	358.5
	43	389.2	365.2	377.2
	50	408.9	383.2	388.9
	57	420.9	390.4	403.7
	64	434.0	398.2	413.9
	71	441.7	407.9	421.6
	78	444.5	417.7	434.1
	85	450.9	420.1	437.2
	90	457.5	419.9	440.6

BODY WEIGHTS (G)

MALES

Group 2 (100 mg/kg)

Animal	11	12	13	14	15	16	17
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ACCLIMATIZATION

Day	1	185.7	191.7	182.0	200.7	200.1	197.9	196.0
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Animal	11	12	13	14	15	16	17
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TREATMENT

Day	1	229.5	238.5	222.8	240.8	248.1	254.5	242.4
	8	265.2	268.7	260.8	279.7	292.1	300.8	272.9
	15	297.1	296.7	286.4	307.9	322.2	334.2	299.7
	22	318.6	312.2	310.1	335.8	344.6	364.2	318.6
	29	345.7	337.3	329.7	361.6	366.1	390.2	335.6
	36	364.6	355.4	346.0	378.0	383.7	417.6	352.1
	43	376.5	364.9	362.2	388.9	396.8	437.0	367.3
	50	393.5	376.4	374.3	409.6	413.3	447.2	377.0
	57	403.5	386.0	388.0	426.2	421.7	458.3	390.7
	64	409.5	400.0	400.9	434.1	432.2	471.3	394.7
	71	421.9	409.3	406.6	444.6	437.3	475.2	410.7
	78	432.2	418.0	415.7	452.6	446.8	489.7	424.4
	85	435.5	423.0	424.6	460.7	450.5	494.7	431.5
	90	441.6	429.3	428.0	468.1	449.1	498.4	435.1

Animal	18	19	20
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ACCLIMATIZATION

Day	1	198.3	182.5	183.0
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Animal	18	19	20
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TREATMENT

Day	1	257.1	242.4	237.5
	8	298.1	288.6	279.6
	15	329.7	320.5	312.1
	22	362.0	352.7	336.5
	29	389.5	376.9	356.1
	36	400.7	397.9	374.2
	43	426.0	414.6	392.3
	50	444.9	434.6	406.7
	57	456.9	451.1	419.7
	64	470.5	463.7	434.0
	71	483.5	471.5	449.5
	78	494.8	485.1	462.4
	85	513.2	489.2	467.3
	90	520.4	488.1	470.9

BODY WEIGHTS (G)

MALES

Group 3 (300 mg/kg)

Animal	21	22	23	24	25	26	27
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ACCLIMATIZATION

Day	1	193.0	185.1	190.3	187.7	198.1	196.4	203.9
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Animal	21	22	23	24	25	26	27
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TREATMENT

Day	1	241.4	223.7	237.8	222.8	242.2	242.5	250.2
	8	275.5	253.5	275.6	253.7	280.2	277.9	278.6
	15	310.5	284.0	317.3	276.4	311.1	309.2	298.3
	22	338.2	300.0	344.0	297.4	333.6	333.7	311.4
	29	365.7	320.4	368.6	314.6	351.8	357.0	324.7
	36	386.5	333.8	395.2	323.1	369.2	376.4	335.6
	43	403.5	342.8	409.9	338.7	381.9	385.9	354.7
	50	420.4	349.5	428.6	349.9	399.3	406.9	363.5
	57	444.3	362.8	446.7	357.8	406.7	420.6	379.8
	64	451.3	375.2	457.8	364.7	414.8	431.3	386.1
	71	463.3	383.3	463.9	367.5	418.7	439.5	394.9
	78	474.1	393.7	476.1	373.7	426.9	448.6	405.6
	85	483.2	397.5	483.2	376.6	428.4	454.1	409.1
	90	467.8	396.4	485.8	376.3	438.6	454.8	408.0

Animal	28	29	30
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ACCLIMATIZATION

Day	1	197.3	195.8	198.4
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Animal	28	29	30
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TREATMENT

Day	1	246.5	238.9	257.5
	8	288.3	272.3	304.9
	15	322.3	296.0	341.6
	22	344.9	315.8	368.0
	29	368.6	333.0	396.8
	36	383.7	348.5	417.1
	43	393.4	362.9	433.9
	50	411.7	377.1	455.7
	57	421.6	388.4	470.8
	64	431.4	399.2	486.7
	71	442.4	407.1	499.6
	78	450.6	416.9	512.8
	85	456.2	424.2	525.4
	90	460.0	425.5	528.9

BODY WEIGHTS (G)

MALES

Group 4 (1000 mg/kg)

Animal	31	32	33	34	35	36	37
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ACCLIMATIZATION

Day	1	193.6	196.7	182.2	189.3	185.0	202.0	190.2
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Animal	31	32	33	34	35	36	37
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TREATMENT

Day	1	234.1	252.1	238.1	238.0	229.1	242.7	239.4
	8	279.9	298.7	280.4	280.5	257.6	276.9	280.1
	15	315.6	336.9	314.7	311.1	288.1	307.8	312.0
	22	342.1	361.3	340.1	329.0	305.4	327.2	334.9
	29	363.4	387.5	362.3	348.8	321.1	343.0	361.0
	36	381.0	407.8	387.1	363.5	336.1	359.9	379.8
	43	395.4	428.3	399.6	381.3	348.0	373.7	392.9
	50	408.7	448.8	415.7	396.9	358.2	388.2	412.8
	57	421.7	461.7	430.8	406.0	370.0	400.8	424.1
	64	431.8	477.9	446.7	418.8	380.7	410.3	429.9
	71	443.4	486.0	457.0	430.8	383.1	418.0	434.2
	78	449.5	497.3	464.0	444.3	390.8	425.7	444.2
	85	457.1	500.7	469.3	453.6	400.0	429.9	452.8
	90	460.8	509.1	472.1	452.3	399.1	436.5	457.2

Animal	38	39	40
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ACCLIMATIZATION

Day	1	183.2	183.9	185.9
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Animal	38	39	40
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TREATMENT

Day	1	228.5	231.2	233.4
	8	268.4	262.5	273.9
	15	303.3	297.8	305.6
	22	328.0	318.7	328.7
	29	345.9	338.6	349.7
	36	364.0	357.6	373.3
	43	376.5	374.7	385.1
	50	393.4	388.8	400.9
	57	406.4	401.9	411.9
	64	414.7	414.3	427.7
	71	421.8	423.1	432.8
	78	430.6	432.3	446.4
	85	433.4	440.3	450.7
	90	434.9	441.2	456.8

BODY WEIGHTS (G)

FEMALES

Group 1 (0 mg/kg)

Animal	41	42	43	44	45	46	47
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ACCLIMATIZATION

Day	1	151.6	151.7	150.0	148.2	150.3	153.7	158.5
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Animal	41	42	43	44	45	46	47
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TREATMENT

Day	1	164.1	168.3	172.0	176.6	174.3	173.7	181.8
	8	179.2	185.7	182.8	187.6	186.5	182.7	191.2
	15	190.5	204.4	197.7	196.8	193.3	204.4	210.5
	22	199.6	205.0	202.8	198.7	203.6	213.9	218.2
	29	205.3	212.1	210.6	213.6	217.7	219.8	223.5
	36	215.6	223.7	220.0	224.5	225.5	221.0	225.9
	43	223.1	228.4	221.8	230.3	223.8	238.2	241.2
	50	227.5	233.8	229.2	226.1	235.2	248.0	247.8
	57	225.7	225.9	234.2	238.4	240.7	249.8	246.6
	64	235.0	234.1	241.5	239.7	239.4	244.7	245.2
	71	242.7	239.7	247.6	242.3	235.0	260.8	256.7
	78	242.1	242.4	245.3	236.5	245.5	264.1	256.8
	85	238.8	235.6	246.7	242.3	250.0	260.6	259.1
	90	242.3	243.8	243.1	238.2	248.1	265.9	263.7

Animal	48	49	50
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ACCLIMATIZATION

Day	1	150.0	155.8	147.9
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Animal	48	49	50
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TREATMENT

Day	1	175.0	182.9	163.0
	8	188.0	200.5	175.8
	15	203.0	212.9	191.2
	22	218.0	225.4	201.7
	29	231.5	236.1	209.4
	36	241.9	241.6	211.6
	43	243.6	244.8	223.5
	50	255.0	251.9	231.1
	57	265.0	256.8	232.0
	64	269.4	263.1	231.7
	71	268.7	260.5	241.0
	78	275.0	267.4	243.5
	85	279.4	268.7	241.3
	90	278.8	268.8	243.3

BODY WEIGHTS (G)

FEMALES

Group 2 (100 mg/kg)

Animal	51	52	53	54	55	56	57
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ACCLIMATIZATION

Day	1	147.0	140.8	142.3	158.1	143.8	155.6	158.3
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Animal	51	52	53	54	55	56	57
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TREATMENT

Day	1	169.7	171.7	159.9	177.7	164.9	173.8	179.1
	8	189.4	184.0	176.7	189.7	179.6	182.6	191.6
	15	202.2	199.7	187.6	201.1	192.7	193.2	212.0
	22	209.4	199.7	193.8	213.6	195.8	197.6	221.2
	29	217.5	218.8	197.9	227.5	209.4	205.2	232.1
	36	230.8	229.9	210.6	239.1	222.5	209.5	234.7
	43	233.2	230.2	217.8	237.5	221.7	219.7	244.9
	50	243.1	227.2	220.2	249.2	220.9	219.2	251.7
	57	243.8	239.9	213.9	252.3	233.2	229.0	253.1
	64	248.7	246.5	224.1	256.3	236.0	227.5	252.1
	71	251.7	248.4	232.6	258.0	235.9	239.1	259.2
	78	258.2	242.3	233.5	264.4	233.8	246.3	265.0
	85	255.1	251.3	222.5	263.2	243.3	233.0	263.8
	90	259.5	244.3	232.1	259.8	240.0	232.5	270.4

Animal	58	59	60
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ACCLIMATIZATION

Day	1	162.4	159.6	151.5
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Animal	58	59	60
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TREATMENT

Day	1	188.8	183.6	168.3
	8	204.0	201.0	174.6
	15	218.7	215.7	191.4
	22	230.3	226.9	201.0
	29	246.4	240.1	212.9
	36	250.6	249.0	214.4
	43	254.6	251.5	225.6
	50	255.0	252.5	231.6
	57	267.3	260.8	233.2
	64	271.7	266.6	232.8
	71	277.3	267.4	239.7
	78	272.0	262.5	246.9
	85	282.2	269.7	246.6
	90	275.3	269.0	251.5

BODY WEIGHTS (G)
FEMALES

Group 3 (300 mg/kg)

Animal	61	62	63	64	65	66	67
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ACCLIMATIZATION

Day	1	146.3	143.9	149.3	154.7	147.4	145.3	160.5
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Animal	61	62	63	64	65	66	67
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TREATMENT

Day	1	165.9	164.3	178.9	169.1	174.7	172.7	179.4
	8	181.0	173.5	191.7	183.7	194.0	190.1	198.7
	15	195.7	185.0	211.8	193.3	212.8	203.7	212.8
	22	203.4	185.9	217.5	200.6	219.0	208.9	221.5
	29	209.3	200.0	234.8	211.3	226.4	221.9	223.0
	36	219.2	206.9	243.4	219.8	236.8	232.6	238.5
	43	226.3	209.0	248.4	223.6	244.4	234.0	240.5
	50	230.2	205.8	245.0	225.4	250.0	237.9	247.9
	57	227.2	216.5	259.8	233.5	244.3	248.7	241.0
	64	234.5	221.8	266.2	240.4	254.5	249.0	252.5
	71	240.4	224.7	273.4	239.5	261.4	245.9	256.5
	78	242.5	220.3	266.7	236.3	267.5	258.4	254.7
	85	242.7	227.4	278.8	248.4	263.0	255.0	257.4
	90	247.2	223.2	269.5	240.0	273.6	254.3	254.3

Animal	68	69	70
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ACCLIMATIZATION

Day	1	146.3	154.3	162.3
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Animal	68	69	70
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TREATMENT

Day	1	170.3	181.3	183.9
	8	187.1	197.0	204.1
	15	200.9	202.8	220.1
	22	201.1	215.8	222.5
	29	217.9	228.9	236.0
	36	225.5	236.7	242.5
	43	231.0	232.4	248.6
	50	231.3	246.8	249.2
	57	240.9	248.6	262.0
	64	244.6	259.0	268.6
	71	241.4	248.2	261.1
	78	248.4	263.3	276.3
	85	254.7	263.5	277.6
	90	259.7	264.6	277.0

BODY WEIGHTS (G)
FEMALES

Group 4 (1000 mg/kg)

Animal	71	72	73	74	75	76	77
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ACCLIMATIZATION

Day	1	152.8	151.2	161.1	138.2	154.5	146.6	148.5
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Animal	71	72	73	74	75	76	77
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TREATMENT

Day	1	183.5	185.5	172.8	156.8	181.0	162.7	173.7
	8	200.3	194.6	183.7	168.8	194.7	173.5	188.4
	15	213.7	203.4	189.8	180.8	206.2	194.4	198.9
	22	223.5	214.4	206.1	188.0	221.3	203.1	211.1
	29	239.8	247.1	223.3	201.9	234.2	211.7	223.6
	36	247.3	254.6	228.2	206.8	237.8	211.6	225.7
	43	252.4	248.9	229.0	210.1	242.1	224.4	229.2
	50	254.3	254.9	239.4	211.5	249.9	230.0	239.5
	57	258.8	266.6	244.6	221.1	246.2	230.1	238.4
	64	266.6	264.4	244.5	226.6	257.1	230.7	239.6
	71	268.1	258.8	242.4	226.8	260.8	238.5	241.1
	78	266.8	269.0	252.0	227.4	260.6	244.3	249.7
	85	273.7	274.8	253.4	230.7	263.3	245.4	252.1
	90	270.6	268.5	253.3	228.3	258.8	249.6	249.6

Animal	78	79	80
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ACCLIMATIZATION

Day	1	140.3	161.0	151.3
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Animal	78	79	80
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TREATMENT

Day	1	157.8	185.4	173.2
	8	178.2	197.3	185.2
	15	189.5	208.3	209.9
	22	194.8	213.6	214.6
	29	200.1	231.2	225.9
	36	212.2	239.7	226.6
	43	218.7	237.9	237.8
	50	223.4	242.8	238.7
	57	221.2	247.2	240.7
	64	226.5	251.0	238.3
	71	234.1	253.6	248.9
	78	239.5	252.8	256.1
	85	235.2	260.5	253.4
	90	238.1	256.8	256.1

BODY WEIGHT GAIN (%)

Comments

Data excluded from Summary Report

Not Reported

All Study Phases

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

BODY WEIGHT GAIN (%)

MALES

Group 1 (0 mg/kg)

Animal	1	2	3	4	5	6	7
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ACCLIMATIZATION

Day	1	0	0	0	0	0	0
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Animal	1	2	3	4	5	6	7
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TREATMENT

Day	1	0	0	0	0	0	0	0
	8	15	15	17	12	14	14	15
	15	27	29	32	26	26	28	27
	22	37	38	42	35	36	38	36
	29	43	48	54	44	42	47	43
	36	50	55	61	54	47	54	51
	43	58	60	70	62	55	60	59
	50	67	68	76	70	63	67	64
	57	74	74	82	76	68	72	71
	64	79	78	85	81	70	75	76
	71	82	81	87	87	76	79	82
	78	88	84	92	89	81	83	88
	85	92	87	94	91	85	87	91
	90	93	88	95	92	87	88	91

Animal	8	9	10
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ACCLIMATIZATION

Day	1	0	0
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Animal	8	9	10
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TREATMENT

Day	1	0	0	0
	8	15	12	13
	15	29	27	24
	22	40	34	34
	29	48	41	40
	36	57	46	47
	43	61	52	54
	50	69	59	59
	57	74	62	65
	64	79	66	69
	71	82	70	73
	78	84	74	78
	85	86	75	79
	90	89	75	80

BODY WEIGHT GAIN (%)

MALES

Group 2 (100 mg/kg)

Animal	11	12	13	14	15	16	17
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ACCLIMATIZATION

Day	1	0	0	0	0	0	0
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Animal	11	12	13	14	15	16	17
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TREATMENT

Day	1	0	0	0	0	0	0
	8	16	13	17	16	18	18
	15	29	24	29	28	30	31
	22	39	31	39	39	39	43
	29	51	41	48	50	48	53
	36	59	49	55	57	55	64
	43	64	53	63	62	60	72
	50	71	58	68	70	67	76
	57	76	62	74	77	70	80
	64	78	68	80	80	74	85
	71	84	72	82	85	76	87
	78	88	75	87	88	80	92
	85	90	77	91	91	82	94
	90	92	80	92	94	81	96

Animal	18	19	20
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ACCLIMATIZATION

Day	1	0	0
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Animal	18	19	20
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TREATMENT

Day	1	0	0
	8	16	19
	15	28	32
	22	41	45
	29	51	55
	36	56	64
	43	66	71
	50	73	79
	57	78	86
	64	83	91
	71	88	95
	78	92	100
	85	100	102
	90	102	101

BODY WEIGHT GAIN (%)

MALES

Group 3 (300 mg/kg)

Animal	21	22	23	24	25	26	27
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ACCLIMATIZATION

Day	1	0	0	0	0	0	0
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Animal	21	22	23	24	25	26	27
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TREATMENT

Day	1	0	0	0	0	0	0	0
	8	14	13	16	14	16	15	11
	15	29	27	33	24	28	28	19
	22	40	34	45	33	38	38	24
	29	52	43	55	41	45	47	30
	36	60	49	66	45	52	55	34
	43	67	53	72	52	58	59	42
	50	74	56	80	57	65	68	45
	57	84	62	88	61	68	73	52
	64	87	68	92	64	71	78	54
	71	92	71	95	65	73	81	58
	78	96	76	100	68	76	85	62
	85	100	78	103	69	77	87	64
	90	94	77	104	69	81	88	63

Animal	28	29	30
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ACCLIMATIZATION

Day	1	0	0
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Animal	28	29	30
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TREATMENT

Day	1	0	0	0
	8	17	14	18
	15	31	24	33
	22	40	32	43
	29	50	39	54
	36	56	46	62
	43	60	52	68
	50	67	58	77
	57	71	63	83
	64	75	67	89
	71	79	70	94
	78	83	74	99
	85	85	78	104
	90	87	78	105

BODY WEIGHT GAIN (%)

MALES

Group 4 (1000 mg/kg)

Animal	31	32	33	34	35	36	37
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ACCLIMATIZATION

Day	1	0	0	0	0	0	0
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Animal	31	32	33	34	35	36	37
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TREATMENT

Day	1	0	0	0	0	0	0
	8	20	18	18	18	12	14
	15	35	34	32	31	26	27
	22	46	43	43	38	33	35
	29	55	54	52	47	40	41
	36	63	62	63	53	47	48
	43	69	70	68	60	52	54
	50	75	78	75	67	56	60
	57	80	83	81	71	61	65
	64	84	90	88	76	66	69
	71	89	93	92	81	67	72
	78	92	97	95	87	71	75
	85	95	99	97	91	75	77
	90	97	102	98	90	74	80

Animal	38	39	40
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ACCLIMATIZATION

Day	1	0	0
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Animal	38	39	40
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TREATMENT

Day	1	0	0
	8	17	14
	15	33	29
	22	44	38
	29	51	46
	36	59	55
	43	65	62
	50	72	68
	57	78	74
	64	81	79
	71	85	83
	78	88	87
	85	90	90
	90	90	91

BODY WEIGHT GAIN (%)

FEMALES

Group 1 (0 mg/kg)

Animal	41	42	43	44	45	46	47
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ACCLIMATIZATION

Day	1	0	0	0	0	0	0
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Animal	41	42	43	44	45	46	47
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TREATMENT

Day	1	0	0	0	0	0	0	0
	8	9	10	6	6	7	5	5
	15	16	21	15	11	11	18	16
	22	22	22	18	13	17	23	20
	29	25	26	22	21	25	27	23
	36	31	33	28	27	29	27	24
	43	36	36	29	30	28	37	33
	50	39	39	33	28	35	43	36
	57	38	34	36	35	38	44	36
	64	43	39	40	36	37	41	35
	71	48	42	44	37	35	50	41
	78	47	44	43	34	41	52	41
	85	45	40	43	37	43	50	43
	90	48	45	41	35	42	53	45

Animal	48	49	50
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ACCLIMATIZATION

Day	1	0	0
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Animal	48	49	50
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TREATMENT

Day	1	0	0	0
	8	7	10	8
	15	16	16	17
	22	25	23	24
	29	32	29	28
	36	38	32	30
	43	39	34	37
	50	46	38	42
	57	51	40	42
	64	54	44	42
	71	54	42	48
	78	57	46	49
	85	60	47	48
	90	59	47	49

BODY WEIGHT GAIN (%)

FEMALES

Group 2 (100 mg/kg)

Animal	51	52	53	54	55	56	57
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ACCLIMATIZATION

Day	1	0	0	0	0	0	0
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Animal	51	52	53	54	55	56	57
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TREATMENT

Day	1	0	0	0	0	0	0	0
	8	12	7	11	7	9	5	7
	15	19	16	17	13	17	11	18
	22	23	16	21	20	19	14	23
	29	28	27	24	28	27	18	30
	36	36	34	32	35	35	21	31
	43	37	34	36	34	34	26	37
	50	43	32	38	40	34	26	41
	57	44	40	34	42	41	32	41
	64	47	44	40	44	43	31	41
	71	48	45	46	45	43	38	45
	78	52	41	46	49	42	42	48
	85	50	46	39	48	48	34	47
	90	53	42	45	46	46	34	51

Animal	58	59	60
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ACCLIMATIZATION

Day	1	0	0
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Animal	58	59	60
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TREATMENT

Day	1	0	0	0
	8	8	10	4
	15	16	18	14
	22	22	24	19
	29	30	31	27
	36	33	36	27
	43	35	37	34
	50	35	38	38
	57	42	42	39
	64	44	45	38
	71	47	46	42
	78	44	43	47
	85	49	47	47
	90	46	47	49

BODY WEIGHT GAIN (%)
FEMALES

Group 3 (300 mg/kg)

Animal	61	62	63	64	65	66	67
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ACCLIMATIZATION

Day	1	0	0	0	0	0	0
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Animal	61	62	63	64	65	66	67
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TREATMENT

Day	1	0	0	0	0	0	0
	8	9	6	7	9	11	10
	15	18	13	18	14	22	18
	22	23	13	22	19	25	21
	29	26	22	31	25	30	29
	36	32	26	36	30	36	35
	43	36	27	39	32	40	35
	50	39	25	37	33	43	38
	57	37	32	45	38	40	44
	64	41	35	49	42	46	44
	71	45	37	53	42	50	42
	78	46	34	49	40	53	50
	85	46	38	56	47	51	48
	90	49	36	51	42	57	47

Animal	68	69	70
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ACCLIMATIZATION

Day	1	0	0
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Animal	68	69	70
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TREATMENT

Day	1	0	0
	8	10	9
	15	18	12
	22	18	19
	29	28	26
	36	32	31
	43	36	28
	50	36	36
	57	41	37
	64	44	43
	71	42	37
	78	46	45
	85	50	45
	90	52	46

BODY WEIGHT GAIN (%)
FEMALES

Group 4 (1000 mg/kg)

Animal	71	72	73	74	75	76	77
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ACCLIMATIZATION

Day	1	0	0	0	0	0	0
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Animal	71	72	73	74	75	76	77
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TREATMENT

Day	1	0	0	0	0	0	0
	8	9	5	6	8	8	7
	15	16	10	10	15	14	20
	22	22	16	19	20	22	25
	29	31	33	29	29	29	30
	36	35	37	32	32	31	30
	43	38	34	33	34	34	38
	50	39	37	39	35	38	41
	57	41	44	42	41	36	41
	64	45	43	42	45	42	42
	71	46	39	40	45	44	47
	78	45	45	46	45	44	50
	85	49	48	47	47	46	51
	90	47	45	47	46	43	53

Animal	78	79	80
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ACCLIMATIZATION

Day	1	0	0
-----	---	---	---

Animal	78	79	80
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TREATMENT

Day	1	0	0
	8	13	6
	15	20	12
	22	23	15
	29	27	25
	36	34	29
	43	39	28
	50	42	31
	57	40	33
	64	44	35
	71	48	37
	78	52	36
	85	49	40
	90	51	38

OPHTHALMOSCOPIC EXAMINATIONS

Comments

Data excluded from Summary Report

Not Reported

All Study Phases

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

OPHTHALMOSCOPIC EXAMINATIONS
ACCLIMATIZATION, Day 6, OPTHALMOSCOPY
MALES
Group 1 (0 mg/kg)

	Animal	1	2	3	4	5	6	7	8	9	10
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
	(LEFT EYE)	0	1	0	0	0	0	0	0	0	0
	(RIGHT EYE)	0	1	0	1	0	0	0	1	0	0
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
	(LEFT EYE)	0	0	0	0	0	0	1	1	0	0
	(RIGHT EYE)	0	0	0	0	0	0	1	0	0	1
VITREOUS BODY											
- PERSISTENT HYALOID VESSEL (1)											
	(LEFT EYE)	1	1	1	0	0	0	1	0	0	1
	(RIGHT EYE)	0	1	1	0	1	1	0	0	1	1

OPHTHALMOSCOPIC EXAMINATIONS
ACCLIMATIZATION, Day 6, OPTHALMOSCOPY
MALES
Group 2 (100 mg/kg)

	Animal	11	12	13	14	15	16	17	18	19	20
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		0	1	0	0	0	1	0	0	0	1
(RIGHT EYE)		0	2	1	0	0	0	0	1	0	0
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(LEFT EYE)		0	0	0	0	0	0	0	0	0	0
(RIGHT EYE)		0	0	0	0	0	0	0	0	0	0
VITREOUS BODY											
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		0	0	0	1	0	0	0	1	0	0
(RIGHT EYE)		0	0	1	1	0	1	0	1	0	0

OPHTHALMOSCOPIC EXAMINATIONS
ACCLIMATIZATION, Day 6, OPTHALMOSCOPY
MALES
Group 3 (300 mg/kg)

	Animal	21	22	23	24	25	26	27	28	29	30
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		0	1	0	0	0	0	0	0	0	1
(RIGHT EYE)		0	0	0	1	0	0	0	0	1	0
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(LEFT EYE)		0	0	0	0	0	0	0	0	0	0
(RIGHT EYE)		0	0	0	0	0	0	0	0	0	0
VITREOUS BODY											
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		1	1	0	0	1	0	1	0	1	1
(RIGHT EYE)		1	1	0	0	1	0	1	1	0	1

OPHTHALMOSCOPIC EXAMINATIONS
ACCLIMATIZATION, Day 6, OPHTHALMOSCOPY
MALES
Group 4 (1000 mg/kg)

	Animal	31	32	33	34	35	36	37	38	39	40
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		0	0	0	0	1	0	0	0	0	0
(RIGHT EYE)		1	0	1	1	0	1	0	0	0	0
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(LEFT EYE)		0	0	0	0	0	0	0	0	0	0
(RIGHT EYE)		0	0	0	0	1	0	0	0	0	0
VITREOUS BODY											
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		0	0	1	0	0	1	0	1	1	0
(RIGHT EYE)		1	1	1	0	1	0	0	1	0	0

OPHTHALMOSCOPIC EXAMINATIONS
ACCLIMATIZATION, Day 6, OPTHALMOSCOPY
FEMALES
Group 1 (0 mg/kg)

	Animal	41	42	43	44	45	46	47	48	49	50
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		0	0	1	2	0	0	0	0	0	0
(RIGHT EYE)		0	1	0	0	0	0	1	0	1	0
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(RIGHT EYE)		0	0	0	0	0	0	0	0	0	0
VITREOUS BODY											
- HEMORRHAGE IN VITREOUS (3)											
(RIGHT EYE)		0	0	0	0	0	0	0	0	0	0
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		1	0	0	0	0	0	0	1	1	0
(RIGHT EYE)		1	0	1	1	0	0	1	1	0	0

OPHTHALMOSCOPIC EXAMINATIONS
ACCLIMATIZATION, Day 6, OPTHALMOSCOPY
FEMALES
Group 2 (100 mg/kg)

	Animal	51	52	53	54	55	56	57	58	59	60
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		0	0	0	0	0	0	0	0	0	0
(RIGHT EYE)		1	0	0	0	0	0	0	0	0	0
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(RIGHT EYE)		0	0	0	0	0	0	0	0	0	0
VITREOUS BODY											
- HEMORRHAGE IN VITREOUS (3)											
(RIGHT EYE)		0	1	0	0	0	0	0	0	0	0
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		1	0	1	0	0	1	0	1	1	0
(RIGHT EYE)		0	0	1	0	0	1	0	1	1	0

OPHTHALMOSCOPIC EXAMINATIONS
ACCLIMATIZATION, Day 6, OPTHALMOSCOPY
FEMALES
Group 3 (300 mg/kg)

	Animal	61	62	63	64	65	66	67	68	69	70
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		0	0	0	2	0	0	0	0	0	0
(RIGHT EYE)		1	1	0	1	0	1	0	0	0	0
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(RIGHT EYE)		0	0	0	0	0	0	0	0	0	0
VITREOUS BODY											
- HEMORRHAGE IN VITREOUS (3)											
(RIGHT EYE)		0	0	0	0	0	0	0	0	0	0
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		0	1	0	0	1	0	1	0	0	1
(RIGHT EYE)		0	1	1	0	1	0	1	0	0	1

OPHTHALMOSCOPIC EXAMINATIONS
ACCLIMATIZATION, Day 6, OPTHALMOSCOPY
FEMALES
Group 4 (1000 mg/kg)

	Animal	71	72	73	74	75	76	77	78	79	80
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		0	0	0	0	0	0	0	0	0	0
(RIGHT EYE)		0	0	0	0	0	0	0	0	1	0
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(RIGHT EYE)		0	0	0	0	1	0	0	0	0	0
VITREOUS BODY											
- HEMORRHAGE IN VITREOUS (3)											
(RIGHT EYE)		0	0	0	0	0	0	0	0	0	0
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		1	1	0	0	0	0	0	1	1	0
(RIGHT EYE)		1	1	0	0	0	0	0	0	1	0

OPHTHALMOSCOPIC EXAMINATIONS
TREATMENT, Day 84, OPTHALMOSCOPY
MALES
Group 1 (0 mg/kg)

	Animal	1	2	3	4	5	6	7	8	9	10
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
	(LEFT EYE)	0	1	0	0	0	0	0	0	0	0
	(RIGHT EYE)	0	1	0	0	0	0	0	0	0	0
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
	(LEFT EYE)	0	0	0	0	0	0	1	1	0	0
	(RIGHT EYE)	0	0	0	0	0	0	1	0	0	1
VITREOUS BODY											
- PERSISTENT HYALOID VESSEL (1)											
	(LEFT EYE)	0	0	0	0	0	0	0	0	0	0
	(RIGHT EYE)	0	0	1	0	1	1	0	0	0	0

OPHTHALMOSCOPIC EXAMINATIONS
TREATMENT, Day 84, OPHTHALMOSCOPY
MALES
Group 2 (100 mg/kg)

	Animal	11	12	13	14	15	16	17	18	19	20
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		-	-	-	-	-	-	-	-	-	-
(RIGHT EYE)		-	-	-	-	-	-	-	-	-	-
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(LEFT EYE)		-	-	-	-	-	-	-	-	-	-
(RIGHT EYE)		-	-	-	-	-	-	-	-	-	-
VITREOUS BODY											
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		-	-	-	-	-	-	-	-	-	-
(RIGHT EYE)		-	-	-	-	-	-	-	-	-	-

OPHTHALMOSCOPIC EXAMINATIONS
TREATMENT, Day 84, OPHTHALMOSCOPY
MALES
Group 3 (300 mg/kg)

	Animal	21	22	23	24	25	26	27	28	29	30
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		-	-	-	-	-	-	-	-	-	-
(RIGHT EYE)		-	-	-	-	-	-	-	-	-	-
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(LEFT EYE)		-	-	-	-	-	-	-	-	-	-
(RIGHT EYE)		-	-	-	-	-	-	-	-	-	-
VITREOUS BODY											
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		-	-	-	-	-	-	-	-	-	-
(RIGHT EYE)		-	-	-	-	-	-	-	-	-	-

OPHTHALMOSCOPIC EXAMINATIONS
TREATMENT, Day 84, OPHTHALMOSCOPY
MALES
Group 4 (1000 mg/kg)

	Animal	31	32	33	34	35	36	37	38	39	40
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		0	1	0	0	0	0	0	0	0	0
(RIGHT EYE)		0	1	0	1	0	1	0	1	0	0
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(LEFT EYE)		0	0	0	0	0	0	0	0	0	0
(RIGHT EYE)		0	0	0	0	1	0	0	0	0	0
VITREOUS BODY											
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		0	0	0	0	0	1	0	0	0	0
(RIGHT EYE)		0	0	0	0	0	0	0	1	0	0

OPHTHALMOSCOPIC EXAMINATIONS
TREATMENT, Day 84, OPHTHALMOSCOPY
FEMALES
Group 1 (0 mg/kg)

	Animal	41	42	43	44	45	46	47	48	49	50
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		1	1	0	1	0	0	0	0	0	0
(RIGHT EYE)		1	0	0	1	0	1	0	0	0	1
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(RIGHT EYE)		0	0	0	0	0	0	0	0	0	0
VITREOUS BODY											
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		1	0	0	0	0	0	0	0	1	0
(RIGHT EYE)		0	0	1	0	0	0	0	0	1	0

OPHTHALMOSCOPIC EXAMINATIONS
TREATMENT, Day 84, OPTHALMOSCOPY
FEMALES
Group 2 (100 mg/kg)

	Animal	51	52	53	54	55	56	57	58	59	60
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		-	-	-	-	-	-	-	-	-	-
(RIGHT EYE)		-	-	-	-	-	-	-	-	-	-
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(RIGHT EYE)		-	-	-	-	-	-	-	-	-	-
VITREOUS BODY											
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		-	-	-	-	-	-	-	-	-	-
(RIGHT EYE)		-	-	-	-	-	-	-	-	-	-

OPHTHALMOSCOPIC EXAMINATIONS
TREATMENT, Day 84, OPHTHALMOSCOPY
FEMALES
Group 3 (300 mg/kg)

	Animal	61	62	63	64	65	66	67	68	69	70
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		-	-	-	-	-	-	-	-	-	-
(RIGHT EYE)		-	-	-	-	-	-	-	-	-	-
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(RIGHT EYE)		-	-	-	-	-	-	-	-	-	-
VITREOUS BODY											
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		-	-	-	-	-	-	-	-	-	-
(RIGHT EYE)		-	-	-	-	-	-	-	-	-	-

OPHTHALMOSCOPIC EXAMINATIONS
TREATMENT, Day 84, OPTHALMOSCOPY
FEMALES
Group 4 (1000 mg/kg)

	Animal	71	72	73	74	75	76	77	78	79	80
Unscheduled Findings											
CORNEA											
- CORNEAL OPACITY (3)											
(LEFT EYE)		0	0	0	0	0	0	0	0	0	0
(RIGHT EYE)		0	0	1	0	0	0	0	0	0	0
LENS											
- PERSISTENT PUPIL MEMBRANE (1)											
(RIGHT EYE)		0	0	0	0	1	0	0	0	0	0
VITREOUS BODY											
- PERSISTENT HYALOID VESSEL (1)											
(LEFT EYE)		0	1	0	0	0	0	0	0	0	0
(RIGHT EYE)		0	1	0	0	0	0	0	0	0	0

Hematology

Comments

a coagulated sample

Data excluded from Summary Report

Not Reported

All Measurements

Animal 81 Male Group 10 Reserve Removed
Animal 82 Female Group 10 Reserve Removed

Reported Parameter

After 13 Weeks

RBC	ERYTHROCYTES (RBC)
HB	HEMOGLOBIN (HB)
HCT	HEMATOCRIT (HCT)
MCV	MEAN CORPUSCULAR VOLUME (MCV)
RDW	RED CELL VOL. DISTR. WIDTH (RDW)
MCH	MEAN CORPUSCULAR HEMOGLOBIN (MCH)
MCHC	MEAN CORPUSCULAR HEMOGLOBIN CONC. (MCHC)
HDW	HEMOGLOBIN CONC. DISTR. WIDTH
RETI	RETICULOCYTE (REL)
RETI	RETICULOCYTE (ABS)
L RETI	MATURITY INDEX (L-RETI)
M RETI	MATURITY INDEX (M-RETI)
H RETI	MATURITY INDEX (H-RETI)
WBC	LEUKOCYTES, TOTAL (WBC)
NEUT	NEUTROPHILS (NEUT)
EOS	EOSINOPHILS (EOS)
BASO	BASOPHILS (BASO)
LYMPH	LYMPHOCYTES (LYMPH)
MONO	MONOCYTES (MONO)
LUC	LARGE UNSTAINED CELLS (LUC)
NEUT	NEUTROPHILS (NEUT)
EOS	EOSINOPHILS (EOS)
BASO	BASOPHILS (BASO)
LYMPH	LYMPHOCYTES (LYMPH)
MONO	MONOCYTES (MONO)
LUC	LARGE UNSTAINED CELLS (LUC)
PLATELETS	THROMBOCYTES (PLATELETS)
MET-HB	METHEMOGLOBIN (MET-HB)
PT	PROTHROMBIN TIME (PT)
PTT	PARTIAL THROMBOPLASTIN TIME (PTT)

Hematology
After 13 Weeks
MALES

Group 1 (0 mg/kg)

GENERAL							
	RBC	HB	HCT	MCV	RDW	MCH	MCHC
	T/l	mmol/l	rel. 1	fl	rel. 1	fmol	mmol/l
1	8.45	9.5	0.43	51.2	0.124	1.12	21.91
2	8.67	9.0	0.42	48.5	0.126	1.03	21.30
3	9.00	9.4	0.43	47.8	0.123	1.04	21.80
4	8.75	9.1	0.42	47.7	0.131	1.04	21.89
5	7.85	9.6	0.42	54.0	0.223	1.22	22.61
6	8.96	9.6	0.44	48.6	0.124	1.07	22.09
7	9.40	9.9	0.45	47.4	0.125	1.05	22.12
8	8.77	9.5	0.43	48.9	0.127	1.08	22.04
9	7.98	9.2	0.40	50.0	0.135	1.15	23.11
10	8.61	9.8	0.43	50.1	0.131	1.13	22.65

GENERAL	RETICULOCYTE COUNT					GENERAL	
HDW	RETI	RETI	L RETI	M RETI	H RETI	WBC	
mmol/l	rel. 1	G/l	rel. 1	rel. 1	rel. 1	G/l	
1	1.65	0.025	209	0.488	0.386	0.127	5.40
2	1.68	0.018	159	0.540	0.366	0.095	4.61
3	1.61	0.017	156	0.556	0.364	0.081	6.22
4	1.76	0.018	155	0.530	0.393	0.077	5.61
5	1.95	0.021	165	0.552	0.370	0.078	6.59
6	1.52	0.016	141	0.655	0.302	0.043	4.47
7	1.58	0.017	157	0.591	0.354	0.056	5.82
8	1.69	0.019	165	0.503	0.406	0.091	5.59
9	1.79	0.015	118	0.584	0.350	0.066	4.25
10	1.78	0.017	147	0.518	0.383	0.099	5.82

DIFF.WBC COUNT (REL)						
NEUT	EOS	BASO	LYMPH	MONO	LUC	
rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1
1	0.231	0.015	0.005	0.719	0.024	0.005
2	0.172	0.009	0.005	0.796	0.014	0.004
3	0.209	0.016	0.007	0.747	0.017	0.003
4	0.238	0.015	0.009	0.701	0.032	0.005
5	0.290	0.017	0.009	0.654	0.025	0.005
6	0.246	0.017	0.015	0.673	0.034	0.015
7	0.248	0.016	0.006	0.714	0.012	0.004
8	0.333	0.015	0.006	0.605	0.033	0.008
9	0.229	0.009	0.005	0.724	0.027	0.006
10	0.220	0.010	0.009	0.731	0.028	0.004

Hematology
After 13 Weeks
MALES

Group 1 (0 mg/kg)

	DIFF.WBC COUNT (ABS)						GENERAL
	NEUT	EOS	BASO	LYMPH	MONO	LUC	PLATELETS
	G/1	G/1	G/1	G/1	G/1	G/1	G/1
1	1.25	0.08	0.03	3.89	0.13	0.03	929
2	0.79	0.04	0.02	3.67	0.06	0.02	1271
3	1.30	0.10	0.05	4.65	0.10	0.02	1156
4	1.34	0.09	0.05	3.93	0.18	0.03	872
5	1.91	0.11	0.06	4.31	0.16	0.03	914
6	1.10	0.08	0.07	3.01	0.15	0.07	839
7	1.44	0.09	0.04	4.16	0.07	0.02	806
8	1.86	0.09	0.03	3.38	0.18	0.04	930
9	0.97	0.04	0.02	3.08	0.11	0.03	872
10	1.28	0.06	0.05	4.25	0.16	0.02	866

	GENERAL	COAGULATION	
	MET-HB	PT	PTT
	rel. 1	rel. 1	sec
1	0.011	0.92	22.2
2	0.009	0.87	22.2
3	0.010	0.79	25.6
4	0.009	0.82	26.2
5	0.010	0.84	22.8
6	0.010	0.82	26.3
7	0.009	0.81	22.2
8	0.010	0.85	22.5
9	0.010	0.70	31.5
10	0.009	0.79	24.1

Hematology
After 13 Weeks
MALES

Group 2 (100 mg/kg)

GENERAL							
	RBC	HB	HCT	MCV	RDW	MCH	MCHC
	T/l	mmol/l	rel. 1	fl	rel. 1	fmol	mmol/l
11	9.00	9.3	0.43	47.5	0.128	1.03	21.70
12	8.67	9.6	0.43	49.4	0.132	1.11	22.47
13	8.68	9.3	0.42	48.2	0.125	1.07	22.21
14	8.59	9.6	0.43	49.8	0.131	1.12	22.55
15	8.55	9.5	0.43	50.7	0.132	1.11	21.94
16	8.57	9.3	0.42	48.6	0.123	1.09	22.33
17	8.43	9.3	0.42	50.4	0.236	1.11	21.95
18	8.43	9.2	0.43	50.9	0.129	1.10	21.53
19	8.44	9.4	0.42	49.8	0.129	1.12	22.39
20	9.17	9.7	0.44	47.9	0.131	1.05	22.00

GENERAL	RETICULOCYTE COUNT					GENERAL	
HDW	RETI	RETI	L RETI	M RETI	H RETI	WBC	
mmol/l	rel. 1	G/l	rel. 1	rel. 1	rel. 1	G/l	
11	1.61	0.018	165	0.586	0.339	0.075	5.67
12	1.74	0.019	164	0.552	0.361	0.087	5.37
13	1.69	0.016	138	0.524	0.376	0.100	3.60
14	1.70	0.022	191	0.508	0.389	0.102	5.83
15	1.90	0.015	125	0.592	0.351	0.057	5.61
16	1.86	0.020	168	0.565	0.334	0.100	5.90
17	2.16	0.017	147	0.590	0.352	0.059	5.98
18	1.73	0.022	188	0.496	0.381	0.123	4.75
19	1.82	0.021	173	0.527	0.386	0.086	3.78
20	1.76	0.020	182	0.568	0.350	0.082	4.82

DIFF.WBC COUNT (REL)						
NEUT	EOS	BASO	LYMPH	MONO	LUC	
rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	
11	0.243	0.017	0.006	0.717	0.010	0.005
12	0.274	0.006	0.010	0.671	0.024	0.015
13	0.221	0.013	0.008	0.725	0.031	0.003
14	0.219	0.009	0.012	0.723	0.028	0.008
15	0.238	0.011	0.006	0.718	0.019	0.009
16	0.237	0.013	0.006	0.727	0.015	0.003
17	0.180	0.010	0.004	0.779	0.018	0.009
18	0.186	0.016	0.006	0.773	0.016	0.003
19	0.327	0.021	0.007	0.620	0.021	0.004
20	0.289	0.028	0.004	0.647	0.030	0.002

Hematology
After 13 Weeks
MALES

Group 2 (100 mg/kg)

	DIFF.WBC COUNT (ABS)						GENERAL
	NEUT	EOS	BASO	LYMPH	MONO	LUC	PLATELETS
	G/1	G/1	G/1	G/1	G/1	G/1	G/1
11	1.38	0.10	0.04	4.07	0.06	0.03	893
12	1.47	0.03	0.05	3.61	0.13	0.08	925
13	0.79	0.05	0.03	2.61	0.11	0.01	671
14	1.28	0.05	0.07	4.21	0.17	0.05	932
15	1.33	0.06	0.03	4.03	0.11	0.05	1058
16	1.40	0.07	0.04	4.29	0.09	0.02	887
17	1.08	0.06	0.02	4.66	0.11	0.05	1149
18	0.88	0.08	0.03	3.67	0.07	0.02	876
19	1.24	0.08	0.03	2.35	0.08	0.02	981
20	1.39	0.14	0.02	3.12	0.14	0.01	1066

	GENERAL	COAGULATION	
	MET-HB	PT	PTT
	rel. 1	rel. 1	sec
11	0.011	0.82	19.2
12	0.010	0.77	22.8
13	0.009	0.82	21.1
14	0.010	0.80	24.7
15	0.009	0.82	23.4
16	0.009	0.84	19.1
17	0.008	0.78	27.2
18	0.010	0.78	23.0
19	0.008	0.82	25.3
20	0.010	0.86	22.2

Hematology
After 13 Weeks
MALES

Group 3 (300 mg/kg)

GENERAL							
	RBC	HB	HCT	MCV	RDW	MCH	MCHC
	T/l	mmol/l	rel. 1	fl	rel. 1	fmol	mmol/l
21	8.67	9.8	0.44	50.7	0.215	1.14	22.38
22	8.97	9.7	0.45	50.0	0.126	1.08	21.62
23	7.97	9.7	0.43	54.0	0.148	1.22	22.67
24	8.68	9.6	0.43	49.6	0.134	1.10	22.17
25	9.11	9.6	0.43	47.4	0.138	1.06	22.29
26	8.28	8.9	0.40	48.8	0.141	1.07	22.00
27	9.30	9.8	0.46	49.4	0.126	1.05	21.36
28	8.04	9.6	0.42	52.6	0.191	1.19	22.72
29	9.43	9.8	0.45	47.9	0.123	1.03	21.61
30	9.00	9.7	0.43	48.3	0.136	1.08	22.41

GENERAL	RETICULOCYTE COUNT					GENERAL	
HDW	RETI	RETI	L RETI	M RETI	H RETI	WBC	
mmol/l	rel. 1	G/l	rel. 1	rel. 1	rel. 1	G/l	
21	1.87	0.022	188	0.528	0.395	0.077	5.59
22	1.71	0.018	161	0.545	0.365	0.090	4.97
23	1.72	0.020	160	0.528	0.373	0.099	6.23
24	1.67	0.018	152	0.591	0.355	0.054	3.94
25	1.77	0.019	173	0.546	0.375	0.079	6.02
26	1.68	0.027	226	0.521	0.385	0.094	3.92
27	1.65	0.018	170	0.530	0.394	0.075	3.57
28	1.78	0.018	146	0.581	0.342	0.078	3.78
29	1.51	0.019	182	0.558	0.345	0.097	6.33
30	1.77	0.021	193	0.476	0.392	0.132	5.88

DIFF.WBC COUNT (REL)						
NEUT	EOS	BASO	LYMPH	MONO	LUC	
rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1
21	0.212	0.029	0.005	0.726	0.024	0.004
22	0.301	0.029	0.004	0.648	0.015	0.003
23	0.240	0.009	0.009	0.721	0.016	0.005
24	0.275	0.010	0.004	0.682	0.024	0.005
25	0.309	0.018	0.008	0.631	0.030	0.004
26	0.237	0.009	0.005	0.731	0.018	0.002
27	0.185	0.020	0.007	0.769	0.012	0.007
28	0.230	0.012	0.006	0.726	0.018	0.009
29	0.177	0.015	0.006	0.772	0.026	0.004
30	0.281	0.032	0.007	0.648	0.027	0.005

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MALES

Group 3 (300 mg/kg)

	DIFF. WBC COUNT (ABS)						GENERAL
	NEUT	EOS	BASO	LYMPH	MONO	LUC	PLATELETS
	G/1	G/1	G/1	G/1	G/1	G/1	G/1
21	1.18	0.16	0.03	4.06	0.13	0.02	932
22	1.50	0.14	0.02	3.23	0.08	0.01	877
23	1.49	0.06	0.05	4.49	0.10	0.03	996
24	1.09	0.04	0.02	2.69	0.09	0.02	875
25	1.86	0.11	0.05	3.80	0.18	0.02	885
26	0.93	0.04	0.02	2.87	0.07	0.01	817
27	0.66	0.07	0.03	2.75	0.04	0.02	949
28	0.87	0.04	0.02	2.74	0.07	0.03	1130
29	1.12	0.09	0.04	4.89	0.17	0.02	931
30	1.65	0.19	0.04	3.81	0.16	0.03	1050

	GENERAL	COAGULATION	
	MET-HB	PT	PTT
	rel. 1	rel. 1	sec
21	0.010	0.84	26.2
22	0.010	0.85	21.2
23	0.009	0.77	26.2
24	0.008	0.81	24.1
25	0.009	0.79	26.9
26	0.010	0.76	28.9
27	0.009	0.83	24.5
28	0.010	0.84	23.9
29	0.009	0.85	25.4
30	0.009	0.81	23.0

Hematology
After 13 Weeks
MALES

Group 4 (1000 mg/kg)

GENERAL							
	RBC	HB	HCT	MCV	RDW	MCH	MCHC
	T/l	mmol/l	rel. 1	fl	rel. 1	fmol	mmol/l
31	8.04	8.9	0.40	50.3	0.132	1.11	22.12
32	8.85	9.4	0.44	49.4	0.130	1.07	21.58
33	8.79	9.4	0.43	48.9	0.134	1.07	21.88
34	8.45	10.0	0.45	52.7	0.232	1.18	22.40
35	9.39	10.2	0.47	50.1	0.125	1.09	21.74
36	---	a	---	---	---	---	---
37	7.46	9.2	0.40	54.0	0.223	1.23	22.75
38	8.45	8.9	0.41	48.8	0.123	1.05	21.59
39	9.39	9.9	0.46	48.6	0.125	1.05	21.60
40	8.21	9.3	0.42	50.9	0.124	1.14	22.34

GENERAL	RETICULOCYTE COUNT					GENERAL	
HDW	RETI	RETI	L RETI	M RETI	H RETI	WBC	
mmol/l	rel. 1	G/l	rel. 1	rel. 1	rel. 1	G/l	
31	1.64	0.020	158	0.502	0.392	0.106	3.94
32	1.51	0.022	198	0.477	0.381	0.142	5.68
33	1.75	0.020	172	0.476	0.421	0.103	5.07
34	1.71	0.017	140	0.610	0.317	0.073	4.52
35	1.55	0.018	172	0.600	0.344	0.056	7.59
36	---	---	---	---	---	---	---
37	1.83	0.022	161	0.507	0.362	0.132	5.54
38	1.42	0.020	165	0.530	0.378	0.093	4.39
39	1.48	0.019	178	0.550	0.372	0.078	6.69
40	1.59	0.013	111	0.609	0.319	0.072	3.70

DIFF.WBC COUNT (REL)						
NEUT	EOS	BASO	LYMPH	MONO	LUC	
rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	
31	0.212	0.010	0.003	0.752	0.018	0.006
32	0.255	0.021	0.005	0.676	0.030	0.013
33	0.275	0.022	0.006	0.671	0.024	0.003
34	0.208	0.029	0.006	0.732	0.021	0.004
35	0.235	0.008	0.007	0.730	0.015	0.005
36	---	---	---	---	---	---
37	0.145	0.009	0.003	0.815	0.024	0.003
38	0.203	0.013	0.005	0.751	0.025	0.004
39	0.173	0.010	0.006	0.794	0.014	0.003
40	0.216	0.013	0.005	0.723	0.035	0.007

a: See explanation on section cover page

Hematology
After 13 Weeks
MALES

Group 4 (1000 mg/kg)

	DIFF.WBC COUNT (ABS)						GENERAL
	NEUT	EOS	BASO	LYMPH	MONO	LUC	PLATELETS
	G/l	G/l	G/l	G/l	G/l	G/l	G/l
31	0.83	0.04	0.01	2.96	0.07	0.03	1144
32	1.45	0.12	0.03	3.84	0.17	0.07	876
33	1.40	0.11	0.03	3.40	0.12	0.01	1101
34	0.94	0.13	0.03	3.31	0.10	0.02	661
35	1.78	0.06	0.05	5.54	0.11	0.04	904
36	---	---	---	---	---	---	---
37	0.80	0.05	0.02	4.52	0.13	0.01	896
38	0.89	0.06	0.02	3.30	0.11	0.02	1186
39	1.16	0.07	0.04	5.31	0.09	0.02	924
40	0.80	0.05	0.02	2.67	0.13	0.03	883

	GENERAL	COAGULATION	
	MET-HB	PT	PTT
	rel. 1	rel. 1	sec
31	0.009	0.92	20.8
32	0.009	0.89	19.2
33	0.009	0.89	25.7
34	0.009	0.85	25.5
35	0.006	0.89	23.7
36	0.008	0.81	27.5
37	0.010	0.82	25.0
38	0.009	0.82	24.7
39	0.010	0.87	27.0
40	0.010	0.87	25.9

Hematology
After 13 Weeks
FEMALES

Group 1 (0 mg/kg)

GENERAL							
	RBC	HB	HCT	MCV	RDW	MCH	MCHC
	T/l	mmol/l	rel. 1	fl	rel. 1	fmol	mmol/l
41	7.59	8.7	0.39	51.1	0.120	1.15	22.42
42	6.85	8.7	0.37	54.1	0.247	1.27	23.44
43	7.52	9.1	0.40	53.8	0.107	1.21	22.49
44	7.90	9.1	0.40	51.0	0.113	1.15	22.51
45	7.32	8.8	0.38	52.1	0.144	1.20	23.01
46	7.44	9.1	0.39	51.9	0.134	1.22	23.48
47	8.12	9.9	0.43	52.8	0.146	1.22	23.08
48	7.65	8.9	0.40	51.8	0.127	1.16	22.34
49	7.81	9.4	0.40	51.8	0.143	1.21	23.33
50	7.66	9.5	0.41	53.3	0.137	1.24	23.30

GENERAL	RETICULOCYTE COUNT					GENERAL	
HDW	RETI	RETI	L RETI	M RETI	H RETI	WBC	
mmol/l	rel. 1	G/l	rel. 1	rel. 1	rel. 1	G/l	
41	1.47	0.015	116	0.672	0.275	0.054	2.38
42	1.82	0.020	137	0.564	0.346	0.090	1.88
43	1.28	0.018	138	0.698	0.281	0.021	1.87
44	1.41	0.020	158	0.715	0.268	0.017	4.11
45	1.64	0.030	218	0.582	0.362	0.056	3.00
46	1.61	0.024	178	0.594	0.372	0.034	2.28
47	1.62	0.028	226	0.584	0.380	0.036	4.70
48	1.48	0.023	172	0.682	0.284	0.035	1.93
49	1.68	0.028	216	0.619	0.332	0.049	2.35
50	1.61	0.025	190	0.530	0.382	0.088	2.07

DIFF.WBC COUNT (REL)						
NEUT	EOS	BASO	LYMPH	MONO	LUC	
rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1
41	0.281	0.036	0.012	0.640	0.024	0.007
42	0.195	0.030	0.009	0.734	0.021	0.011
43	0.343	0.046	0.005	0.587	0.012	0.007
44	0.107	0.010	0.004	0.857	0.011	0.011
45	0.210	0.025	0.006	0.735	0.015	0.009
46	0.152	0.017	0.008	0.792	0.023	0.009
47	0.209	0.033	0.011	0.724	0.015	0.008
48	0.373	0.015	0.003	0.574	0.024	0.011
49	0.251	0.026	0.006	0.690	0.020	0.007
50	0.150	0.011	0.011	0.799	0.023	0.006

Hematology
After 13 Weeks
FEMALES

Group 1 (0 mg/kg)

	DIFF.WBC COUNT (ABS)						GENERAL
	NEUT	EOS	BASO	LYMPH	MONO	LUC	PLATELETS
	G/1	G/1	G/1	G/1	G/1	G/1	G/1
41	0.67	0.09	0.03	1.52	0.06	0.02	1105
42	0.37	0.06	0.02	1.38	0.04	0.02	951
43	0.64	0.09	0.01	1.10	0.02	0.01	800
44	0.44	0.04	0.02	3.52	0.05	0.05	1458
45	0.63	0.08	0.02	2.20	0.05	0.03	944
46	0.35	0.04	0.02	1.81	0.05	0.02	1218
47	0.98	0.15	0.05	3.40	0.07	0.04	1324
48	0.72	0.03	0.01	1.11	0.05	0.02	1048
49	0.59	0.06	0.01	1.62	0.05	0.02	950
50	0.31	0.02	0.02	1.65	0.05	0.01	1217

	GENERAL	COAGULATION	
	MET-HB	PT	PTT
	rel. 1	rel. 1	sec
41	0.010	0.80	39.8
42	0.009	0.83	51.2
43	0.008	0.76	36.3
44	0.009	0.80	35.1
45	0.011	0.79	28.5
46	0.010	0.76	40.6
47	0.008	0.88	34.8
48	0.010	0.89	28.9
49	0.010	0.84	34.9
50	0.010	0.79	32.6

Hematology
After 13 Weeks
FEMALES

Group 2 (100 mg/kg)

GENERAL							
	RBC	HB	HCT	MCV	RDW	MCH	MCHC
	T/l	mmol/l	rel. 1	fl	rel. 1	fmol	mmol/l
51	7.39	9.3	0.40	54.7	0.132	1.26	22.96
52	7.20	9.4	0.40	55.0	0.246	1.31	23.78
53	---	---	---	---	---	---	---
54	6.98	9.0	0.39	55.9	0.150	1.30	23.18
55	7.25	9.0	0.39	54.1	0.131	1.25	23.07
56	8.71	9.3	0.41	47.6	0.117	1.06	22.35
57	7.85	9.4	0.41	52.8	0.116	1.19	22.60
58	8.09	9.4	0.41	50.8	0.117	1.16	22.89
59	7.82	9.5	0.42	53.1	0.108	1.22	22.93
60	7.54	9.1	0.39	52.3	0.144	1.21	23.16

GENERAL	RETICULOCYTE COUNT					GENERAL	
HDW	RETI	RETI	L RETI	M RETI	H RETI	WBC	
mmol/l	rel. 1	G/l	rel. 1	rel. 1	rel. 1	G/l	
51	1.49	0.020	149	0.599	0.349	0.052	2.15
52	1.76	0.023	164	0.690	0.278	0.033	2.01
53	---	---	---	---	---	---	---
54	1.50	0.022	153	0.549	0.375	0.076	2.06
55	1.51	0.022	162	0.695	0.274	0.030	2.74
56	1.39	0.010	89	0.746	0.231	0.023	2.17
57	1.44	0.020	158	0.607	0.345	0.049	2.74
58	1.52	0.021	168	0.719	0.257	0.024	2.70
59	1.34	0.022	173	0.692	0.273	0.035	2.29
60	1.55	0.028	213	0.507	0.415	0.078	2.64

DIFF.WBC COUNT (REL)						
NEUT	EOS	BASO	LYMPH	MONO	LUC	
rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1
51	0.227	0.032	0.005	0.713	0.013	0.010
52	0.190	0.037	0.006	0.739	0.021	0.007
53	---	---	---	---	---	---
54	0.138	0.024	0.009	0.800	0.017	0.012
55	0.167	0.033	0.006	0.768	0.016	0.009
56	0.205	0.019	0.002	0.759	0.011	0.004
57	0.255	0.015	0.009	0.679	0.031	0.011
58	0.196	0.021	0.012	0.733	0.030	0.008
59	0.154	0.010	0.008	0.810	0.014	0.004
60	0.152	0.035	0.005	0.785	0.017	0.005

a: See explanation on section cover page

Hematology
After 13 Weeks
FEMALES

Group 2 (100 mg/kg)

	DIFF.WBC COUNT (ABS)						GENERAL
	NEUT	EOS	BASO	LYMPH	MONO	LUC	PLATELETS
	G/1	G/1	G/1	G/1	G/1	G/1	G/1
51	0.49	0.07	0.01	1.53	0.03	0.02	958
52	0.38	0.07	0.01	1.49	0.04	0.01	944
53	---	---	---	---	---	---	---
54	0.28	0.05	0.02	1.65	0.04	0.02	905
55	0.46	0.09	0.02	2.11	0.04	0.03	836
56	0.44	0.04	0.01	1.65	0.02	0.01	1028
57	0.70	0.04	0.02	1.86	0.08	0.03	979
58	0.53	0.06	0.03	1.98	0.08	0.02	1116
59	0.35	0.02	0.02	1.85	0.03	0.01	1072
60	0.40	0.09	0.01	2.07	0.05	0.01	926

	GENERAL	COAGULATION	
	MET-HB	PT	PTT
	rel. 1	rel. 1	sec
51	0.010	0.92	30.0
52	0.010	0.88	32.1
53	0.009	0.83	46.6
54	0.010	0.92	23.7
55	0.010	0.83	29.3
56	0.009	0.83	31.3
57	0.009	0.89	33.8
58	0.010	0.88	36.8
59	0.010	0.88	31.4
60	0.009	0.84	43.0

Hematology
After 13 Weeks
FEMALES

Group 3 (300 mg/kg)

GENERAL							
	RBC	HB	HCT	MCV	RDW	MCH	MCHC
	T/l	mmol/l	rel. 1	fl	rel. 1	fmol	mmol/l
61	7.10	8.6	0.37	52.2	0.146	1.21	23.12
62	8.13	9.5	0.41	50.5	0.127	1.17	23.17
63	7.37	9.0	0.39	53.3	0.157	1.23	23.01
64	7.70	8.9	0.39	50.3	0.121	1.15	22.96
65	7.45	9.2	0.40	53.2	0.148	1.23	23.10
66	7.41	8.7	0.38	51.3	0.133	1.17	22.89
67	7.28	8.9	0.39	53.1	0.129	1.23	23.09
68	6.94	9.0	0.39	55.8	0.146	1.30	23.25
69	7.42	9.0	0.39	52.0	0.156	1.21	23.33
70	8.22	8.7	0.39	47.6	0.124	1.06	22.35

GENERAL	RETICULOCYTE COUNT					GENERAL	
HDW	RETI	RETI	L RETI	M RETI	H RETI	WBC	
mmol/l	rel. 1	G/l	rel. 1	rel. 1	rel. 1	G/l	
61	1.58	0.024	172	0.535	0.378	0.087	3.41
62	1.54	0.015	126	0.777	0.198	0.025	5.06
63	1.60	0.023	169	0.656	0.299	0.045	2.88
64	1.36	0.017	128	0.669	0.293	0.038	2.14
65	1.58	0.017	128	0.669	0.291	0.040	2.27
66	1.63	0.030	225	0.632	0.333	0.034	2.22
67	1.48	0.021	153	0.600	0.348	0.053	2.01
68	1.54	0.029	199	0.520	0.416	0.064	2.01
69	1.63	0.023	173	0.670	0.306	0.024	2.21
70	1.45	0.017	142	0.757	0.221	0.022	2.37

DIFF.WBC COUNT (REL)						
NEUT	EOS	BASO	LYMPH	MONO	LUC	
rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1
61	0.160	0.025	0.011	0.778	0.016	0.010
62	0.125	0.012	0.010	0.825	0.021	0.006
63	0.218	0.020	0.008	0.731	0.014	0.009
64	0.237	0.025	0.011	0.701	0.021	0.006
65	0.136	0.014	0.007	0.823	0.014	0.006
66	0.385	0.007	0.009	0.572	0.017	0.009
67	0.199	0.009	0.011	0.761	0.014	0.007
68	0.261	0.074	0.004	0.637	0.018	0.006
69	0.359	0.032	0.010	0.578	0.017	0.005
70	0.395	0.010	0.005	0.567	0.017	0.005

Hematology
After 13 Weeks
FEMALES

Group 3 (300 mg/kg)

	DIFF.WBC COUNT (ABS)						GENERAL
	NEUT	EOS	BASO	LYMPH	MONO	LUC	PLATELETS
	G/1	G/1	G/1	G/1	G/1	G/1	G/1
61	0.54	0.09	0.04	2.65	0.05	0.03	853
62	0.63	0.06	0.05	4.17	0.11	0.03	1373
63	0.63	0.06	0.02	2.11	0.04	0.03	1027
64	0.51	0.05	0.02	1.50	0.04	0.01	1077
65	0.31	0.03	0.01	1.87	0.03	0.01	1019
66	0.85	0.02	0.02	1.27	0.04	0.02	1080
67	0.40	0.02	0.02	1.53	0.03	0.01	903
68	0.52	0.15	0.01	1.28	0.04	0.01	993
69	0.79	0.07	0.02	1.28	0.04	0.01	842
70	0.94	0.02	0.01	1.34	0.04	0.01	845

	GENERAL	COAGULATION	
	MET-HB	PT	PTT
	rel. 1	rel. 1	sec
61	0.012	0.89	31.5
62	0.009	0.84	29.7
63	0.011	0.83	30.7
64	0.010	0.81	31.7
65	0.009	0.78	26.3
66	0.009	0.89	35.1
67	0.009	0.87	35.5
68	0.009	0.86	43.4
69	0.009	0.00	0.0
70	0.009	0.83	32.1

Hematology
After 13 Weeks
FEMALES

Group 4 (1000 mg/kg)

GENERAL							
	RBC	HB	HCT	MCV	RDW	MCH	MCHC
	T/l	mmol/l	rel. 1	fl	rel. 1	fmol	mmol/l
71	7.48	9.2	0.39	52.6	0.114	1.23	23.29
72	6.08	8.0	0.34	55.8	0.155	1.31	23.48
73	7.48	9.1	0.40	53.0	0.142	1.21	22.89
74	8.41	9.5	0.42	50.4	0.114	1.13	22.51
75	7.72	8.7	0.38	48.8	0.133	1.12	23.02
76	7.04	9.1	0.39	55.9	0.198	1.30	23.17
77	7.43	9.2	0.39	52.8	0.122	1.23	23.38
78	7.43	8.8	0.39	52.6	0.112	1.18	22.51
79	7.86	9.3	0.41	51.9	0.109	1.18	22.70
80	7.92	9.4	0.41	52.2	0.117	1.18	22.68

GENERAL	RETICULOCYTE COUNT					GENERAL	
HDW	RETI	RETI	L RETI	M RETI	H RETI	WBC	
mmol/l	rel. 1	G/l	rel. 1	rel. 1	rel. 1	G/l	
71	1.40	0.022	164	0.605	0.355	0.040	4.61
72	1.44	0.036	221	0.501	0.357	0.142	1.67
73	1.59	0.030	226	0.575	0.361	0.064	2.48
74	1.33	0.021	176	0.692	0.272	0.036	3.11
75	1.63	0.022	167	0.628	0.332	0.040	2.09
76	1.68	0.028	196	0.506	0.424	0.070	2.33
77	1.44	0.032	238	0.654	0.316	0.030	2.25
78	1.31	0.020	149	0.581	0.365	0.054	2.42
79	1.27	0.018	144	0.702	0.278	0.021	2.74
80	1.39	0.024	189	0.619	0.350	0.031	2.55

DIFF.WBC COUNT (REL)						
NEUT	EOS	BASO	LYMPH	MONO	LUC	
rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1	rel. 1
71	0.181	0.016	0.007	0.773	0.010	0.014
72	0.169	0.012	0.006	0.770	0.029	0.021
73	0.226	0.029	0.007	0.694	0.029	0.014
74	0.315	0.013	0.009	0.630	0.026	0.009
75	0.398	0.030	0.004	0.544	0.019	0.006
76	0.152	0.066	0.008	0.749	0.017	0.008
77	0.309	0.038	0.006	0.615	0.023	0.009
78	0.247	0.043	0.005	0.665	0.024	0.016
79	0.108	0.019	0.005	0.841	0.014	0.013
80	0.132	0.006	0.009	0.830	0.015	0.008

Hematology
After 13 Weeks
FEMALES

Group 4 (1000 mg/kg)

	DIFF.WBC COUNT (ABS)						GENERAL
	NEUT	EOS	BASO	LYMPH	MONO	LUC	PLATELETS
	G/1	G/1	G/1	G/1	G/1	G/1	G/1
71	0.83	0.07	0.03	3.56	0.05	0.06	1221
72	0.28	0.02	0.01	1.29	0.05	0.03	1203
73	0.56	0.07	0.02	1.72	0.07	0.03	993
74	0.98	0.04	0.03	1.96	0.08	0.03	1172
75	0.83	0.06	0.01	1.14	0.04	0.01	983
76	0.36	0.16	0.02	1.75	0.04	0.02	831
77	0.69	0.09	0.01	1.38	0.05	0.02	774
78	0.60	0.10	0.01	1.61	0.06	0.04	1028
79	0.30	0.05	0.01	2.31	0.04	0.03	825
80	0.34	0.02	0.02	2.12	0.04	0.02	938

	GENERAL	COAGULATION	
	MET-HB	PT	PTT
	rel. 1	rel. 1	sec
71	0.009	0.88	26.4
72	0.010	0.77	43.2
73	0.009	0.79	36.8
74	0.009	0.88	29.2
75	0.009	0.86	32.8
76	0.010	0.80	37.4
77	0.009	0.86	44.2
78	0.009	0.82	45.9
79	0.010	0.76	33.0
80	0.009	0.92	30.5

Biochemistry

Comments

a not enough sample

Data excluded from Summary Report

Not Reported

All Measurements

Animal 81 Male Group 10 Reserve Removed
Animal 82 Female Group 10 Reserve Removed

Reported Parameter

After 13 Weeks

GLUCOSE	GLUCOSE
UREA	UREA
CREAT	CREATININE
BILI-T	BILIRUBIN, TOTAL
CHOLEST	CHOLESTEROL, TOTAL
TRIGLY	TRIGLYCERIDES
PHOS-LIP	PHOSPHOLIPIDS
ASAT	ASPARTATE AMINOTRANSFERASE (ASAT)
ALAT	ALANINE AMINOTRANSFERASE (ALAT)
LDH	LACTATE DEHYDROGENASE (LDH)
GLDH	GLUTAMATE-DEHYDROGENASE (GLDH)
ALP	ALKALINE PHOSPHATASE (ALP)
GGT	GAMMA-GLUTAMYLTRANSFERASE (GGT)
CK	CREATINE KINASE (CK)
SODIUM	SODIUM
POTASSIUM	POTASSIUM
CHLORIDE	CHLORIDE
CALCIUM	CALCIUM
PHOSPHORUS	PHOSPHORUS
PROTEIN	PROTEIN, TOTAL
ALBUMIN	ALBUMIN
GLOBULIN	GLOBULIN
A/G RATIO	A/G RATIO

Biochemistry
After 13 Weeks
MALES

Group 1 (0 mg/kg)

GENERAL							
	GLUCOSE	UREA	CREAT	BILI-T	CHOLEST	TRIGLY	PHOS-LIP
	mmol/l	mmol/l	µmol/l	µmol/l	mmol/l	mmol/l	mmol/l
1	8.41	4.96	22.3	2.10	1.60	0.45	1.39
2	6.22	6.77	33.0	1.30	1.85	0.35	1.46
3	7.40	6.74	29.7	1.90	1.78	0.27	1.48
4	6.56	5.09	24.7	1.90	1.34	1.25	1.42
5	6.99	4.95	25.8	1.80	2.25	0.47	1.82
6	5.57	5.73	29.2	1.70	1.83	0.39	1.62
7	6.62	6.23	31.3	2.30	1.75	0.38	1.42
8	6.62	3.99	27.9	2.00	1.70	0.36	1.43
9	5.28	7.41	37.3	1.80	1.08	0.39	1.07
10	5.47	4.88	30.3	2.10	1.45	0.34	1.26

GENERAL							
	ASAT	ALAT	LDH	GLDH	ALP	GGT	CK
	U/l	U/l	U/l	U/l	U/l	U/l	U/l
1	68.8	30.3	140.4	5.3	55.0	0.0	126.5
2	92.5	29.8	132.4	3.2	38.3	0.0	101.6
3	89.6	39.5	119.4	9.3	46.4	0.0	125.6
4	104.6	39.1	85.6	9.6	42.1	0.0	94.0
5	86.5	39.7	109.7	11.8	62.4	0.0	118.4
6	82.1	36.8	112.7	10.2	68.6	0.0	117.4
7	78.3	38.7	114.4	5.9	47.5	0.0	158.2
8	123.4	45.7	129.6	8.0	33.8	0.0	109.0
9	78.9	29.8	67.3	2.9	59.6	0.0	61.9
10	90.8	38.4	89.2	8.1	53.5	0.0	146.1

GENERAL							
	SODIUM	POTASSIUM	CHLORIDE	CALCIUM	PHOSPHORUS	PROTEIN	ALBUMIN
	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	g/l	g/l
1	142.5	3.81	102.8	2.67	1.85	67.65	41.43
2	142.5	3.56	103.5	2.54	1.84	66.38	38.21
3	143.1	3.41	102.1	2.67	1.58	73.90	47.03
4	143.0	3.46	102.3	2.64	1.73	73.22	40.88
5	143.1	4.06	103.5	2.76	1.69	75.03	43.10
6	143.5	3.22	102.2	2.59	1.79	69.14	42.11
7	143.5	3.64	102.5	2.69	1.50	71.65	42.42
8	144.0	3.78	103.3	2.74	1.53	74.40	43.83
9	143.4	3.30	103.6	2.54	1.62	69.69	51.95
10	145.2	3.52	104.4	2.69	1.57	72.34	44.22

Biochemistry
After 13 Weeks
MALES

Group 1 (0 mg/kg)

	GENERAL	
	GLOBULIN	A/G RATIO
	g/l	
1	26.22	1.58
2	28.17	1.36
3	26.87	1.75
4	32.34	1.26
5	31.93	1.35
6	27.03	1.56
7	29.23	1.45
8	30.57	1.43
9	17.74	2.93
10	28.12	1.57

Biochemistry
After 13 Weeks
MALES

Group 2 (100 mg/kg)

GENERAL							
	GLUCOSE	UREA	CREAT	BILI-T	CHOLEST	TRIGLY	PHOS-LIP
	mmol/l	mmol/l	µmol/l	µmol/l	mmol/l	mmol/l	mmol/l
11	5.80	6.49	35.1	1.90	1.84	0.37	1.48
12	6.02	5.87	24.9	1.60	1.07	0.20	0.99
13	5.42	4.49	26.6	1.40	2.12	0.42	1.72
14	6.25	6.06	29.8	2.10	1.51	0.29	1.40
15	6.26	5.26	27.3	1.90	1.86	0.26	1.55
16	5.27	5.72	31.6	2.50	2.01	0.36	1.50
17	6.41	6.26	34.8	1.80	1.51	0.55	1.42
18	7.16	4.87	28.3	2.00	2.86	0.67	2.25
19	6.80	5.90	27.7	2.00	1.91	0.34	1.54
20	5.80	5.63	25.6	2.10	2.04	0.28	1.58

GENERAL							
	ASAT	ALAT	LDH	GLDH	ALP	GGT	CK
	U/l	U/l	U/l	U/l	U/l	U/l	U/l
11	74.6	35.5	121.5	5.3	25.9	0.0	116.1
12	81.8	37.2	127.5	4.3	35.3	0.0	151.4
13	74.4	35.0	94.6	7.5	67.7	0.0	282.2
14	111.6	34.3	174.1	4.9	67.9	0.0	123.8
15	80.5	34.0	97.7	6.3	65.7	0.0	94.4
16	79.3	29.9	87.2	5.4	53.1	0.0	76.6
17	145.8	33.4	97.8	4.9	46.5	0.0	103.4
18	76.5	33.3	126.1	8.4	37.7	0.0	126.4
19	66.5	31.1	135.8	12.5	26.3	0.0	143.4
20	125.9	44.6	93.1	7.0	56.2	0.0	131.0

GENERAL							
	SODIUM	POTASSIUM	CHLORIDE	CALCIUM	PHOSPHORUS	PROTEIN	ALBUMIN
	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	g/l	g/l
11	144.4	3.50	103.6	2.63	1.78	69.37	48.70
12	144.2	3.57	103.3	2.66	1.79	72.96	46.43
13	144.4	3.55	104.0	2.77	1.61	73.30	42.69
14	143.7	3.70	103.1	2.78	1.86	75.16	48.14
15	144.6	3.28	103.0	2.72	1.66	74.47	45.80
16	144.2	3.78	103.3	2.81	1.98	69.74	41.17
17	145.4	3.42	104.3	2.65	1.68	68.22	42.31
18	145.1	3.83	103.9	2.75	1.62	74.32	43.62
19	145.5	3.45	104.1	2.76	1.60	73.13	45.13
20	144.9	3.65	102.6	2.86	1.76	76.68	43.96

Biochemistry
After 13 Weeks
MALES

Group 2 (100 mg/kg)

	GENERAL	
	GLOBULIN	A/G RATIO
	g/l	
11	20.67	2.36
12	26.53	1.75
13	30.61	1.39
14	27.02	1.78
15	28.67	1.60
16	28.57	1.44
17	25.91	1.63
18	30.70	1.42
19	28.00	1.61
20	32.72	1.34

Biochemistry
After 13 Weeks
MALES

Group 3 (300 mg/kg)

GENERAL							
	GLUCOSE	UREA	CREAT	BILI-T	CHOLEST	TRIGLY	PHOS-LIP
	mmol/l	mmol/l	µmol/l	µmol/l	mmol/l	mmol/l	mmol/l
21	6.31	4.95	26.7	1.90	1.94	0.41	1.54
22	5.73	6.48	27.1	1.80	1.32	0.24	1.28
23	7.04	5.32	30.4	2.10	1.79	0.27	1.36
24	6.56	5.98	29.4	2.20	1.80	0.24	1.56
25	6.59	5.04	23.9	1.70	1.23	0.47	1.24
26	6.94	4.32	29.1	2.10	1.19	0.26	1.17
27	6.82	6.83	40.1	2.00	1.70	0.31	1.45
28	5.70	4.23	26.6	1.70	1.17	0.72	1.33
29	6.04	5.69	28.5	2.20	1.68	0.29	1.46
30	6.58	4.82	31.2	2.10	1.82	0.42	1.59

GENERAL							
	ASAT	ALAT	LDH	GLDH	ALP	GGT	CK
	U/l	U/l	U/l	U/l	U/l	U/l	U/l
21	76.9	33.4	85.6	7.4	48.2	0.0	113.8
22	71.7	32.9	105.7	3.4	57.8	0.0	117.5
23	79.4	34.3	89.7	6.3	49.3	0.0	91.8
24	81.1	38.0	99.9	8.2	54.6	0.0	84.6
25	118.7	49.9	120.9	11.4	67.3	0.0	247.1
26	67.9	30.2	77.7	5.0	61.8	0.0	88.0
27	92.9	39.0	115.0	7.2	36.6	0.0	143.2
28	81.4	32.8	97.1	7.5	46.3	0.0	93.8
29	77.2	31.0	137.6	7.8	56.0	0.0	125.0
30	78.6	30.2	97.9	3.3	57.5	0.0	96.1

GENERAL							
	SODIUM	POTASSIUM	CHLORIDE	CALCIUM	PHOSPHORUS	PROTEIN	ALBUMIN
	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	g/l	g/l
21	146.2	3.50	105.1	2.72	1.70	72.39	43.11
22	143.3	3.57	102.1	2.68	1.80	72.10	42.65
23	145.0	3.87	103.9	2.76	1.82	70.54	44.31
24	146.3	3.61	104.8	2.77	1.66	74.18	44.02
25	145.3	3.58	103.8	2.75	1.75	74.78	42.72
26	145.2	3.59	103.1	2.66	1.83	74.05	44.82
27	147.2	3.30	102.9	2.70	1.79	79.66	52.66
28	146.6	3.85	106.2	2.73	1.53	71.37	44.10
29	145.4	3.57	103.5	2.71	1.75	73.38	42.78
30	147.2	3.20	104.8	2.73	1.77	76.12	55.81

Biochemistry
After 13 Weeks
MALES

Group 3 (300 mg/kg)

	GENERAL	
	GLOBULIN	A/G RATIO
	g/l	
21	29.28	1.47
22	29.45	1.45
23	26.23	1.69
24	30.16	1.46
25	32.06	1.33
26	29.23	1.53
27	27.00	1.95
28	27.27	1.62
29	30.60	1.40
30	20.31	2.75

Biochemistry
After 13 Weeks
MALES

Group 4 (1000 mg/kg)

GENERAL							
	GLUCOSE	UREA	CREAT	BILI-T	CHOLEST	TRIGLY	PHOS-LIP
	mmol/l	mmol/l	µmol/l	µmol/l	mmol/l	mmol/l	mmol/l
31	7.07	6.28	25.7	1.60	1.95	0.85	1.80
32	7.94	5.15	27.8	2.20	1.81	0.49	1.42
33	5.69	5.72	30.0	2.40	1.89	0.31	1.47
34	5.62	4.54	25.2	2.50	2.24	0.28	1.72
35	5.31	5.31	30.6	2.30	2.10	0.34	1.61
36	4.81	5.95	33.4	2.20	1.99	0.32	1.53
37	7.22	6.29	27.7	2.40	2.48	0.27	1.71
38	7.04	5.36	27.2	2.30	1.65	0.36	1.52
39	6.35	4.86	27.9	1.80	2.21	0.30	1.70
40	5.65	4.81	24.7	2.30	2.11	0.31	1.66

GENERAL							
	ASAT	ALAT	LDH	GLDH	ALP	GGT	CK
	U/l	U/l	U/l	U/l	U/l	U/l	U/l
31	73.8	40.0	89.7	4.8	51.4	0.0	103.5
32	64.4	26.9	143.7	6.0	42.9	0.0	96.8
33	82.2	31.3	82.0	5.8	44.8	0.0	88.2
34	80.8	32.7	169.3	6.4	47.7	0.0	297.8
35	75.9	42.3	118.1	5.9	72.5	0.0	137.2
36	97.0	27.5	281.5	4.3	48.6	0.0	1132.2
37	106.5	38.8	137.4	7.0	66.7	0.0	112.7
38	75.9	32.8	89.4	10.3	73.8	0.0	185.8
39	64.6	34.5	102.8	5.0	45.0	0.0	103.2
40	100.2	32.2	81.5	8.9	47.0	0.0	93.7

GENERAL							
	SODIUM	POTASSIUM	CHLORIDE	CALCIUM	PHOSPHORUS	PROTEIN	ALBUMIN
	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	g/l	g/l
31	145.3	3.54	104.9	2.68	1.65	70.20	39.75
32	146.3	3.95	105.8	2.77	1.79	69.51	51.47
33	147.2	3.60	105.1	2.78	1.72	72.87	43.02
34	147.5	3.69	104.9	2.77	1.68	74.83	44.35
35	148.1	3.57	106.0	2.76	1.70	72.63	41.34
36	145.8	3.42	102.5	2.67	1.84	73.32	43.32
37	146.6	3.71	104.0	2.69	1.76	74.43	45.01
38	146.3	3.71	105.3	2.71	1.66	72.71	44.15
39	147.2	3.89	106.7	2.81	1.61	74.33	44.35
40	147.1	3.67	104.9	2.77	1.69	76.71	35.07

Biochemistry
After 13 Weeks
MALES

Group 4 (1000 mg/kg)

	GENERAL	
	GLOBULIN	A/G RATIO
	g/l	
31	30.45	1.31
32	18.04	2.85
33	29.85	1.44
34	30.48	1.46
35	31.29	1.32
36	30.00	1.44
37	29.42	1.53
38	28.56	1.55
39	29.98	1.48
40	41.64	0.84

Biochemistry
After 13 Weeks
FEMALES

Group 1 (0 mg/kg)

GENERAL							
	GLUCOSE	UREA	CREAT	BILI-T	CHOLEST	TRIGLY	PHOS-LIP
	mmol/l	mmol/l	µmol/l	µmol/l	mmol/l	mmol/l	mmol/l
41	4.86	6.01	24.7	1.50	0.83	0.19	1.00
42	5.12	5.17	24.5	2.70	1.28	0.31	1.46
43	4.41	4.97	31.5	2.60	1.67	0.32	1.80
44	3.85	6.18	30.3	1.90	1.25	0.29	1.24
45	5.38	5.25	25.5	1.50	1.55	0.53	1.95
46	4.98	5.96	33.9	2.70	0.90	0.25	1.14
47	4.24	7.01	32.0	1.80	1.16	0.17	1.28
48	6.32	6.02	28.4	2.80	1.34	0.21	1.54
49	5.32	7.33	30.1	1.70	1.92	0.31	2.17
50	5.63	7.56	33.3	2.10	1.53	0.25	1.52

GENERAL							
	ASAT	ALAT	LDH	GLDH	ALP	GGT	CK
	U/l	U/l	U/l	U/l	U/l	U/l	U/l
41	69.4	24.6	89.2	10.2	23.8	0.0	145.8
42	65.3	28.8	100.9	12.6	23.7	0.0	79.4
43	73.3	22.7	158.3	1.7	21.2	0.0	356.7
44	71.7	32.9	150.3	6.7	18.6	0.0	129.7
45	92.8	41.5	79.3	4.8	25.4	0.0	102.5
46	78.2	32.7	90.9	8.4	22.3	0.0	153.0
47	78.8	31.2	155.1	6.1	22.8	0.0	132.3
48	97.8	35.2	124.6	5.1	19.6	0.0	84.1
49	67.2	30.7	102.0	4.1	24.7	0.0	133.3
50	86.1	38.6	108.7	7.2	24.2	0.0	87.9

GENERAL							
	SODIUM	POTASSIUM	CHLORIDE	CALCIUM	PHOSPHORUS	PROTEIN	ALBUMIN
	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	g/l	g/l
41	135.9	3.14	97.2	2.58	1.43	70.69	42.26
42	136.0	2.83	97.9	2.60	1.60	72.53	49.85
43	136.4	3.37	96.4	2.75	1.13	79.79	52.53
44	136.1	3.25	97.4	2.58	1.41	71.68	44.07
45	136.1	3.08	97.9	2.62	1.12	76.72	49.80
46	136.5	3.16	97.4	2.62	1.42	74.46	48.18
47	136.3	3.01	97.7	2.59	1.05	73.43	47.83
48	135.0	3.47	98.0	2.66	0.61	78.25	50.93
49	135.2	3.09	97.4	2.60	0.64	74.04	49.07
50	137.1	3.25	97.5	2.59	0.84	71.44	46.97

Biochemistry
After 13 Weeks
FEMALES

Group 1 (0 mg/kg)

	GENERAL	
	GLOBULIN	A/G RATIO
	g/l	
41	28.43	1.49
42	22.68	2.20
43	27.26	1.93
44	27.61	1.60
45	26.92	1.85
46	26.28	1.83
47	25.60	1.87
48	27.32	1.86
49	24.97	1.97
50	24.47	1.92

Biochemistry
After 13 Weeks
FEMALES

Group 2 (100 mg/kg)

GENERAL							
	GLUCOSE	UREA	CREAT	BILI-T	CHOLEST	TRIGLY	PHOS-LIP
	mmol/l	mmol/l	µmol/l	µmol/l	mmol/l	mmol/l	mmol/l
51	4.81	7.13	27.6	1.60	1.55	0.22	1.66
52	4.94	7.15	29.3	2.40	1.54	0.21	1.68
53	3.57	7.62	27.7	2.10	1.09	0.16	1.23
54	5.94	8.34	33.8	2.20	1.80	0.30	1.91
55	4.94	7.60	36.5	1.60	1.77	0.29	1.81
56	4.68	6.47	31.3	2.50	1.82	0.18	1.81
57	4.15	7.41	35.4	2.20	2.17	0.47	2.30
58	5.04	6.62	35.7	2.20	1.17	0.26	1.39
59	5.07	6.68	26.7	2.30	2.15	0.31	2.19
60	5.49	7.90	31.0	2.50	1.36	0.24	1.55

GENERAL							
	ASAT	ALAT	LDH	GLDH	ALP	GGT	CK
	U/l	U/l	U/l	U/l	U/l	U/l	U/l
51	60.0	25.5	184.5	2.6	21.5	0.0	202.4
52	71.6	32.0	119.0	11.3	20.8	0.0	114.5
53	63.8	24.8	137.9	--- a	19.0	0.0	122.0
54	62.2	29.8	99.8	8.6	14.5	0.0	106.1
55	119.0	37.6	81.3	6.7	64.2	0.0	127.5
56	94.6	25.3	80.2	2.6	34.0	0.0	82.6
57	107.1	36.4	128.5	12.9	23.4	0.0	125.5
58	84.7	42.0	95.1	16.9	19.7	0.0	79.4
59	102.8	35.5	65.0	3.1	16.4	0.0	81.5
60	66.7	34.7	115.2	6.2	19.5	0.0	125.8

GENERAL							
	SODIUM	POTASSIUM	CHLORIDE	CALCIUM	PHOSPHORUS	PROTEIN	ALBUMIN
	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	g/l	g/l
51	137.3	3.24	99.8	2.65	1.21	74.27	48.12
52	138.2	2.46	97.9	2.73	1.47	77.88	52.96
53	136.8	3.25	96.3	2.72	1.42	78.82	51.98
54	139.6	2.88	100.2	2.84	1.12	80.94	55.62
55	136.1	3.13	96.3	2.69	1.13	74.66	49.00
56	137.0	3.07	96.7	2.66	1.30	76.83	50.24
57	136.3	3.56	97.4	2.74	1.28	76.51	50.20
58	135.2	3.21	95.0	2.70	1.40	75.34	48.61
59	135.8	3.28	96.0	2.81	1.54	76.73	50.77
60	135.7	3.46	98.0	2.67	1.10	72.22	48.92

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Biochemistry
After 13 Weeks
FEMALES

Group 2 (100 mg/kg)

	GENERAL	
	GLOBULIN	A/G RATIO
	g/l	
51	26.15	1.84
52	24.92	2.13
53	26.84	1.94
54	25.32	2.20
55	25.66	1.91
56	26.59	1.89
57	26.31	1.91
58	26.73	1.82
59	25.96	1.96
60	23.30	2.10

Biochemistry
After 13 Weeks
FEMALES

Group 3 (300 mg/kg)

GENERAL							
	GLUCOSE	UREA	CREAT	BILI-T	CHOLEST	TRIGLY	PHOS-LIP
	mmol/l	mmol/l	µmol/l	µmol/l	mmol/l	mmol/l	mmol/l
61	5.64	8.85	38.0	2.50	1.32	0.36	1.58
62	3.91	7.02	26.5	2.40	0.95	0.18	1.12
63	5.20	6.01	33.1	2.60	2.29	0.23	2.20
64	5.84	7.18	33.6	2.20	1.13	0.20	1.34
65	5.01	7.91	29.7	1.50	1.56	0.26	1.68
66	4.51	7.39	30.8	2.30	2.41	0.22	2.59
67	6.41	8.46	31.6	1.90	2.51	0.23	2.51
68	4.04	6.18	34.6	2.20	2.12	0.30	2.06
69	5.52	5.75	26.8	2.00	1.13	0.24	1.46
70	6.36	7.23	34.7	2.60	1.26	0.19	1.54

GENERAL							
	ASAT	ALAT	LDH	GLDH	ALP	GGT	CK
	U/l	U/l	U/l	U/l	U/l	U/l	U/l
61	126.1	30.8	412.0	6.9	27.8	0.0	1454.3
62	76.3	30.2	147.0	4.1	31.1	0.0	150.9
63	67.4	25.3	92.4	5.8	26.0	0.0	107.3
64	70.2	30.3	108.5	4.9	27.5	0.0	92.4
65	64.2	30.9	68.1	1.8	20.1	0.0	113.5
66	78.0	23.6	101.6	5.0	17.8	0.0	162.0
67	63.6	28.0	72.2	5.1	18.1	0.0	71.1
68	81.0	32.0	154.0	5.4	25.0	0.0	152.3
69	66.9	32.3	124.1	3.2	28.4	0.0	96.8
70	74.8	24.0	114.2	5.7	28.2	0.0	105.9

GENERAL							
	SODIUM	POTASSIUM	CHLORIDE	CALCIUM	PHOSPHORUS	PROTEIN	ALBUMIN
	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	g/l	g/l
61	136.3	3.53	98.1	2.61	1.33	74.49	49.08
62	137.8	2.95	99.2	2.67	1.71	68.91	46.19
63	136.9	3.06	98.4	2.74	1.26	77.84	52.41
64	136.7	2.89	96.8	2.71	1.18	77.26	51.00
65	136.0	3.51	98.3	2.62	1.34	68.66	45.73
66	137.2	2.79	97.1	2.66	1.17	77.19	47.05
67	135.6	2.94	98.2	2.68	1.05	83.03	55.85
68	139.4	3.10	100.8	2.70	1.11	76.30	50.05
69	135.2	2.76	96.0	2.61	0.88	80.24	53.39
70	137.0	3.07	98.3	2.59	0.75	77.26	51.91

Biochemistry
After 13 Weeks
FEMALES

Group 3 (300 mg/kg)

	GENERAL	
	GLOBULIN	A/G RATIO
	g/l	
61	25.41	1.93
62	22.72	2.03
63	25.43	2.06
64	26.26	1.94
65	22.93	1.99
66	30.14	1.56
67	27.18	2.05
68	26.25	1.91
69	26.85	1.99
70	25.35	2.05

Biochemistry
After 13 Weeks
FEMALES

Group 4 (1000 mg/kg)

GENERAL							
	GLUCOSE	UREA	CREAT	BILI-T	CHOLEST	TRIGLY	PHOS-LIP
	mmol/l	mmol/l	µmol/l	µmol/l	mmol/l	mmol/l	mmol/l
71	4.06	7.41	32.8	2.50	2.20	0.34	1.92
72	5.59	6.89	35.2	2.80	1.15	0.29	1.51
73	5.45	6.87	28.9	3.30	1.11	0.29	1.44
74	4.43	6.10	29.9	3.30	1.59	0.20	1.68
75	6.30	5.74	30.4	2.90	1.55	0.20	1.75
76	5.04	10.98	51.7	2.90	1.53	0.20	1.60
77	3.97	7.08	32.7	2.50	1.58	0.34	1.67
78	4.62	8.51	33.6	3.50	1.37	0.24	1.48
79	4.85	8.08	32.3	3.10	1.31	0.31	1.56
80	5.04	8.59	35.6	2.60	1.48	0.32	1.69

GENERAL							
	ASAT	ALAT	LDH	GLDH	ALP	GGT	CK
	U/l	U/l	U/l	U/l	U/l	U/l	U/l
71	68.2	32.1	100.5	8.0	15.8	0.0	115.6
72	70.2	21.1	93.2	3.9	23.8	0.0	70.6
73	60.4	29.1	144.7	6.6	25.0	0.0	98.5
74	82.4	40.7	114.8	33.2	22.4	0.0	92.4
75	82.9	25.3	132.6	5.2	26.6	0.0	230.8
76	74.8	24.6	144.7	9.7	24.3	0.0	113.1
77	65.4	22.5	144.3	3.2	21.4	0.0	131.8
78	96.1	40.8	156.7	19.6	22.9	0.0	134.8
79	75.2	32.1	107.9	---	19.4	0.0	142.5
80	63.2	26.5	102.7	3.8	20.7	0.0	116.7

GENERAL							
	SODIUM	POTASSIUM	CHLORIDE	CALCIUM	PHOSPHORUS	PROTEIN	ALBUMIN
	mmol/l	mmol/l	mmol/l	mmol/l	mmol/l	g/l	g/l
71	137.5	3.43	98.2	2.75	1.30	78.43	50.10
72	136.5	2.79	99.5	2.51	1.26	63.39	42.91
73	137.2	2.71	97.9	2.53	1.10	76.25	49.21
74	140.1	3.08	98.3	2.84	1.43	80.49	53.07
75	138.5	2.45	98.2	2.58	1.01	74.15	50.10
76	141.2	3.30	104.3	2.66	1.00	74.37	48.64
77	137.2	3.00	98.3	2.65	1.20	73.19	48.26
78	138.4	3.03	99.7	2.70	1.17	73.99	50.64
79	137.6	3.17	98.9	2.65	1.28	73.09	47.54
80	141.6	3.14	102.9	2.77	1.05	79.09	53.22

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Biochemistry
After 13 Weeks
FEMALES

Group 4 (1000 mg/kg)

	GENERAL	
	GLOBULIN	A/G RATIO
	g/l	
71	28.33	1.77
72	20.48	2.10
73	27.04	1.82
74	27.42	1.94
75	24.05	2.08
76	25.73	1.89
77	24.93	1.94
78	23.35	2.17
79	25.55	1.86
80	25.87	2.06

Urinalysis

Comments

Data excluded from Summary Report

Not Reported

All Measurements

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

Reported Parameter

After 13 Weeks

VOLUME/18h	VOLUME/18h
REL DENS	RELATIVE DENSITY
COLOR	COLOR
APPEARANCE	APPEARANCE
pH	pH
NITRITE	NITRITE
PROTEIN	PROTEIN
GLUCOSE	GLUCOSE
KETONES	KETONES
UROBILI	UROBILINOGEN
BILIRUBIN	BILIRUBIN
ERY	ERYTHROCYTES
LEU	LEUCOCYTES

Urinalysis
After 13 Weeks
MALES

Group 1 (0 mg/kg)

GENERAL							
	VOLUME/18h ml	REL DENS rel. 1	COLOR	APPEARANCE	pH	NITRITE SCORE 0/1	PROTEIN g/l
1	6.4	1.045	yellow	clear	6.5	0	0.25
2	13.2	1.022	light yel	clear	7.0	0	0.25
3	3.8	1.051	yellow	clear	6.5	1	0.25
4	6.6	1.041	yellow	clear	7.0	1	0.25
5	2.7	1.075	yellow	clear	7.0	1	0.75
6	5.1	1.055	yellow	clear	6.5	0	0.25
7	4.4	1.048	yellow	clear	6.5	1	0.75
8	18.9	1.017	light yel	clear	7.0	0	0.25
9	4.1	1.055	yellow	clear	6.0	1	0.75
10	3.9	1.046	yellow	clear	7.0	1	0.75

GENERAL						
	GLUCOSE mmol/l	KETONES mmol/l	UROBILI µmol/l	BILIRUBIN µmol/l	ERY per µl	LEU per µl
1	0	1.5	0	0	25	25
2	0	0.0	0	0	10	25
3	0	0.5	0	0	25	100
4	0	1.5	0	0	25	25
5	0	1.5	0	17	10	100
6	0	1.5	0	0	10	25
7	0	1.5	0	0	10	25
8	0	0.5	0	0	10	0
9	0	0.5	0	0	10	25
10	0	0.5	0	0	25	25

Urinalysis
After 13 Weeks
MALES

Group 2 (100 mg/kg)

GENERAL							
	VOLUME/18h ml	REL DENS rel. 1	COLOR	APPEARANCE	pH	NITRITE SCORE 0/1	PROTEIN g/l
11	6.0	1.044	yellow	clear	7.0	1	0.25
12	7.5	1.036	yellow	clear	7.0	1	0.25
13	4.1	1.048	yellow	clear	7.0	0	0.25
14	5.8	1.045	yellow	clear	6.0	1	0.75
15	6.7	1.043	yellow	clear	6.5	0	0.25
16	4.7	1.055	yellow	clear	7.0	1	0.25
17	7.4	1.035	yellow	clear	7.0	1	0.25
18	6.0	1.035	yellow	clear	8.0	1	0.25
19	6.9	1.033	yellow	clear	7.0	1	0.25
20	7.3	1.041	yellow	clear	6.5	0	0.25

GENERAL						
	GLUCOSE mmol/l	KETONES mmol/l	UROBILI µmol/l	BILIRUBIN µmol/l	ERY per µl	LEU per µl
11	0	1.5	0	0	25	25
12	0	0.5	0	0	25	25
13	0	1.5	0	0	10	25
14	0	1.5	0	0	25	25
15	0	0.5	0	0	25	25
16	0	1.5	0	0	10	25
17	0	0.5	0	0	10	25
18	0	1.5	0	0	25	25
19	0	1.5	0	0	25	25
20	0	5.0	0	0	10	25

Urinalysis
After 13 Weeks
MALES

Group 3 (300 mg/kg)

GENERAL							
	VOLUME/18h ml	REL DENS rel. 1	COLOR	APPEARANCE	pH	NITRITE SCORE 0/1	PROTEIN g/l
21	9.3	1.029	yellow	clear	6.5	0	0.25
22	5.0	1.044	yellow	clear	7.0	1	0.25
23	5.2	1.050	yellow	clear	6.5	1	0.25
24	23.8	1.012	light yel	clear	7.0	0	0.00
25	5.3	1.047	yellow	clear	6.5	1	0.25
26	10.7	1.025	yellow	clear	7.0	0	0.25
27	1.9	1.100	yellow	clear	6.5	1	0.75
28	6.2	1.033	yellow	clear	7.0	0	0.25
29	4.7	1.048	yellow	clear	7.0	1	0.75
30	6.9	1.041	yellow	clear	6.5	0	0.25

GENERAL						
	GLUCOSE mmol/l	KETONES mmol/l	UROBILI µmol/l	BILIRUBIN µmol/l	ERY per µl	LEU per µl
21	0	0.0	0	0	10	25
22	0	0.5	0	0	10	25
23	0	0.5	0	0	25	25
24	0	0.0	0	0	0	0
25	0	0.5	0	0	10	25
26	0	0.5	0	0	10	25
27	0	5.0	0	0	10	25
28	0	0.5	0	0	10	25
29	0	1.5	0	17	10	25
30	0	0.5	0	0	25	25

Urinalysis
After 13 Weeks
MALES

Group 4 (1000 mg/kg)

GENERAL							
	VOLUME/18h ml	REL DENS rel. 1	COLOR	APPEARANCE	pH	NITRITE SCORE 0/1	PROTEIN g/l
31	5.0	1.058	yellow	clear	6.5	0	0.25
32	3.7	1.053	yellow	clear	7.0	1	0.75
33	4.4	1.057	yellow	clear	7.0	1	0.75
34	5.2	1.049	yellow	clear	6.5	0	0.25
35	23.3	1.014	light yel	clear	7.0	0	0.00
36	13.7	1.023	yellow	clear	7.0	0	0.25
37	5.3	1.055	yellow	clear	6.0	1	0.75
38	13.1	1.022	yellow	clear	7.0	0	0.25
39	13.0	1.024	yellow	clear	7.0	0	0.25
40	7.2	1.038	yellow	clear	6.5	0	0.25

GENERAL						
	GLUCOSE mmol/l	KETONES mmol/l	UROBILI µmol/l	BILIRUBIN µmol/l	ERY per µl	LEU per µl
31	0	1.5	0	17	25	25
32	0	1.5	0	0	10	25
33	0	1.5	0	17	10	25
34	0	1.5	0	17	10	25
35	0	0.0	0	0	10	0
36	0	0.5	0	0	10	25
37	0	1.5	0	0	10	25
38	0	0.5	0	0	0	25
39	0	0.5	0	0	10	25
40	0	0.5	0	0	10	25

Urinalysis
After 13 Weeks
FEMALES

Group 1 (0 mg/kg)

GENERAL							
	VOLUME/18h ml	REL DENS rel. 1	COLOR	APPEARANCE	pH	NITRITE SCORE 0/1	PROTEIN g/l
41	6.3	1.037	yellow	clear	6.0	0	0.25
42	20.2	1.013	yellow	clear	6.0	0	0.00
43	8.3	1.024	yellow	clear	6.0	0	0.25
44	4.7	1.039	yellow	clear	5.0	0	0.25
45	7.0	1.036	yellow	clear	6.0	0	0.25
46	3.7	1.055	yellow	clear	6.0	1	0.25
47	6.7	1.040	yellow	clear	5.0	1	0.25
48	5.5	1.042	yellow	clear	6.0	1	0.25
49	7.1	1.034	yellow	clear	6.0	0	0.25
50	5.6	1.034	yellow	clear	6.5	1	0.25

GENERAL						
	GLUCOSE mmol/l	KETONES mmol/l	UROBILI µmol/l	BILIRUBIN µmol/l	ERY per µl	LEU per µl
41	0	0.0	0	0	10	0
42	0	0.0	0	0	0	0
43	0	0.0	0	0	10	0
44	0	0.0	0	0	0	0
45	0	0.5	0	0	0	25
46	0	0.0	0	0	0	0
47	0	0.0	0	0	0	0
48	0	0.0	0	0	0	0
49	0	0.5	0	0	0	0
50	0	0.0	0	0	10	0

Urinalysis
After 13 Weeks
FEMALES

Group 2 (100 mg/kg)

GENERAL							
	VOLUME/18h ml	REL DENS rel. 1	COLOR	APPEARANCE	pH	NITRITE SCORE 0/1	PROTEIN g/l
51	5.3	1.038	yellow	clear	6.0	0	0.00
52	5.0	1.037	yellow	clear	6.0	1	0.25
53	6.0	1.030	yellow	cloudy	6.0	0	0.00
54	2.9	1.063	yellow	clear	5.0	1	0.75
55	9.3	1.027	yellow	clear	5.0	0	0.00
56	2.5	1.060	yellow	clear	6.0	1	0.25
57	7.1	1.039	yellow	clear	6.0	0	0.25
58	21.3	1.013	light yel	clear	6.0	0	0.25
59	4.3	1.060	yellow	clear	5.0	1	0.25
60	6.6	1.039	yellow	clear	6.0	1	0.25

GENERAL						
	GLUCOSE mmol/l	KETONES mmol/l	UROBILI µmol/l	BILIRUBIN µmol/l	ERY per µl	LEU per µl
51	0	0.0	0	0	0	0
52	0	0.0	0	0	10	0
53	0	0.0	0	0	0	0
54	0	0.5	0	17	0	25
55	0	0.0	0	0	0	0
56	0	0.0	0	0	0	0
57	0	0.5	0	0	0	0
58	0	0.0	0	0	0	0
59	0	0.5	0	17	0	25
60	0	0.0	0	0	0	0

Urinalysis
After 13 Weeks
FEMALES

Group 3 (300 mg/kg)

GENERAL							
	VOLUME/18h ml	REL DENS rel. 1	COLOR	APPEARANCE	pH	NITRITE SCORE 0/1	PROTEIN g/l
61	5.2	1.039	yellow	clear	6.0	1	0.25
62	4.0	1.043	yellow	clear	5.0	1	0.25
63	4.9	1.043	yellow	clear	6.0	1	0.25
64	8.8	1.025	yellow	clear	6.0	0	0.00
65	4.7	1.044	yellow	clear	6.0	1	0.25
66	9.5	1.031	yellow	clear	6.0	0	0.00
67	6.3	1.040	yellow	clear	5.0	0	0.25
68	14.3	1.021	yellow	clear	6.5	0	0.00
69	9.2	1.026	yellow	clear	6.0	1	0.00
70	6.4	1.032	yellow	clear	6.0	0	0.00

GENERAL						
	GLUCOSE mmol/l	KETONES mmol/l	UROBILI µmol/l	BILIRUBIN µmol/l	ERY per µl	LEU per µl
61	0	0.5	0	0	0	0
62	0	0.5	0	0	0	0
63	0	0.0	0	0	0	0
64	0	0.0	0	0	0	0
65	0	0.0	0	0	0	0
66	0	0.0	0	0	0	0
67	0	0.5	0	0	0	25
68	0	0.0	0	0	0	0
69	0	0.0	0	0	0	0
70	0	0.0	0	0	0	0

Urinalysis
After 13 Weeks
FEMALES

Group 4 (1000 mg/kg)

GENERAL							
	VOLUME/18h ml	REL DENS rel. 1	COLOR	APPEARANCE	pH	NITRITE SCORE 0/1	PROTEIN g/l
71	4.1	1.056	yellow	clear	5.0	1	0.25
72	3.3	1.043	yellow	clear	5.0	0	0.25
73	5.6	1.038	yellow	clear	6.0	0	0.25
74	9.6	1.019	yellow	clear	6.0	0	0.00
75	7.9	1.034	yellow	clear	6.0	0	0.25
76	2.5	1.070	yellow	clear	5.0	1	0.25
77	8.2	1.026	yellow	clear	6.0	1	0.25
78	2.5	1.063	yellow	clear	6.0	1	0.25
79	3.7	1.064	yellow	clear	5.0	0	0.25
80	4.6	1.038	yellow	clear	6.0	1	0.25

GENERAL						
	GLUCOSE mmol/l	KETONES mmol/l	UROBILI µmol/l	BILIRUBIN µmol/l	ERY per µl	LEU per µl
71	0	0.5	0	17	0	0
72	0	0.5	0	17	0	0
73	0	0.5	0	0	0	0
74	0	0.0	0	0	0	0
75	0	0.0	0	0	0	0
76	0	0.5	0	17	0	0
77	0	0.0	0	0	10	0
78	0	0.5	0	17	0	0
79	0	0.5	0	17	0	0
80	0	0.0	0	0	0	0

ORGAN WEIGHTS (GRAM)

Comments

Exclusions

Not Reported

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

Selection of Organs

All organs reported

Animals without scheduled necropsy

**ORGAN WEIGHTS (GRAM)
AFTER WEEK 13 OF TREATMENT
MALES**

Group 1 (0 mg/kg)

Animal	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS
1	445.3	2.09	1.11	10.37	0.309	2.44
2	450.5	2.20	1.46	9.91	0.330	2.10
3	435.7	2.14	1.17	10.49	0.271	2.05
4	447.8	2.14	1.27	11.18	0.316	2.65
5	431.1	2.01	1.05	11.39	0.213	2.32
6	445.2	2.16	1.19	11.69	0.340	2.29
7	442.5	2.08	1.16	13.55	0.257	2.58
8	433.7	2.15	1.03	12.27	0.372	2.42
9	409.9	2.03	1.10	10.28	0.159	1.99
10	418.8	2.11	1.00	11.09	0.402	2.09

Animal	ADRENALS	SPLEEN	TESTES	EPIDIDYMIC
1	0.069	0.85	3.95	1.617
2	0.054	0.63	3.27	1.339
3	0.057	0.64	3.67	1.389
4	0.065	0.66	4.07	1.853
5	0.057	0.77	4.12	1.513
6	0.046	0.90	4.26	1.692
7	0.069	0.89	4.07	1.732
8	0.059	0.70	3.65	1.530
9	0.063	0.65	3.92	1.439
10	0.064	0.62	3.50	1.412

**ORGAN WEIGHTS (GRAM)
AFTER WEEK 13 OF TREATMENT
MALES**

Group 2 (100 mg/kg)

Animal	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS
11	422.9	2.12	1.06	10.03	0.272	1.98
12	418.7	2.05	1.12	9.60	0.242	2.36
13	406.5	1.97	0.96	10.45	0.247	1.97
14	448.6	2.11	1.03	10.85	0.320	2.29
15	435.2	2.10	1.03	9.62	0.247	2.21
16	485.7	2.12	1.14	11.31	0.313	2.37
17	419.3	2.02	1.62	9.83	0.259	1.82
18	512.4	2.08	1.17	15.22	0.264	2.45
19	475.2	2.13	1.11	12.53	0.273	2.15
20	447.0	2.13	1.08	11.14	0.237	2.24

Animal	ADRENALS	SPLEEN	TESTES	EPIDIDYMIC
11	0.059	0.75	3.95	1.640
12	0.072	0.63	3.97	1.445
13	0.058	0.67	3.36	1.378
14	0.059	0.72	3.83	1.315
15	0.057	0.61	3.68	1.330
16	0.063	0.72	4.00	1.502
17	0.056	0.71	3.90	1.372
18	0.056	0.74	4.39	1.731
19	0.065	0.73	4.12	1.584
20	0.055	0.60	3.85	1.570

**ORGAN WEIGHTS (GRAM)
AFTER WEEK 13 OF TREATMENT
MALES**

Group 3 (300 mg/kg)

Animal	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS
21	463.0	2.23	1.30	11.55	0.492	2.03
22	386.6	2.05	1.16	9.87	0.212	2.36
23	453.0	2.22	1.04	11.15	0.434	2.19
24	352.0	2.02	0.89	8.55	0.266	1.68
25	408.5	2.18	1.02	10.25	0.308	2.41
26	443.8	2.09	1.08	10.09	0.257	2.03
27	395.0	1.94	0.99	10.70	0.241	2.01
28	437.3	2.06	1.07	11.37	0.263	2.07
29	408.4	2.17	1.02	10.72	0.306	2.02
30	504.4	2.21	1.18	13.29	0.231	2.19

Animal	ADRENALS	SPLEEN	TESTES	EPIDIDYDYMID
21	0.068	0.81	4.14	1.337
22	0.059	0.65	3.94	1.445
23	0.069	0.85	3.77	1.432
24	0.047	0.60	3.54	1.301
25	0.068	0.64	3.61	1.504
26	0.051	0.62	4.15	1.649
27	0.062	0.56	3.79	1.517
28	0.052	0.89	3.21	1.402
29	0.069	0.76	3.77	1.475
30	0.079	0.83	4.28	1.602

**ORGAN WEIGHTS (GRAM)
AFTER WEEK 13 OF TREATMENT
MALES**

Group 4 (1000 mg/kg)

Animal	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS
31	441.7	2.07	0.92	11.00	0.350	2.16
32	483.2	2.15	1.15	10.89	0.344	2.39
33	450.2	2.11	1.13	9.80	0.277	2.21
34	433.7	2.20	0.97	9.99	0.377	1.87
35	372.7	2.09	0.90	9.24	0.405	1.94
36	410.0	1.98	1.01	10.58	0.263	2.09
37	430.3	1.99	1.02	11.64	0.224	2.27
38	410.2	2.08	0.94	10.25	0.259	1.98
39	424.1	2.16	1.00	11.62	0.423	2.09
40	435.2	2.00	0.97	10.84	0.330	2.00

Animal	ADRENALS	SPLEEN	TESTES	EPIDIDYMIC
31	0.054	0.58	3.02	1.399
32	0.071	0.94	3.82	1.494
33	0.054	0.67	3.79	1.368
34	0.063	0.64	4.14	1.486
35	0.051	0.81	3.15	1.321
36	0.070	0.57	3.70	1.555
37	0.072	0.71	3.82	1.485
38	0.066	0.66	3.25	1.323
39	0.063	0.82	3.81	1.414
40	0.051	0.56	3.64	1.361

ORGAN/BODY WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
MALES

Group 1 (0 mg/kg)

Animal	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
1	445.3	0.47	0.25	2.33	0.069	0.55
2	450.5	0.49	0.32	2.20	0.073	0.47
3	435.7	0.49	0.27	2.41	0.062	0.47
4	447.8	0.48	0.28	2.50	0.071	0.59
5	431.1	0.47	0.24	2.64	0.049	0.54
6	445.2	0.49	0.27	2.63	0.076	0.51
7	442.5	0.47	0.26	3.06	0.058	0.58
8	433.7	0.50	0.24	2.83	0.086	0.56
9	409.9	0.50	0.27	2.51	0.039	0.49
10	418.8	0.50	0.24	2.65	0.096	0.50

Animal	ADRENALS (%)	SPLEEN (%)	TESTES (%)	EPIDIDYDYMID (%)
1	0.015	0.19	0.89	0.363
2	0.012	0.14	0.73	0.297
3	0.013	0.15	0.84	0.319
4	0.015	0.15	0.91	0.414
5	0.013	0.18	0.96	0.351
6	0.010	0.20	0.96	0.380
7	0.016	0.20	0.92	0.391
8	0.014	0.16	0.84	0.353
9	0.015	0.16	0.96	0.351
10	0.015	0.15	0.84	0.337

ORGAN/BODY WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
MALES

Group 2 (100 mg/kg)

Animal	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
11	422.9	0.50	0.25	2.37	0.064	0.47
12	418.7	0.49	0.27	2.29	0.058	0.56
13	406.5	0.48	0.24	2.57	0.061	0.48
14	448.6	0.47	0.23	2.42	0.071	0.51
15	435.2	0.48	0.24	2.21	0.057	0.51
16	485.7	0.44	0.23	2.33	0.064	0.49
17	419.3	0.48	0.39	2.34	0.062	0.43
18	512.4	0.41	0.23	2.97	0.052	0.48
19	475.2	0.45	0.23	2.64	0.057	0.45
20	447.0	0.48	0.24	2.49	0.053	0.50

Animal	ADRENALS (%)	SPLEEN (%)	TESTES (%)	EPIDIDYDYMID (%)
11	0.014	0.18	0.93	0.388
12	0.017	0.15	0.95	0.345
13	0.014	0.16	0.83	0.339
14	0.013	0.16	0.85	0.293
15	0.013	0.14	0.85	0.306
16	0.013	0.15	0.82	0.309
17	0.013	0.17	0.93	0.327
18	0.011	0.14	0.86	0.338
19	0.014	0.15	0.87	0.333
20	0.012	0.13	0.86	0.351

ORGAN/BODY WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
MALES

Group 3 (300 mg/kg)

Animal	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
21	463.0	0.48	0.28	2.49	0.106	0.44
22	386.6	0.53	0.30	2.55	0.055	0.61
23	453.0	0.49	0.23	2.46	0.096	0.48
24	352.0	0.57	0.25	2.43	0.076	0.48
25	408.5	0.53	0.25	2.51	0.075	0.59
26	443.8	0.47	0.24	2.27	0.058	0.46
27	395.0	0.49	0.25	2.71	0.061	0.51
28	437.3	0.47	0.24	2.60	0.060	0.47
29	408.4	0.53	0.25	2.62	0.075	0.49
30	504.4	0.44	0.23	2.63	0.046	0.43

Animal	ADRENALS (%)	SPLEEN (%)	TESTES (%)	EPIDIDYDYMID (%)
21	0.015	0.17	0.89	0.289
22	0.015	0.17	1.02	0.374
23	0.015	0.19	0.83	0.316
24	0.013	0.17	1.01	0.370
25	0.017	0.16	0.88	0.368
26	0.011	0.14	0.94	0.372
27	0.016	0.14	0.96	0.384
28	0.012	0.20	0.73	0.321
29	0.017	0.19	0.92	0.361
30	0.016	0.16	0.85	0.318

ORGAN/BODY WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
MALES

Group 4 (1000 mg/kg)

Animal	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
31	441.7	0.47	0.21	2.49	0.079	0.49
32	483.2	0.44	0.24	2.25	0.071	0.49
33	450.2	0.47	0.25	2.18	0.062	0.49
34	433.7	0.51	0.22	2.30	0.087	0.43
35	372.7	0.56	0.24	2.48	0.109	0.52
36	410.0	0.48	0.25	2.58	0.064	0.51
37	430.3	0.46	0.24	2.71	0.052	0.53
38	410.2	0.51	0.23	2.50	0.063	0.48
39	424.1	0.51	0.24	2.74	0.100	0.49
40	435.2	0.46	0.22	2.49	0.076	0.46

Animal	ADRENALS (%)	SPLEEN (%)	TESTES (%)	EPIDIDYDYMID (%)
31	0.012	0.13	0.68	0.317
32	0.015	0.19	0.79	0.309
33	0.012	0.15	0.84	0.304
34	0.015	0.15	0.95	0.343
35	0.014	0.22	0.85	0.354
36	0.017	0.14	0.90	0.379
37	0.017	0.17	0.89	0.345
38	0.016	0.16	0.79	0.323
39	0.015	0.19	0.90	0.333
40	0.012	0.13	0.84	0.313

ORGAN/BRAIN WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
MALES

Group 1 (0 mg/kg)

Animal	BRAIN (GRAM)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
1	2.09	53.11	496.17	14.785	116.75
2	2.20	66.36	450.45	15.000	95.45
3	2.14	54.67	490.19	12.664	95.79
4	2.14	59.35	522.43	14.766	123.83
5	2.01	52.24	566.67	10.597	115.42
6	2.16	55.09	541.20	15.741	106.02
7	2.08	55.77	651.44	12.356	124.04
8	2.15	47.91	570.70	17.302	112.56
9	2.03	54.19	506.40	7.833	98.03
10	2.11	47.39	525.59	19.052	99.05

Animal	ADRENALS (%)	SPLEEN (%)	TESTES (%)	EPIDIDYMIUM (%)
1	3.301	40.67	189.00	77.368
2	2.455	28.64	148.64	60.864
3	2.664	29.91	171.50	64.907
4	3.037	30.84	190.19	86.589
5	2.836	38.31	204.98	75.274
6	2.130	41.67	197.22	78.333
7	3.317	42.79	195.67	83.269
8	2.744	32.56	169.77	71.163
9	3.103	32.02	193.10	70.887
10	3.033	29.38	165.88	66.919

ORGAN/BRAIN WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
MALES

Group 2 (100 mg/kg)

Animal	BRAIN (GRAM)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
11	2.12	50.00	473.11	12.830	93.40
12	2.05	54.63	468.29	11.805	115.12
13	1.97	48.73	530.46	12.538	100.00
14	2.11	48.82	514.22	15.166	108.53
15	2.10	49.05	458.10	11.762	105.24
16	2.12	53.77	533.49	14.764	111.79
17	2.02	80.20	486.63	12.822	90.10
18	2.08	56.25	731.73	12.692	117.79
19	2.13	52.11	588.26	12.817	100.94
20	2.13	50.70	523.00	11.127	105.16

Animal	ADRENALS (%)	SPLEEN (%)	TESTES (%)	EPIDIDYMI (%)
11	2.783	35.38	186.32	77.358
12	3.512	30.73	193.66	70.488
13	2.944	34.01	170.56	69.949
14	2.796	34.12	181.52	62.322
15	2.714	29.05	175.24	63.333
16	2.972	33.96	188.68	70.849
17	2.772	35.15	193.07	67.921
18	2.692	35.58	211.06	83.221
19	3.052	34.27	193.43	74.366
20	2.582	28.17	180.75	73.709

ORGAN/BRAIN WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
MALES

Group 3 (300 mg/kg)

Animal	BRAIN (GRAM)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
21	2.23	58.30	517.94	22.063	91.03
22	2.05	56.59	481.46	10.341	115.12
23	2.22	46.85	502.25	19.550	98.65
24	2.02	44.06	423.27	13.168	83.17
25	2.18	46.79	470.18	14.128	110.55
26	2.09	51.67	482.78	12.297	97.13
27	1.94	51.03	551.55	12.423	103.61
28	2.06	51.94	551.94	12.767	100.49
29	2.17	47.00	494.01	14.101	93.09
30	2.21	53.39	601.36	10.452	99.10

Animal	ADRENALS (%)	SPLEEN (%)	TESTES (%)	EPIDIDYMI (%)
21	3.049	36.32	185.65	59.955
22	2.878	31.71	192.20	70.488
23	3.108	38.29	169.82	64.505
24	2.327	29.70	175.25	64.406
25	3.119	29.36	165.60	68.991
26	2.440	29.67	198.56	78.900
27	3.196	28.87	195.36	78.196
28	2.524	43.20	155.83	68.058
29	3.180	35.02	173.73	67.972
30	3.575	37.56	193.67	72.489

ORGAN/BRAIN WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
MALES

Group 4 (1000 mg/kg)

Animal	BRAIN (GRAM)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
31	2.07	44.44	531.40	16.908	104.35
32	2.15	53.49	506.51	16.000	111.16
33	2.11	53.55	464.45	13.128	104.74
34	2.20	44.09	454.09	17.136	85.00
35	2.09	43.06	442.11	19.378	92.82
36	1.98	51.01	534.34	13.283	105.56
37	1.99	51.26	584.92	11.256	114.07
38	2.08	45.19	492.79	12.452	95.19
39	2.16	46.30	537.96	19.583	96.76
40	2.00	48.50	542.00	16.500	100.00

Animal	ADRENALS (%)	SPLEEN (%)	TESTES (%)	EPIDIDYMIUM (%)
31	2.609	28.02	145.89	67.585
32	3.302	43.72	177.67	69.488
33	2.559	31.75	179.62	64.834
34	2.864	29.09	188.18	67.545
35	2.440	38.76	150.72	63.206
36	3.535	28.79	186.87	78.535
37	3.618	35.68	191.96	74.623
38	3.173	31.73	156.25	63.606
39	2.917	37.96	176.39	65.463
40	2.550	28.00	182.00	68.050

**ORGAN WEIGHTS (GRAM)
AFTER WEEK 13 OF TREATMENT
FEMALES**

Group 1 (0 mg/kg)

Animal	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS
41	232.0	1.82	0.78	6.03	0.246	1.54
42	232.4	2.06	0.75	6.37	0.235	1.49
43	242.1	1.99	0.82	6.25	0.289	1.50
44	233.2	1.92	0.74	5.88	0.318	1.35
45	230.6	2.00	0.74	7.20	0.296	1.64
46	254.2	1.87	0.71	6.58	0.293	1.62
47	251.9	1.98	0.73	6.87	0.360	1.73
48	262.0	1.81	0.78	6.83	0.222	1.59
49	260.9	1.95	0.76	7.90	0.364	1.60
50	229.9	1.90	0.66	6.05	0.269	1.31

Animal	ADRENALS	SPLEEN	OVARIES	UTERUS
41	0.084	0.51	0.134	0.67
42	0.076	0.53	0.110	0.88
43	0.072	0.47	0.101	0.82
44	0.075	0.40	0.112	0.79
45	0.062	0.49	0.114	2.31
46	0.081	0.76	0.154	1.18
47	0.089	0.65	0.117	1.52
48	0.068	0.51	0.118	0.90
49	0.088	0.63	0.134	1.06
50	0.075	0.42	0.067	1.24

**ORGAN WEIGHTS (GRAM)
AFTER WEEK 13 OF TREATMENT
FEMALES**

Group 2 (100 mg/kg)

Animal	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS
51	249.1	1.95	0.73	6.73	0.319	1.53
52	233.6	2.04	0.68	5.68	0.186	1.45
53	222.9	2.01	0.73	6.09	0.226	1.45
54	250.7	1.96	0.73	7.57	0.280	1.45
55	228.6	1.98	0.66	6.67	0.234	1.32
56	231.4	1.88	0.72	6.20	0.239	1.33
57	250.5	1.87	0.71	7.73	0.279	1.30
58	265.1	2.07	0.75	7.03	0.239	1.39
59	263.4	1.95	0.73	8.10	0.308	1.46
60	236.1	1.93	0.68	6.48	0.263	1.37

Animal	ADRENALS	SPLEEN	OVARIES	UTERUS
51	0.061	0.53	0.123	0.75
52	0.055	0.41	0.102	0.71
53	0.070	0.50	0.105	0.88
54	0.080	0.56	0.101	0.88
55	0.076	0.49	0.119	0.70
56	0.072	0.52	0.121	0.79
57	0.069	0.65	0.121	1.05
58	0.090	0.50	0.112	0.80
59	0.067	0.62	0.116	0.67
60	0.070	0.56	0.107	1.11

**ORGAN WEIGHTS (GRAM)
AFTER WEEK 13 OF TREATMENT
FEMALES**

Group 3 (300 mg/kg)

Animal	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS
61	233.7	1.96	0.79	6.43	0.293	1.17
62	211.4	1.98	0.61	5.14	0.257	1.34
63	264.1	2.05	0.83	7.44	0.318	1.45
64	237.3	2.00	0.71	6.24	0.271	1.37
65	250.7	1.86	0.70	6.92	0.264	1.47
66	237.0	2.02	0.69	7.10	0.388	1.57
67	240.0	2.03	0.84	8.01	0.260	1.36
68	245.5	1.97	0.79	6.91	0.253	1.52
69	252.0	2.03	0.79	8.04	0.301	1.61
70	261.1	2.00	0.76	6.75	0.292	1.29

Animal	ADRENALS	SPLEEN	OVARIES	UTERUS
61	0.069	0.56	0.075	0.80
62	0.069	0.58	0.094	0.80
63	0.073	0.59	0.114	0.74
64	0.072	0.44	0.117	0.83
65	0.058	0.61	0.107	0.73
66	0.080	0.43	0.089	1.04
67	0.087	0.54	0.096	0.89
68	0.073	0.56	0.089	1.31
69	0.076	0.53	0.090	1.06
70	0.068	0.46	0.094	0.80

**ORGAN WEIGHTS (GRAM)
AFTER WEEK 13 OF TREATMENT
FEMALES**

Group 4 (1000 mg/kg)

Animal	BODY W.	BRAIN	HEART	LIVER	THYMUS	KIDNEYS
71	256.1	1.98	0.80	7.30	0.341	1.49
72	255.4	1.90	0.60	5.15	0.065	1.26
73	236.3	1.86	0.79	5.88	0.234	1.39
74	217.9	1.87	0.67	5.57	0.205	1.26
75	236.0	2.06	0.74	6.15	0.246	1.46
76	228.5	1.92	0.66	6.07	0.261	1.36
77	234.9	1.93	0.68	6.65	0.349	1.30
78	223.2	1.94	0.70	6.00	0.276	1.35
79	244.3	1.99	0.74	6.72	0.274	1.41
80	234.9	1.91	0.68	6.68	0.307	1.22

Animal	ADRENALS	SPLEEN	OVARIES	UTERUS
71	0.086	0.54	0.095	0.69
72	0.064	0.50	0.093	0.92
73	0.074	0.49	0.144	0.93
74	0.080	0.41	0.092	0.81
75	0.086	0.44	0.104	1.00
76	0.070	0.52	0.108	1.34
77	0.086	0.73	0.130	0.94
78	0.077	0.39	0.098	0.76
79	0.069	0.54	0.119	0.72
80	0.063	0.51	0.106	1.14

ORGAN/BODY WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
FEMALES

Group 1 (0 mg/kg)

Animal	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
41	232.0	0.78	0.34	2.60	0.106	0.66
42	232.4	0.89	0.32	2.74	0.101	0.64
43	242.1	0.82	0.34	2.58	0.119	0.62
44	233.2	0.82	0.32	2.52	0.136	0.58
45	230.6	0.87	0.32	3.12	0.128	0.71
46	254.2	0.74	0.28	2.59	0.115	0.64
47	251.9	0.79	0.29	2.73	0.143	0.69
48	262.0	0.69	0.30	2.61	0.085	0.61
49	260.9	0.75	0.29	3.03	0.140	0.61
50	229.9	0.83	0.29	2.63	0.117	0.57

Animal	ADRENALS (%)	SPLEEN (%)	OVARIES (%)	UTERUS (%)
41	0.036	0.22	0.058	0.29
42	0.033	0.23	0.047	0.38
43	0.030	0.19	0.042	0.34
44	0.032	0.17	0.048	0.34
45	0.027	0.21	0.049	1.00
46	0.032	0.30	0.061	0.46
47	0.035	0.26	0.046	0.60
48	0.026	0.19	0.045	0.34
49	0.034	0.24	0.051	0.41
50	0.033	0.18	0.029	0.54

ORGAN/BODY WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
FEMALES

Group 2 (100 mg/kg)

Animal	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
51	249.1	0.78	0.29	2.70	0.128	0.61
52	233.6	0.87	0.29	2.43	0.080	0.62
53	222.9	0.90	0.33	2.73	0.101	0.65
54	250.7	0.78	0.29	3.02	0.112	0.58
55	228.6	0.87	0.29	2.92	0.102	0.58
56	231.4	0.81	0.31	2.68	0.103	0.57
57	250.5	0.75	0.28	3.09	0.111	0.52
58	265.1	0.78	0.28	2.65	0.090	0.52
59	263.4	0.74	0.28	3.08	0.117	0.55
60	236.1	0.82	0.29	2.74	0.111	0.58

Animal	ADRENALS (%)	SPLEEN (%)	OVARIES (%)	UTERUS (%)
51	0.024	0.21	0.049	0.30
52	0.024	0.18	0.044	0.30
53	0.031	0.22	0.047	0.39
54	0.032	0.22	0.040	0.35
55	0.033	0.21	0.052	0.31
56	0.031	0.22	0.052	0.34
57	0.028	0.26	0.048	0.42
58	0.034	0.19	0.042	0.30
59	0.025	0.24	0.044	0.25
60	0.030	0.24	0.045	0.47

ORGAN/BODY WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
FEMALES

Group 3 (300 mg/kg)

Animal	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
61	233.7	0.84	0.34	2.75	0.125	0.50
62	211.4	0.94	0.29	2.43	0.122	0.63
63	264.1	0.78	0.31	2.82	0.120	0.55
64	237.3	0.84	0.30	2.63	0.114	0.58
65	250.7	0.74	0.28	2.76	0.105	0.59
66	237.0	0.85	0.29	3.00	0.164	0.66
67	240.0	0.85	0.35	3.34	0.108	0.57
68	245.5	0.80	0.32	2.81	0.103	0.62
69	252.0	0.81	0.31	3.19	0.119	0.64
70	261.1	0.77	0.29	2.59	0.112	0.49

Animal	ADRENALS (%)	SPLEEN (%)	OVARIES (%)	UTERUS (%)
61	0.030	0.24	0.032	0.34
62	0.033	0.27	0.044	0.38
63	0.028	0.22	0.043	0.28
64	0.030	0.19	0.049	0.35
65	0.023	0.24	0.043	0.29
66	0.034	0.18	0.038	0.44
67	0.036	0.23	0.040	0.37
68	0.030	0.23	0.036	0.53
69	0.030	0.21	0.036	0.42
70	0.026	0.18	0.036	0.31

ORGAN/BODY WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
FEMALES

Group 4 (1000 mg/kg)

Animal	BODY W. (GRAM)	BRAIN (%)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
71	256.1	0.77	0.31	2.85	0.133	0.58
72	255.4	0.74	0.23	2.02	0.025	0.49
73	236.3	0.79	0.33	2.49	0.099	0.59
74	217.9	0.86	0.31	2.56	0.094	0.58
75	236.0	0.87	0.31	2.61	0.104	0.62
76	228.5	0.84	0.29	2.66	0.114	0.60
77	234.9	0.82	0.29	2.83	0.149	0.55
78	223.2	0.87	0.31	2.69	0.124	0.60
79	244.3	0.81	0.30	2.75	0.112	0.58
80	234.9	0.81	0.29	2.84	0.131	0.52

Animal	ADRENALS (%)	SPLEEN (%)	OVARIES (%)	UTERUS (%)
71	0.034	0.21	0.037	0.27
72	0.025	0.20	0.036	0.36
73	0.031	0.21	0.061	0.39
74	0.037	0.19	0.042	0.37
75	0.036	0.19	0.044	0.42
76	0.031	0.23	0.047	0.59
77	0.037	0.31	0.055	0.40
78	0.034	0.17	0.044	0.34
79	0.028	0.22	0.049	0.29
80	0.027	0.22	0.045	0.49

ORGAN/BRAIN WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
FEMALES

Group 1 (0 mg/kg)

Animal	BRAIN (GRAM)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
41	1.82	42.86	331.32	13.516	84.62
42	2.06	36.41	309.22	11.408	72.33
43	1.99	41.21	314.07	14.523	75.38
44	1.92	38.54	306.25	16.563	70.31
45	2.00	37.00	360.00	14.800	82.00
46	1.87	37.97	351.87	15.668	86.63
47	1.98	36.87	346.97	18.182	87.37
48	1.81	43.09	377.35	12.265	87.85
49	1.95	38.97	405.13	18.667	82.05
50	1.90	34.74	318.42	14.158	68.95

Animal	ADRENALS (%)	SPLEEN (%)	OVARIES (%)	UTERUS (%)
41	4.615	28.02	7.363	36.81
42	3.689	25.73	5.340	42.72
43	3.618	23.62	5.075	41.21
44	3.906	20.83	5.833	41.15
45	3.100	24.50	5.700	115.50
46	4.332	40.64	8.235	63.10
47	4.495	32.83	5.909	76.77
48	3.757	28.18	6.519	49.72
49	4.513	32.31	6.872	54.36
50	3.947	22.11	3.526	65.26

ORGAN/BRAIN WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
FEMALES

Group 2 (100 mg/kg)

Animal	BRAIN (GRAM)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
51	1.95	37.44	345.13	16.359	78.46
52	2.04	33.33	278.43	9.118	71.08
53	2.01	36.32	302.99	11.244	72.14
54	1.96	37.24	386.22	14.286	73.98
55	1.98	33.33	336.87	11.818	66.67
56	1.88	38.30	329.79	12.713	70.74
57	1.87	37.97	413.37	14.920	69.52
58	2.07	36.23	339.61	11.546	67.15
59	1.95	37.44	415.38	15.795	74.87
60	1.93	35.23	335.75	13.627	70.98

Animal	ADRENALS (%)	SPLEEN (%)	OVARIES (%)	UTERUS (%)
51	3.128	27.18	6.308	38.46
52	2.696	20.10	5.000	34.80
53	3.483	24.88	5.224	43.78
54	4.082	28.57	5.153	44.90
55	3.838	24.75	6.010	35.35
56	3.830	27.66	6.436	42.02
57	3.690	34.76	6.471	56.15
58	4.348	24.15	5.411	38.65
59	3.436	31.79	5.949	34.36
60	3.627	29.02	5.544	57.51

ORGAN/BRAIN WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
FEMALES

Group 3 (300 mg/kg)

Animal	BRAIN (GRAM)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
61	1.96	40.31	328.06	14.949	59.69
62	1.98	30.81	259.60	12.980	67.68
63	2.05	40.49	362.93	15.512	70.73
64	2.00	35.50	312.00	13.550	68.50
65	1.86	37.63	372.04	14.194	79.03
66	2.02	34.16	351.49	19.208	77.72
67	2.03	41.38	394.58	12.808	67.00
68	1.97	40.10	350.76	12.843	77.16
69	2.03	38.92	396.06	14.828	79.31
70	2.00	38.00	337.50	14.600	64.50

Animal	ADRENALS (%)	SPLEEN (%)	OVARIES (%)	UTERUS (%)
61	3.520	28.57	3.827	40.82
62	3.485	29.29	4.747	40.40
63	3.561	28.78	5.561	36.10
64	3.600	22.00	5.850	41.50
65	3.118	32.80	5.753	39.25
66	3.960	21.29	4.406	51.49
67	4.286	26.60	4.729	43.84
68	3.706	28.43	4.518	66.50
69	3.744	26.11	4.433	52.22
70	3.400	23.00	4.700	40.00

ORGAN/BRAIN WEIGHT RATIOS (%)
AFTER WEEK 13 OF TREATMENT
FEMALES

Group 4 (1000 mg/kg)

Animal	BRAIN (GRAM)	HEART (%)	LIVER (%)	THYMUS (%)	KIDNEYS (%)
71	1.98	40.40	368.69	17.222	75.25
72	1.90	31.58	271.05	3.421	66.32
73	1.86	42.47	316.13	12.581	74.73
74	1.87	35.83	297.86	10.963	67.38
75	2.06	35.92	298.54	11.942	70.87
76	1.92	34.38	316.15	13.594	70.83
77	1.93	35.23	344.56	18.083	67.36
78	1.94	36.08	309.28	14.227	69.59
79	1.99	37.19	337.69	13.769	70.85
80	1.91	35.60	349.74	16.073	63.87

Animal	ADRENALS (%)	SPLEEN (%)	OVARIES (%)	UTERUS (%)
71	4.343	27.27	4.798	34.85
72	3.368	26.32	4.895	48.42
73	3.978	26.34	7.742	50.00
74	4.278	21.93	4.920	43.32
75	4.175	21.36	5.049	48.54
76	3.646	27.08	5.625	69.79
77	4.456	37.82	6.736	48.70
78	3.969	20.10	5.052	39.18
79	3.467	27.14	5.980	36.18
80	3.298	26.70	5.550	59.69

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES**

Animals without necropsy

Animals not recorded

Animals not completed

Animals with not translated finding

Not Reported

Animal 81	Male	Group 10	Reserve Removed
Animal 82	Female	Group 10	Reserve Removed

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
MALES**

Group 1 (0 mg/kg)

Animal 1 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 2 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 3 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 4 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 5 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 6 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 7 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 8 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 9 PLANNED NECROPSY , 07-JAN-2009

THYMUS FOCUS/FOCI, MANY, D=1 MM, DARK RED.

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
MALES**

Group 1 (0 mg/kg)

Animal 10 PLANNED NECROPSY , 07-JAN-2009

STOMACH MUCOSA, FUNDUS: FOCUS/FOCI, D=6X1 MM, REDDISH.

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
MALES**

Group 2 (100 mg/kg)

Animal 11 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 12 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 13 PLANNED NECROPSY , 07-JAN-2009

THYMUS FOCUS/FOCI, SEVERAL, D=1 MM, DARK RED.

Animal 14 PLANNED NECROPSY , 07-JAN-2009

THYMUS FOCUS/FOCI, ISOLATED, D=1 MM, DARK RED.

Animal 15 PLANNED NECROPSY , 07-JAN-2009

THYMUS FOCUS/FOCI, MANY, D=1 MM, DARK RED.

Animal 16 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 17 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 18 PLANNED NECROPSY , 07-JAN-2009

STOMACH MUCOSA, FUNDUS: FOCUS/FOCI, ISOLATED, D=3X1 MM, REDDISH.

Animal 19 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
MALES**

Group 2 (100 mg/kg)

Animal 20 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
MALES**

Group 3 (300 mg/kg)

Animal 21 PLANNED NECROPSY , 07-JAN-2009

SKIN TIP OF TAIL: KINKED TAIL.

Animal 22 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 23 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 24 PLANNED NECROPSY , 07-JAN-2009

MANDIBULAR L.NODE FOCUS/FOCI, SEVERAL, D=1 MM, DARK RED.

Animal 25 PLANNED NECROPSY , 07-JAN-2009

STOMACH MUCOSA, FUNDUS: FOCUS/FOCI, ISOLATED, D=3X1 MM, REDDISH.

Animal 26 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 27 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 28 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 29 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
MALES**

Group 3 (300 mg/kg)

Animal 30 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
MALES**

Group 4 (1000 mg/kg)

Animal 31 PLANNED NECROPSY , 07-JAN-2009

THYMUS FOCUS/FOCI, MANY, D=1 MM, DARK RED.

Animal 32 PLANNED NECROPSY , 07-JAN-2009

KIDNEYS RIGHT SIDE: PELVIC DILATION.

Animal 33 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 34 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 35 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 36 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 37 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 38 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

Animal 39 PLANNED NECROPSY , 07-JAN-2009

LUNGS RIGHT CRANIAL LOBE: FOCUS/FOCI, D=3 MM, REDDISH.

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
MALES**

Group 4 (1000 mg/kg)

Animal 40 PLANNED NECROPSY , 07-JAN-2009

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
FEMALES**

Group 1 (0 mg/kg)

Animal 41 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 42 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 43 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 44 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 45 PLANNED NECROPSY , 06-JAN-2009

UTERUS BOTH HORNS: DILATION, D=5 MM.

Animal 46 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 47 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 48 PLANNED NECROPSY , 06-JAN-2009

MANDIBULAR L.NODE DISCOLORATION, DARK RED.

Animal 49 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
FEMALES**

Group 1 (0 mg/kg)

Animal 50 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
FEMALES**

Group 2 (100 mg/kg)

Animal 51 PLANNED NECROPSY , 06-JAN-2009

SKIN DORSO-LUMBAR REGION, LEFT SIDE: ALOPECIA, D=20 MM, MODERATE.

Animal 52 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 53 PLANNED NECROPSY , 06-JAN-2009

SPLEEN ECTOPIC SPLENIC TISSUE, D=20X10 MM.
MANDIBULAR L.NODE FOCUS/FOCI, ISOLATED, D=1 MM, DARK RED.

Animal 54 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 55 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 56 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 57 PLANNED NECROPSY , 06-JAN-2009

KIDNEYS LEFT SIDE: DISCOLORATION, TAN.
LEFT SIDE: REDUCED IN SIZE, D=8X6 MM.

Animal 58 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 59 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
FEMALES**

Group 2 (100 mg/kg)

Animal 60 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
FEMALES**

Group 3 (300 mg/kg)

Animal 61 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 62 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 63 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 64 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 65 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 66 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 67 PLANNED NECROPSY , 06-JAN-2009

OVARIES RIGHT SIDE: FOCUS/FOCI, D=1 MM, BLACK.

Animal 68 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 69 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
FEMALES**

Group 3 (300 mg/kg)

Animal 70 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
FEMALES**

Group 4 (1000 mg/kg)

Animal 71 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 72 PLANNED NECROPSY , 06-JAN-2009

BODY CAVITIES UTERINE ADIPOSE TISSUE, RIGHT SIDE: NODULE(S), D=13 MM, GRAY WHITE,
REDDISH, FIRM.

Animal 73 PLANNED NECROPSY , 06-JAN-2009

KIDNEYS BOTH SIDES: PELVIC DILATION.

Animal 74 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 75 PLANNED NECROPSY , 06-JAN-2009

STOMACH MUCOSA, FUNDUS: FOCUS/FOCI, ISOLATED, D=2 MM, BLACK.

Animal 76 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 77 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 78 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

Animal 79 PLANNED NECROPSY , 06-JAN-2009

LIVER PAPILLARY PROCESS: DISCOLORATION, DARK RED.

**MACROSCOPICAL FINDINGS
AFTER WEEK 13 OF TREATMENT
ALL NECROPSIES
FEMALES**

Group 4 (1000 mg/kg)

Animal 80 PLANNED NECROPSY , 06-JAN-2009

NO FINDINGS NOTED

REPORT (PART II OF II)

Lyso-Phospholipase

90-Day Oral (Gavage) Toxicity Study in the Wistar Rat

Study Director: W.H. Braun

Test Facility: **Harlan Laboratories Ltd.**
(former RCC Ltd)
Zelgliweg 1
4452 Itingen / Switzerland

Sponsor: **AB Enzymes GmbH**
Feldbergstrasse 78
64293 Darmstadt / Germany

Study Identification: Harlan Laboratories Study **B99180**

Version: Final

Study Completion Date: 29-May-2009

APPENDIX I:
CHEMICAL ANALYSIS OF FEED

LUFA-ITL GmbH

Dr.-Hell-Str. 6, 24107 Kiel, Germany
Tel.: +49(0431)1228-0, Fax: +49(0431)1228-498
eMail: zentrale@lufa-itl.de

LUFA - ITL Dr.-Hell-Str. 6, 24107 Kiel

PROVIMI KLIBA AG
RINAUSTRASSE
4303 KAISERAUGST / SCHWEIZ
SCHWEIZ

AGROLAB
Laborgruppe
www.agrolab.de



Date 24.07.2008
Customer no. 1209835
Page 1 of 2

TEST REPORT

Sample No. 455759

Order No. 520772 GLP Schadstoffuntersuchung
Sample Arrival 09.07.2008
Sample code M/R HALTUNG GLP
Alleinfuttermittel für Mäuse und Ratten
Rezeptur: 3433
GLP-Batch 44/08
Fabr.-Code: 0807002
hergestellt: 03.07.08

Sample packing plastic bag

Unit	Result	limits acc. GV-SOLAS A-08-2001	Substance	Method	
Trace-Elements/Heavy-Metals					
Copper	mg/kg	14,5	OM	VDLUF VII 2.2.2.6	
Selenium	mg/kg	0,38	OM	acc. to VDLUF VII 2.2.2.6; HR-ICPMS	
Cadmium	mg/kg	0,08	0,4	OM	acc. to VDLUF VII 2.2.2.6; HR-ICPMS
Lead	mg/kg	<0,10	1,5	OM	acc. to VDLUF VII 2.2.2.6; HR-ICPMS
Mercury	mg/kg	<0,02	0,1	OM	§64 LFGB L00.00-19
Arsenic	mg/kg	0,14	1	OM	acc. to VDLUF VII 2.2.2.6; HR-ICPMS
Mycotoxins					
Aflatoxine B1	µg/kg	<1,00	10	OM	HPLC-VDLUF Bd. III, 18.1.4
Aflatoxine B2	µg/kg	<1,00	5	OM	HPLC-VDLUF Bd. III, 18.1.4
Aflatoxine G1	µg/kg	<1,00	5	OM	HPLC-VDLUF Bd. III, 18.1.4
Aflatoxine G2	µg/kg	<1,00	5	OM	HPLC-VDLUF Bd. III, 18.1.4
Sum Aflatoxines	µg/kg	n.d.		OM	calculated
PCB					
PCB 28	mg/kg	<0,0020		OM	acc. to §64 LFGB L00.00-34
PCB 52	mg/kg	<0,0020		OM	acc. to §64 LFGB L00.00-34
PCB 101	mg/kg	<0,0020		OM	acc. to §64 LFGB L00.00-34
PCB 118	mg/kg	<0,0020		OM	acc. to §64 LFGB L00.00-34
PCB 138	mg/kg	<0,0020		OM	acc. to §64 LFGB L00.00-34
PCB 153	mg/kg	<0,0020		OM	acc. to §64 LFGB L00.00-34
PCB 180	mg/kg	<0,0020		OM	acc. to §64 LFGB L00.00-34
sum PCB	mg/kg	n.d.	0,05	OM	calculated
Organochlorous-Pesticides GC-Multiresidueanalysis					
Dieldrin	mg/kg	<0,002		OM	acc. to §64 LFGB L00.00-34
HCH-gamma (gammexane)	mg/kg	<0,002	0,1	OM	acc. to §64 LFGB L00.00-34
Heptachlor	mg/kg	<0,00200		OM	acc. to §64 LFGB L00.00-34
Heptachlorepoixide-cis	mg/kg	<0,00200		OM	acc. to §64 LFGB L00.00-34



LUFA-ITL GmbH

Dr.-Hell-Str. 6, 24107 Kiel, Germany
Tel.: +49(0)431)1228-0, Fax: +49(0)431)1228-498
eMail: zentrale@lufa-itl.de

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Date 24.07.2008
Customer no. 1209835
Page 2 of 2

Sample No. 455759

	Unit	limits acc. GV-SOLAS Result A-08-2001		Substance	Method
Heptachlorepoxide-trans	mg/kg	<0,00200		OM	acc. to §64 LFGB L00.00-34
o,p-DDD	mg/kg	<0,00200		OM	acc. to §64 LFGB L00.00-34
o,p-DDE	mg/kg	<0,00200		OM	acc. to §64 LFGB L00.00-34
o,p-DDT	mg/kg	<0,002		OM	acc. to §64 LFGB L00.00-34
p,p-DDD	mg/kg	<0,00200		OM	acc. to §64 LFGB L00.00-34
p,p-DDE	mg/kg	<0,00200		OM	acc. to §64 LFGB L00.00-34
p,p-DDT	mg/kg	<0,00200		OM	acc. to §64 LFGB L00.00-34
Sum DDTs	mg/kg	n.d.	0,05	OM	calculated
Sum Heptachlor	mg/kg	n.d.	0,01	OM	calculated

Organo-Phosphorous Pesticides GC-Multiresidueanalysis

Malathion	mg/kg	<0,010	1	OM	acc. to §64 LFGB L00.00-34
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nitrosamines

N-Nitrosodibutylamin	µg/kg	<5,00		OM	GC-Inhousemethod
N-Nitrosodiethylamin	µg/kg	<5,00	10	OM	GC-Inhousemethod
N-Nitrosodisopropylamin	µg/kg	<5,00		OM	GC-Inhousemethod
N-Nitrosodimethylamin	µg/kg	<5,00	10	OM	GC-Inhousemethod
N-Nitrosodipropylamin	µg/kg	<5,00		OM	GC-Inhousemethod
N-Nitrosomethylethylamin	µg/kg	<5,00		OM	GC-Inhousemethod
N-Nitrosomorpholin	µg/kg	<5,00		OM	GC-Inhousemethod
N-Nitrosopiperidin	µg/kg	<5,00		OM	GC-Inhousemethod
N-Nitrosopyrrolidin	µg/kg	<5,00		OM	GC-Inhousemethod
Sum Nitrosamines	µg/kg	n.d.		OM	calculated

Estrogens

dienestrol	µg/kg	<10,0		OM	no object
diethyl stilbestrol	µg/kg	<1,00		OM	no object
hexestrol	µg/kg	<2,00		OM	no object
Sum Estrogens	µg/kg	n.d.		OM	calculated

Explanation: "<" , n.d. : not detected, below limit of detection .

The actual limit of detection can be different to the standard value for a particular analysis due to matrix effects or insufficient sample volume.

Remark: OM=original matter, DM=dry matter

LUFA - ITL Dr. Wehage, Tel. 0431/1228-220

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External laboratory

Parameter

Sum Nitrosamines
Sum Estrogens

External laboratory

Zentrale Analytik - Organische Henkel KGaA
TIERGESUNDHEITSDIENST

The analytical results are valid for the delivered sample material only. The testing period is the time between the receipt of the sample and the reporting date. Validation of results is not possible for samples of unknown origin .



APPENDIX II:
DRINKING WATER ANALYSIS

BACTERIOLOGICAL ASSAY OF DRINKING WATER, ITINGEN

Official Laboratory	Liestal, September 03, 2008
Basel-Landschaft	Ref.no. 20006941
Sampling point:	59.99.N Net water RCC Ltd, Itingen, Room No. 10
Sampled on:	July 29, 2008
Sample:	
Time of sampling	7.45
Water temperature (°C)	15.9

BACTERIOLOGICAL TEST:

Aerobic mesophilic bacteria / ml	0
E.coli / 100 ml	0
Enterococci / 100 ml	0
Clostridium perfringens	0

ASSESSMENT:

At the time of sampling, the tested bacteriological parameters met the requirements for drinking water according to "Artikel 3 der Verordnung über Trink-, Quell-, und Mineralwasser (SR 817.022.102)

CHEMICAL WATER ANALYSIS, ITINGEN

Official Laboratory
Basel-Landschaft

Liestal, September 03, 2008
Ref. no. 200064390

Sampling point:

59.99.N, Net water
RCC Ltd, Itingen, Room no. 10

Sampled on:

July 29, 2008

Time of sampling

7.45

Water temperature (°C)

15.9

CHEMICAL TEST:

Appearance			Clear, colourless
Odor			not remarkable
Taste			not remarkable
UV-absorption at 254 nm/100 cm			1.39
Conductivity		µS/cm	700
Oxygen demand	(KMnO ₄ cons.)	mg/l	1.8
Turbidity	FNU		0.22
Chloride	Cl ⁻	mg/l	23.6
Nitrate	NO ₃ ⁻	mg/l	19.9
Sulphate	SO ₄ ⁻	mg/l	114.5
Nitrite	NO ₂ ⁻	mg/l	<.005
Total hardness		fr.H°	39.0
Calcium	Ca ⁺⁺	mg/l	135.0
Magnesium	Mg ⁺⁺	mg/l	12.7
Sodium	Na ⁺	mg/l	15.7
Kalium	K	mg/l	3.9

ASSESSMENT:

At the time of sampling, the tested chemical parameters met the requirements for drinking water according to "Artikel 3 der Verordnung über Trink-, Quell-, und Mineralwasser (SR 817.022.102)

CONTAMINANT ASSAY OF DRINKING WATER, ITINGEN

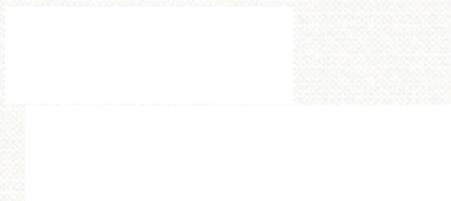
RCC Study No.: C11840
 Date of Sampling: July 29, 2008
 Sample: H₂O, RCC Ltd, Itingen, Room No. 10

PARAMETER	ASSAY LEVEL µg/l	LIMIT * µg/l
Lindane	< 0.05	0.1
Heptachlor	< 0.05	0.1
Malathion	< 0.05	0.1
DDT, total	< 0.05	0.1
Dieldrin	< 0.05	0.1
Cadmium	< 0.5	5
Arsenic	< 3	50
Lead	< 3	50
Mercury	< 1	1
Selenium	< 3	10
Copper	< 4	1500
PCBs (28, 52, 101, 138, 153, 180)	< 0.05	0.1
Nitrosamines, total (DMN, DEN, NPIP, NMORPH)	< 0.05	----

< 0.05 = less than 0.05 microgram per liter

* Schweizer Lebensmittelbuch

Issued by



September 26, 2008

APPENDIX III:
ANALYSIS OF DOSE FORMULATIONS

ANALYTICAL PART REPORT

LYSO-PHOSPHOLIPASE

Analytical Part to:

90-Day Oral (Gavage) Toxicity Study in the Wistar Rat

Subtitle:

Dose Formulation Analysis

Study Scientist:

Test Facility:

Harlan Laboratories Ltd.
(former RCC Ltd.)
Zelgliweg 1
4452 Itingen/Switzerland

Sponsor:

AB Enzymes GmbH
Feldbergstrasse 78
D-64293 Darmstadt / Germany

Study Identification:

Harlan Laboratories Study **B99180**

Version:

Final

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PREFACE

General Information

Test Item:	Lyso-Phospholipase
Analytical Part to:	90-Day Oral (Gavage) Toxicity Study in the Wistar Rat
Subtitle:	Dose Formulation Analysis
Sponsor:	AB Enzymes GmbH Feldbergstrasse 78 D-64293 Darmstadt / Germany
Test Facility:	Harlan Laboratories Ltd. (former RCC Ltd.) Zelgliweg 1 4452 Itingen / Switzerland

Responsibilities

Study Scientist (Analytics):
Technical Coordinator(s):

Schedule of Bioanalytical Part

Experimental Starting Date:	08-Oct-2008
Experimental Completion Date:	31-Dec-2008

1 SUMMARY

The purpose of this study was to determine the content, homogeneity and stability of Lyso-Phospholipase in dose formulation (bidistilled water). Determination was carried out based on the determination of the phospholipase activity using Lyso-phosphatidylcholine as substrate or on the total protein content using a bicinchoninic acid formulation for the colorimetric detection and the test item as reference standard.

Dose formulation samples were taken on 8-Oct-2008, 12-Nov-2008 and 31-Dec-2008. In the dose formulation samples containing 10, 30 and 100 mg Lyso-Phospholipase/mL, mean concentrations of 90.3-108%, 96.3-112% and 91.3-119%, respectively, of the nominal concentrations were obtained at the three sampling occasions.

Homogenous distribution was confirmed by a CV of $\leq 6.29\%$.

Following storage for 4 hours at room temperature and following storage for 7 days at 4°C the recoveries were within 82.3 and 106% of the initial concentrations (88.4-126% of nominal concentrations).

In conclusion, the dose formulations were in the range of 90.3 to 119% of the nominal concentration and homogenous distribution was confirmed by a CV of $\leq 6.29\%$. Lyso-Phospholipase in the dose formulations was concluded to be stable as the recoveries after storage for 4 hours at room temperature and for 7 days at 4°C were within 82.3 and 106% of the initial concentrations.

2 PURPOSE

The purpose of this study was to determine the content, homogeneity and stability of Lyso-Phospholipase in dose formulation (bidistilled water). Determination was carried out based on the dermination of the phospholipase activity using Lyso-phophatidylcholine as substrate or on the total protein content using a bicinchoninic acid formulation for the colorimetric detection and the test item as reference standard.

3 MATERIALS AND METHODS

3.1 Study Samples

Application formulations were prepared on 8-Oct-2008, at the Test Facility with nominal concentrations of 0 mg/mL (Group 1), 10 mg/mL (Group 2), 30 mg/mL (Group 3) and 100 mg/mL (Group 4). 4 Hour stability samples were prepared accordingly 4 hours in advance and stored for 4 hours at room temperature. A sample taken from the top, middle and bottom of each preparation was shipped on ice to the Study Scientist for Dose Formulation Analysis and analysed within 5 days after receipt, using a determination of total protein.

7 Day stability samples were kept for 7 days at 4°C, shipped on ice on 15-Oct-2008, and analysed immediately using a determination of Lyso-phospholipase activity.

Additional samples were prepared on 12-Nov-2008 and 31-Dec-2008 and shipped immediately on ice to the Study Scientist for Dose Formulation Analysis. The samples were analysed immediately after receipt using a determination of Lyso-phospholipase activity.

3.2 Test Item

For further information about the test item (test product, dose and mode of administration), which was used within the in-life phase, see study plan (final version: 09-Sep-2008). The test item was also used as analytical reference item.

3.3 Reagents and Materials

Reagent	Batch	Supplier
BCA Reagent A, containing sodium carbonate, sodium bicarbonate, bicinchoninic acid and sodium tartrate in 0.1 M sodium hydroxide	JC111572	Pierce, Switzerland
BCA Reagent B, containing 4% cupric sulfate	IB111574	Pierce, Switzerland
Working Reagent (WR): Prepare WR by mixing 50 parts of BCA Reagent A with 1 part of BCA Reagent B (50:1, Reagent A:B)	N/A	Pierce, Switzerland
Free Fatty Acid, half micro test	11383175/ 13872420	Roche, Switzerland
L- α -Lysophosphatidylcholine	L4129/ 038K5206	Sigma, Switzerland

Standards and Quality Control samples (QCs) were prepared in bidistilled water with Lyso-Phospholipase.

3.4 Analytical Procedure

3.4.1 Total Protein Determination

For the quantitative determination of Lyso-Phospholipase in dose formulations (bi-distilled water) a photometric assay using bicinchoninic acid was used (Microplate Procedure).

The dose formulation samples were diluted with PBS into the range of the analytical assay.

1. Pipette 25 μ l of each standard or unknown sample replicate into a microplate well (working range = 20-1000 μ g/ml).
2. Add 200 μ l of the WR to each well and mix plate thoroughly on a plate shaker for 30 seconds.
3. Cover plate and incubate at 37°C for 30 minutes.
4. Cool plate to RT.
5. Measure the absorbance at 562 nm on a plate reader.
6. Subtract the average 562 nm absorbance measurement of the Blank standard replicates from the 562 nm measurements of all other individual standard and unknown sample replicates.
7. Prepare a standard curve by plotting the average Blank-corrected 562 nm measurement for each standard vs. its concentration in μ g/ml. Use the standard curve (four-parameter fit) to determine the protein concentration of each unknown sample.

3.4.1.1 Preparation of Standards

Independent standard solutions were prepared containing 23.5 to 1506 μ g/mL Lyso-phospholipase (nominal concentrations) in PBS.

A stock solution of 50 mg Lyso-Phospholipase/ml was prepared in PBS. The stock solution was further diluted with PBS to a final concentration of 5'000 μ g/ml. The working dilution was further diluted in PBS according to the following example:

Standard	Concentration (μ g/ml)	Dilution Factor
Std1	1506	3.32
Std2	753	2
Std3	377	2
Std4	188	2
Std5	94.1	2
Std6	47.1	2
Std7	23.5	2
Std8	0	-

A four parameter logistic fitting of the optical density at 562 nm against the nominal concentration of the standard was used to calculate sample concentrations.

3.4.1.2 Preparation of Quality Control Samples (QCs)

Independent QC solutions were prepared containing 602, 329 and 56.5 µg/mL Lyso-Phospholipase (nominal concentrations) in PBS.

An aliquot of the stock solution (50 mg Lyso-Phospholipase/ml) was diluted with PBS to a final concentration of 5'000 µg/ml. The working dilution was further diluted in PBS according to the following example:

QC	Concentration (µg/ml)	Dilution Factor
QC1	602	2.5
QC2	329	1.83
QC3	56.5	5.83

3.4.2 Determination of Lyso-Phospholipase Activity

Determination was carried out based on the dermination of the Lyso-phospholipase activity using Lyso-phosphatidylcholine as substrate.

The dose formulation samples were diluted with bidistilled water into the analytical range of the assay.

1. 250 µl of substrate (Lyso-phosphatidylcholine, 20 mM in bidistilled water) and 250 µl of buffer (0.02 mM acetate, pH 4.5) were incubated for 5 minutes at 55°C.
2. Then 100 µl of standard, QCs or sample were added and mixed.
3. After exactly 1 and 10 minutes of incubation at 55°C, each, 100 µl were treated with 1 ml reagent A (pre-tempered for 5 min at 37°C) and mixed.
4. After exactly 5 minutes of incubation at 37°C, 100 µl of a solution containing 0.55 ml reagent B and 0.55 ml N-Ethylmaleinimid were added.
5. This mixture was incubated for 5 minutes at 37°C.
6. Following cooling down in a waterbath, the optical density at 546 nm was measured.

3.4.2.1 Preparation of Standards

Two independent standard solutions were prepared containing 0.2 to 0.3 $\mu\text{g/mL}$ Lyso-Phospholipase (nominal concentrations) in bidistilled water.

A stock solution of about 100 mg Lyso-Phospholipase/ml was prepared in bidistilled water. The stock solution was further diluted with bidistilled water to a final concentration of 10 $\mu\text{g/ml}$. The working dilution was further diluted in bidistilled water according to the following typical example:

Standard	Concentration ($\mu\text{g/ml}$)	Dilution Factor
Std1	0.312	32.1
Std2	0.260	1.2

A linear interpolation (extrapolation) of the optical density at 546 nm against the nominal concentration of the standard was used to calculate sample concentrations

3.4.2.2 Preparation of Quality Control Samples (QCs)

Independent QC solutions were prepared containing 0.2 to 0.3 $\mu\text{g/mL}$ Lyso-Phospholipase (nominal concentrations) in bidistilled water.

An aliquot of the stock solution (100 mg Lyso-Phospholipase/ml) was diluted with bidistilled water to a final concentration of 10.0 $\mu\text{g/ml}$. The working dilution was further diluted in bidistilled water according to the following example:

QC	Concentration ($\mu\text{g/ml}$)	Dilution Factor
Std1	0.312	32.1
QC1	0.208	1.5

4 RESULTS

4.1 Accuracy and Precision of Analytical Method

[Table 1](#) and [Table 2](#)

QC samples (two to three concentration levels) revealed mean accuracies of 98.7 to 101% for the total protein determination and of 88.9 to 104% for the LPL activity determination, respectively.

4.2 Dose Formulation Analysis

[Table 3](#) to [Table 5](#)

Dose formulation samples taken on 8-Oct-2008, 12-Nov-2008 and 31-Dec-2008 were diluted with bidistilled water into the analytical range of the assay.

In the dose formulation samples containing 10, 30 and 100 mg Lyso-Phospholipase/mL, mean concentrations of 90.3-108%, 96.3-112% and 91.3-119%, respectively, of the nominal concentrations were obtained at the three sampling time points.

Homogenous distribution was confirmed by a CV of $\leq 6.29\%$.

Following storage for 4 hours at room temperature and following storage for 7 days at 4°C the recoveries were within 82.3 and 106% of the initial concentrations (88.4-126% of nominal concentrations).

5 CONCLUSION

In conclusion, the dose formulations were in the range of 90.3 to 119% of the nominal concentration and homogenous distribution was confirmed by a CV of $\leq 6.29\%$.

Lyso-Phospholipase in the dose formulations was concluded to be stable as the recoveries after storage for 4 hours at room temperature and for 7 days at 4°C were within 82.3 and 106% of the initial concentrations.

6 TABLES

Table 1 Mean Accuracies of QCs (Total Protein Determination)

QC	Concentration µg/mL	Mean Accuracy %
QC1	602	101
QC2	329	98.7
QC3	56.5	100.3
QC 1-3		100

Table 2 Accuracy and Precision of QCs (Lyso-Phospholipase Activity Determination)

QC	Concentration µg/mL	Mean Accuracy %
QC1	0.24	104
QC2	0.31	88.9
QC 1-2		96.5

Table 3 Dose Formulation Analysis (Preparation 8-Oct-2008)

Study Sample	Nominal Concentration (mg/mL)	Determined Concentration (mg/mL)	Mean (mg/mL)	CV	% of Nominal Concentration (% of Initial Concentration)
1 Top ^{a)}	0	0	0	n.a.	n.a.
1 Middle ^{a)}		0			
1 Bottom ^{a)}		0			
1D 4h/RT ^{a)}		0	0		
1E 7d/4°C ^{b)}		0	0		
2 Top ^{a)}	10	10.5	10.7	2.25	107
2 Middle ^{a)}		10.8			
2 Bottom ^{a)}		11.0			
2D 4h/RT ^{a)}		10.1	101 (94.3)		
2E 7d/4°C ^{b)}		8.84	88.4 (82.3)		
3 Top ^{a)}	30	34.6	33.1	6.29	110
3 Middle ^{a)}		33.9			
3 Bottom ^{a)}		30.7			
3D 4h/RT ^{a)}		34.4	115 (104)		
3E 7d/4°C ^{b)}		31.7	106 (95.7)		
4 Top ^{a)}	100	120	119	5.16	119
4 Middle ^{a)}		125			
4 Bottom ^{a)}		113			
4D 4h/RT		126	126 (106)		
4E 7d/4°C ^{b)}		99.7	99.7 (83.6)		

CV Coefficient of Variation

n.a. Not applicable

^{a)} Determination based on total protein content

^{b)} Determination based on Lyso-Phospholipase activity

Table 4 Dose Formulation Analysis (Preparation 12-Nov-2008)

Study Sample	Nominal Concentration (mg/mL)	Determined Concentration (mg/mL)	% of Nominal Concentration
1 ^{b)}	0	0	n.a.
2 ^{b)}	10	10.8	108
3 ^{b)}	30	28.9	96.3
4 ^{b)}	100	91.3	91.3

n.a. Not applicable

b) Determination based on Lyso-Phospholipase activity

Table 5 Dose Formulation Analysis (Preparation 31-Dec-2008)

Study Sample	Nominal Concentration (mg/mL)	Determined Concentration (mg/mL)	% of Nominal Concentration
1 ^{b)}	0	0	n.a.
2 ^{b)}	10	9.03	90.3
3 ^{b)}	30	33.8	112
4 ^{b)}	100	109	109

n.a. Not applicable

b) Determination based on Lyso-Phospholipase activity

APPENDIX IV:
CLINICAL LABORATORY INVESTIGATIONS

Parameter	Abbreviation	Unit		Instrumentation
Mean corpuscular hemoglobin	MCH	fmol		Advia 120
Mean corpuscular hemoglobin concentration	MCHC	mmol/L		Advia 120
Hemoglobin concentration distribution width	HDW	mmol/L		Advia 120
Reticulocyte count	RETI	relative rel.1	absolute G/L	Advia 120
Reticulocyte maturity index (low, medium, high fluorescence)	L RETI	rel.1		Advia 120
	M RETI	rel.1		
	H RETI	rel.1		
Leukocyte count, total	WBC	G/L		Advia 120
Differential leukocyte count		relative	absolute	Advia 120
Neutrophils	NEUT	rel.1	G/L	Advia 120
Eosinophils	EOS	rel.1	G/L	Advia 120
Basophils	BASO	rel.1	G/L	Advia 120
Lymphocytes	LYMPH	rel.1	G/L	Advia 120
Monocytes	MONO	rel.1	G/L	Advia 120
Large unstained cells	LUC	rel.1	G/L	Advia 120
Platelet count	PLATELETS	G/L		Advia 120

Hemoglobin Derivatives

Parameter	Abbreviation	Unit	Method	Instrumentation
Methemoglobin	MET-HB	rel. 1	Spectrometry, results given as ratio of total hemoglobin	OSM3 ²
Heinz bodies	HEINZ BOD	rel.1	Microscopic examination of New Methylene Blue stained films, results given as ratio of total RBC	Microscope

² Hemoximeter OSM3

Coagulation

Parameter	Abbreviation	Unit	Method	Instrumentation
Prothrombin time (=Thromboplastin time)	PT	rel. 1	Clotting assay, thromboplastin from rabbit brain tissue, results as ratio of normal activity	STA ³
Activated partial thromboplastin time	PTT	sec	Clotting assay, cephalin from rabbit cerebral tissue, silica surface activator	STA

³ STA-compact analyzer (Roche Diagnostics)

Clinical Biochemistry

Lithium heparin was used as anticoagulant during blood collection.

Parameter	Abbreviation	Unit	Method	Instrumentation
Glucose		mmol/L	Hexokinase/G6P-DH	Hitachi 917 ⁴
Urea		mmol/L	Urease/GLDH	Hitachi 917
Creatinine	CREAT	µmol/L	Enzymatic colorimetric test	Hitachi 917
Bilirubin, total	BILI-T	µmol/L	Reaction with 2,5-Dichlorophenyl-diazonium salt	Hitachi 917
Cholesterol, total	CHOLEST	mmol/L	Enzymatic, CHOD/PAP	Hitachi 917
Triglycerides	TRIGLY	mmol/L	Glycerol-Kinase GPO/PAP method	Hitachi 917
Phospholipids	PHOS-LIP	mmol/L	Phospholipase- Cholinoxidase-Peroxidase- reaction	Hitachi 917
Aspartate aminotransferase EC 2.6.1.1 ⁵	ASAT	U/L 37 °C	MDH/NADH coupled reaction	Hitachi 917
Alanine aminotransferase EC 2.6.1.2	ALAT	U/L 37 °C	LDH/NADH coupled reaction	Hitachi 917
Lactate dehydrogenase EC 1.1.1.27	LDH	U/L 37 °C	NADH/LDH coupled reaction using pyruvate as substrate	Hitachi 917
Glutamate dehydrogenase EC 1.4.1.3	GLDH	U/L 37 °C	Standard method, optimized (DGKC)	Hitachi 917
Alkaline phosphatase EC 3.1.3.1	ALP	U/L 37 °C	p-Nitrophenyl-phosphate as substrate	Hitachi 917
Gamma-glutamyl transferase EC 2.3.2.2	GGT	U/L 37 °C	Substrate: L-gamma- glutamyl-3-carboxy- 4-nitroanilide	Hitachi 917
Creatine kinase EC 2.7.3.2	CK	U/L 37 °C	HK/ATP and G6P-DH/NADPH coupled reaction method	Hitachi 917

⁴ Hitachi 917 analyzer, Roche Diagnostics

⁵ Identification of enzymes with EC-Number (Enzyme Commission) according to Enzyme Nomenclature, Recommendations (1972) of the IUPAC and IUB, Elsevier Scient. Publ. Comp., Amsterdam, 1973

Parameter	Abbreviation	Unit	Method	Instrumentation
Sodium		mmol/L	Ion selective electrode	Hitachi 917
Potassium		mmol/L	Ion selective electrode	Hitachi 917
Chloride		mmol/L	Ion selective electrode	Hitachi 917
Calcium		mmol/L	o-Cresolphthalein complexone method	Hitachi 917
Phosphorus		mmol/L	Phosphomolybdate reaction	Hitachi 917
Protein, total	PROTEIN	g/L	Biuret reaction	Hitachi 917
Albumin		g/L	Bromocresol green method	Hitachi 917
Globulin		g/L	Calculated value (total protein minus albumin)	
Albumin / Globulin Ratio	A/G RATIO		Calculated value (albumin / globulin)	

Urinalysis

Physical Examination

Parameter	Abbreviation	Unit	Method / Instrumentation
Urine volume (18-hour)		mL	Volumetric ⁶
Relative density (= Specific gravity)	REL DENS	rel.1	Refractometer ⁷
Color			Visual inspection
Appearance			Visual inspection

The following urine components were investigated using a semi-automated test strip analyzer Miditron (Roche Diagnostics) applying reflectance spectroscopy. Results are given as discrete values representing a concentration range (semi-quantitative results).

Chemical Examination

Parameter	Abbreviation	Unit	Set Points	Instrumentation
pH-value	pH		5.0, 6.0, 6.5, 7.0, 8.0, 9.0	Miditron ⁸
Nitrite		score	0 (negative), 1 (positive)	Miditron
Protein		g/L	0, 0.25, 0.75, 1.50, 5.00	Miditron
Glucose		mmol/L	0, 3, 6, 17, 56	Miditron
Ketones		mmol/L	0, 0.5, 1.5, 5.0, 15.0	Miditron
Urobilinogen	UROBILI	µmol/L	0, 17, 68, 135, 203	Miditron
Bilirubin		µmol /L	0, 17, 50, 100	Miditron
Erythrocytes	ERY	per µL	0, 10, 25, 50, 150, 250	Miditron
Leukocytes	LEU	per µL	0, 25, 100, 500	Miditron

⁶ Mettler balance

⁷ Clinical Refractometer SU-202, Kernco

⁸ Miditron semi-automated urine chemistry analyzer and reagent test strips, Roche Diagnostics

HISTORICAL DATA - HEMATOLOGY

STRAIN: RAT / HanRcc:WIST (MALES) AGE: FROM 19 TO 40 WEEKS
 DATA COLLECTION PERIOD: 29-JAN-02 TO 12-JUN-07

PARAMETER	UNIT	N	MEAN	STAND.DEV	95% TOLERANCE LIMITS	
ERYTHROCYTES (RBC)	T/l	1598	8.88	0.46	7.98	9.78
HEMOGLOBIN (HB)	mmol/l	1598	10.0	0.4	9.2	10.8
HEMATOCRIT (HCT)	rel. 1	1598	0.45	0.02	0.41	0.49
MEAN CORPUSCULAR VOLUME (MCV)	fl	1598	50.7	2.4	45.9	55.4
RED CELL VOL. DISTR. WIDTH (RDW)	rel. 1	1544	0.151	0.041	0.117	0.272
MEAN CORPUSCULAR HEMOGLOBIN (MCH)	fmol	1598	1.13	0.06	1.03	1.26
MEAN CORPUSCULAR HEMOGLOBIN CONC.	mmol/l	1598	22.23	1.05	20.45	24.57
HEMOGLOBIN CONC. DISTR. WIDTH	mmol/l	1544	1.79	0.20	1.40	2.14
RETICULOCYTE COUNT						
RETICULOCYTE (REL)	rel. 1	1598	0.020	0.004	0.013	0.029
RETICULOCYTE (ABS)	G/l	1598	176	34	119	250
MATURITY INDEX (L-RETI)	rel. 1	1544	0.597	0.123	0.378	0.798
MATURITY INDEX (M-RETI)	rel. 1	1544	0.309	0.056	0.187	0.392
MATURITY INDEX (H-RETI)	rel. 1	1544	0.094	0.088	0.011	0.315
LEUKOCYTES, TOTAL (WBC)	G/l	1598	6.22	1.49	3.74	9.53
DIFF.WBC COUNT (REL)						
NEUTROPHILS (NEUT)	rel. 1	761	0.209	0.055	0.119	0.339
EOSINOPHILS (EOS)	rel. 1	1598	0.019	0.007	0.010	0.035
BASOPHILS (BASO)	rel. 1	1598	0.004	0.003	0.001	0.013
LYMPHOCYTES (LYMPH)	rel. 1	1598	0.743	0.059	0.611	0.842
MONOCYTES (MONO)	rel. 1	1598	0.022	0.007	0.011	0.038
LARGE UNSTAINED CELLS (LUC)	rel. 1	1598	0.008	0.005	0.002	0.021
DIFF.WBC COUNT (ABS)						
NEUTROPHILS (NEUT)	G/l	761	1.31	0.45	0.66	2.29
EOSINOPHILS (EOS)	G/l	1598	0.12	0.05	0.05	0.22
BASOPHILS (BASO)	G/l	1598	0.03	0.02	0.00	0.08
LYMPHOCYTES (LYMPH)	G/l	1598	4.64	1.23	2.59	7.39
MONOCYTES (MONO)	G/l	1598	0.14	0.05	0.06	0.26
LARGE UNSTAINED CELLS (LUC)	G/l	1598	0.05	0.04	0.01	0.13
THROMBOCYTES (PLATELETS)	G/l	1598	912	120	708	1168
METHEMOGLOBIN (MET-HB)	rel. 1	634	0.009	0.002	0.005	0.012
HEINZ BODIES	rel. 1	230	0.000	0.000	0.000	0.000
COAGULATION						
PROTHROMBIN TIME (PT)	rel. 1	1603	0.81	0.07	0.70	0.97
PARTIAL THROMBOPLASTIN TIME (PTT)	sec	1602	21.2	4.0	14.4	29.9

HISTORICAL DATA - HEMATOLOGY

STRAIN: RAT / HanRcc:WIST (FEMALES)
DATA COLLECTION PERIOD: 29-JAN-02 TO 12-JUN-07

AGE: FROM 19 TO 40 WEEKS

PARAMETER	UNIT	N	MEAN	STAND.DEV	95% TOLERANCE LIMITS	
ERYTHROCYTES (RBC)	T/l	1645	8.05	0.41	7.25	8.86
HEMOGLOBIN (HB)	mmol/l	1645	9.6	0.4	8.8	10.4
HEMATOCRIT (HCT)	rel. l	1645	0.43	0.02	0.39	0.47
MEAN CORPUSCULAR VOLUME (MCV)	fl	1645	53.6	2.4	49.1	58.5
RED CELL VOL. DISTR. WIDTH (RDW)	rel. l	1589	0.133	0.036	0.105	0.249
MEAN CORPUSCULAR HEMOGLOBIN (MCH)	fmol	1645	1.20	0.05	1.10	1.30
MEAN CORPUSCULAR HEMOGLOBIN CONC.	mmol/l	1645	22.33	0.95	20.64	24.32
HEMOGLOBIN CONC. DISTR. WIDTH	mmol/l	1589	1.46	0.15	1.17	1.76
RETICULOCYTE COUNT						
RETICULOCYTE (REL)	rel. l	1645	0.023	0.006	0.014	0.035
RETICULOCYTE (ABS)	G/l	1645	186	43	114	274
MATURITY INDEX (L-RETI)	rel. l	1589	0.563	0.124	0.334	0.783
MATURITY INDEX (M-RETI)	rel. l	1589	0.323	0.056	0.200	0.420
MATURITY INDEX (H-RETI)	rel. l	1589	0.114	0.111	0.009	0.383
LEUKOCYTES, TOTAL (WBC)	G/l	1645	3.64	1.08	1.91	6.14
DIFF.WBC COUNT (REL)						
NEUTROPHILS (NEUT)	rel. l	793	0.197	0.065	0.099	0.343
EOSINOPHILS (EOS)	rel. l	1645	0.021	0.010	0.009	0.045
BASOPHILS (BASO)	rel. l	1645	0.004	0.003	0.001	0.012
LYMPHOCYTES (LYMPH)	rel. l	1645	0.754	0.070	0.598	0.860
MONOCYTES (MONO)	rel. l	1645	0.020	0.007	0.010	0.038
LARGE UNSTAINED CELLS (LUC)	rel. l	1645	0.008	0.004	0.002	0.018
DIFF.WBC COUNT (ABS)						
NEUTROPHILS (NEUT)	G/l	793	0.69	0.25	0.34	1.31
EOSINOPHILS (EOS)	G/l	1645	0.07	0.03	0.03	0.15
BASOPHILS (BASO)	G/l	1645	0.01	0.01	0.00	0.04
LYMPHOCYTES (LYMPH)	G/l	1645	2.77	0.93	1.30	4.86
MONOCYTES (MONO)	G/l	1645	0.07	0.03	0.03	0.15
LARGE UNSTAINED CELLS (LUC)	G/l	1645	0.03	0.02	0.01	0.08
THROMBOCYTES (PLATELETS)	G/l	1645	963	133	723	1235
METHEMOGLOBIN (MET-HB)	rel. l	644	0.009	0.002	0.005	0.012
HEINZ BODIES	rel. l	295	0.000	0.000	0.000	0.000
COAGULATION						
PROTHROMBIN TIME (PT)	rel. l	1643	0.83	0.07	0.70	0.98
PARTIAL THROMBOPLASTIN TIME (PTT)	sec	1633	24.1	7.0	13.5	38.2

HISTORICAL DATA - CLINICAL BIOCHEMISTRY

STRAIN: RAT / HanRcc:WIST (MALES)

AGE: FROM 19 TO 40 WEEKS

DATA COLLECTION PERIOD: 29-JAN-02 TO 12-JUN-07

PARAMETER	UNIT	N	MEAN	STAND.DEV	95% TOLERANCE LIMITS	
GLUCOSE	mmol/l	1613	5.49	1.07	3.83	8.14
UREA	mmol/l	1612	5.36	0.84	3.99	7.19
CREATININE	µmol/l	1611	27.8	3.3	21.9	35.0
BILIRUBIN, TOTAL	µmol/l	1581	1.69	0.35	1.06	2.42
CHOLESTEROL, TOTAL	mmol/l	1612	1.83	0.39	1.15	2.70
TRIGLYCERIDES	mmol/l	1612	0.46	0.24	0.20	1.08
PHOSPHOLIPIDS	mmol/l	1557	1.56	0.25	1.09	2.07
ASPARTATE AMINOTRANSFERASE (ASAT)	U/l	1613	77.4	13.4	59.7	108.2
ALANINE AMINOTRANSFERASE (ALAT)	U/l	1613	33.8	7.1	22.9	48.9
LACTATE DEHYDROGENASE (LDH)	U/l	1410	200.6	159.2	82.8	547.5
GLUTAMATE-DEHYDROGENASE (GLDH)	U/l	1241	8.4	5.2	4.1	17.6
ALKALINE PHOSPHATASE (ALP)	U/l	1611	58.5	13.3	37.3	87.1
GAMMA-GLUTAMYLTRANSFERASE (GGT)	U/l	1575	0.0	0.1	0.0	0.0
CREATINE KINASE (CK)	U/l	1492	170.8	125.8	80.1	479.8
SODIUM	mmol/l	1612	143.7	3.2	138.5	149.2
POTASSIUM	mmol/l	1612	3.74	0.31	3.22	4.47
CHLORIDE	mmol/l	1612	104.3	2.5	99.9	109.2
CALCIUM	mmol/l	1613	2.76	0.11	2.55	2.97
PHOSPHORUS	mmol/l	1612	1.77	0.20	1.37	2.17
PROTEIN, TOTAL	g/l	1612	67.56	2.85	62.10	73.54
ALBUMIN	g/l	1410	42.20	2.03	38.69	46.22
GLOBULIN	g/l	1410	25.37	2.31	21.15	29.84
A/G RATIO	-	1410	1.68	0.21	1.39	2.06

HISTORICAL DATA - CLINICAL BIOCHEMISTRY

STRAIN: RAT / HanRcc:WIST (FEMALES)

AGE: FROM 19 TO 40 WEEKS

DATA COLLECTION PERIOD: 29-JAN-02 TO 12-JUN-07

PARAMETER	UNIT	N	MEAN	STAND.DEV	95% TOLERANCE LIMITS	
GLUCOSE	mmol/l	1642	5.21	0.96	3.67	7.41
UREA	mmol/l	1642	6.54	1.02	4.72	8.70
CREATININE	µmol/l	1641	32.3	4.1	25.0	41.7
BILIRUBIN, TOTAL	µmol/l	1597	2.13	0.57	1.20	3.46
CHOLESTEROL, TOTAL	mmol/l	1640	1.62	0.46	0.85	2.61
TRIGLYCERIDES	mmol/l	1641	0.33	0.11	0.18	0.57
PHOSPHOLIPIDS	mmol/l	1586	1.72	0.39	1.05	2.59
ASPARTATE AMINOTRANSFERASE (ASAT)	U/l	1642	82.7	32.4	56.9	159.8
ALANINE AMINOTRANSFERASE (ALAT)	U/l	1642	32.1	20.2	17.7	77.9
LACTATE DEHYDROGENASE (LDH)	U/l	1428	195.1	107.2	79.3	456.2
GLUTAMATE-DEHYDROGENASE (GLDH)	U/l	1247	15.8	34.9	3.4	81.9
ALKALINE PHOSPHATASE (ALP)	U/l	1639	21.6	6.4	12.1	36.4
GAMMA-GLUTAMYLTRANSFERASE (GGT)	U/l	1593	0.0	0.2	0.0	0.0
CREATINE KINASE (CK)	U/l	1521	153.3	105.1	70.7	414.1
SODIUM	mmol/l	1642	142.7	2.6	137.8	147.8
POTASSIUM	mmol/l	1642	3.27	0.32	2.73	3.90
CHLORIDE	mmol/l	1642	105.1	2.4	100.6	110.3
CALCIUM	mmol/l	1642	2.76	0.12	2.53	2.99
PHOSPHORUS	mmol/l	1642	1.39	0.25	0.90	1.86
PROTEIN, TOTAL	g/l	1642	71.43	4.10	63.62	79.36
ALBUMIN	g/l	1434	49.20	3.39	42.49	55.58
GLOBULIN	g/l	1434	22.33	2.30	18.23	27.08
A/G RATIO	-	1434	2.23	0.39	1.78	2.81

HISTORICAL DATA - URINALYSIS

STRAIN: RAT / HanRcc:WIST (MALES)

AGE: FROM 19 TO 40 WEEKS

DATA COLLECTION PERIOD: 29-JAN-02 TO 12-JUN-07

PARAMETER	UNIT	N	MEAN	STAND.DEV	95% TOLERANCE LIMITS	
VOLUME/18h	ml	1551	8.3	4.6	2.2	22.1
RELATIVE DENSITY	rel. 1	699	1.045	0.023	1.014	1.108
pH	-	1600	6.5	0.5	6.0	7.0
PROTEIN	g/l	1600	0.35	0.25	0.00	0.75
GLUCOSE	mmol/l	1600	0	0	0	0
KETONES	mmol/l	1600	0.6	0.6	0.0	1.5
UROBILINOGEN	µmol/l	1600	0	1	0	0
BILIRUBIN	µmol/l	1600	2	5	0	17
ERYTHROCYTES	per µl	1600	11	19	0	25
LEUCOCYTES	per µl	1600	28	41	0	100

HISTORICAL DATA - URINALYSIS

STRAIN: RAT / HanRcc:WIST (FEMALES)

AGE: FROM 19 TO 40 WEEKS

DATA COLLECTION PERIOD: 29-JAN-02 TO 12-JUN-07

PARAMETER	UNIT	N	MEAN	STAND.DEV	95% TOLERANCE LIMITS	
VOLUME/18h	ml	1581	7.1	5.5	1.5	22.5
RELATIVE DENSITY	rel. 1	711	1.040	0.025	1.010	1.104
pH	-	1630	6.0	0.5	5.0	7.0
PROTEIN	g/l	1630	0.22	0.20	0.00	0.75
GLUCOSE	mmol/l	1630	0	0	0	0
KETONES	mmol/l	1630	0.2	0.3	0.0	1.5
UROBILINOGEN	µmol/l	1630	0	3	0	0
BILIRUBIN	µmol/l	1630	2	5	0	17
ERYTHROCYTES	per µl	1630	3	12	0	10
LEUCOCYTES	per µl	1630	6	21	0	25

APPENDIX V:
PATHOLOGY PART REPORT

PATHOLOGY PART REPORT

LYSO-PHOSPHOLIPASE

Pathology Part to:

90-Day Oral (Gavage) Toxicity Study in the Wistar Rat

Subtitle:

Histopathology Examinations

Study Scientist:

Test Facility:

Harlan Laboratories Ltd.
(former RCC Ltd)
Zelgliweg 1
4452 Itingen/Switzerland

Sponsor:

AB Enzymes GmbH
Feldbergstrasse 78
D-64293 Darmstadt / Germany

Study Identification:

Harlan Laboratories Study **B99180**

Version:

Final

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¹ Animal organ finding table

PREFACE

General Information

Test Item:	Lyso-Phospholipase
Pathology Part to:	90-Day Oral (Gavage) Toxicity Study in the Wistar Rat
Subtitle:	Histopathology Examinations
Sponsor:	AB Enzymes GmbH Feldbergstrasse 78 D-64293 Darmstadt / Germany
Test Facility:	Harlan Laboratories Ltd. (former RCC Ltd) Zelgliweg 1 4452 Itingen / Switzerland

Responsibilities

Study Scientist
(Pathology):
Head of QA:

1 SUMMARY

The purpose of this oral toxicity study was to assess the cumulative toxicity of Lyso-Phospholipase when administered daily to rats by gavage for a period of 90 days (females) or 91 days (males). This study should provide a rational basis for toxicological risk assessment in man.

80 animals were allocated to four groups. The groups comprised 10 animals per sex, which were sacrificed after 90 days for female and 91 days for males of treatment. The animals received the test item, Lyso-Phospholipase, at concentrations of 100, 300 and 1000 mg/kg/day (Group 2, Group 3 and Group 4, respectively) by gavage. Control animals (Group 1) received the vehicle (bidistilled water) only.

At the end of the treatment period all animals were weighed, sacrificed, necropsied and examined *post mortem*. Histological examination was performed on all study plan organs and tissues from control and high dose animals, and on all gross lesions from all animals.

Under the conditions of this study, there were no premature deaths. All animals survived the scheduled study period.

At necropsy, performed at the end of treatment period, no test item-related macroscopic findings were recorded.

The test item, Lyso-Phospholipase produced no histological evidence of toxicological properties in the organs and tissues examined.

2 MATERIALS AND METHODS

2.1 Allocation

Allocation and Dose Levels mg/kg bw/day		Group 1 control [*] 0	Group 2 100	Group 3 300	Group 4 1000
Males	A	1 - 10	11 - 20	21 - 30	31 - 40
Females	A	41 - 50	51 - 60	61 - 70	71 - 80

* Control animals were treated with the vehicle, bidistilled water, only
A Main study animals

2.2 Necropsy and Histopathology

Necropsies and histological preparation of the tissues were performed at Harlan Laboratories Ltd., Itingen / Switzerland. Samples of the following tissues and organs were collected from all animals at necropsy and, unless otherwise indicated, fixed in neutral phosphate buffered 4% formaldehyde solution:

Tissues / Organs	Weight	Collect	Examine
Adrenal glands	X	X	X
Aorta		X	X
Bone (sternum, femur including joint)		X	X
Bone marrow (femur)		X	X
Brain - including section of medulla/pons, cerebral and cerebellar cortex	X	X	X
Cecum		X	X
Colon		X	X
Duodenum		X	X
Epididymides (fixed in Bouin's solution)	X	X	X
Esophagus		X	X
Eyes w/optic nerve (fixed in Davidson's solution)		X	X
Harderian gland (fixed in Davidson's solution)		X	X
Heart including auricles	X	X	X
Ileum, with Peyer's patches		X	X
Jejunum with Peyer's patches		X	X

Tissues / Organs	Weight	Collect	Examine
Kidneys	X	X	X
Larynx		X	X
Lacrimal gland, exorbital		X	X
Liver	X	X	X
Lungs, filled w/formalin at necropsy		X	X
Lymph nodes – mesenteric and mandibular		X	X
Mammary gland area		X	X
Nasal cavity		X	X
Ovaries	X	X	X
Pancreas		X	X
Pharynx		X	X
Pituitary gland		X	X
Prostate gland incl. coagulating glands		X	X
Rectum		X	X
Salivary glands - mandibular, sublingual		X	X
Sciatic nerve		X	X
Seminal vesicles		X	X
Skeletal muscle		X	X
Skin		X	X
Spinal cord - cervical, midthoracic, lumbar		X	X
Spleen	X	X	X
Stomach		X	X
Testes (fixed in Bouin's solution)	X	X	X
Thymus	X	X	X
Thyroid (incl. parathyroid gland, if possible)		X	X
Tongue		X	X
Trachea		X	X
Urinary bladder, filled w/formalin at necropsy		X	X
Uterus with cervix as appropriate	X	X	X
Vagina		X	X
All gross lesions		X	X

Resulting sections were stained by hematoxylin and eosin. Sections from all animals of groups 1 and 4 and all occurring gross lesions of all animals were examined by light microscopy.

2.3 Data Compilation

The animal data and necropsy findings were transferred electronically via transfer file into the PathData System.

The microscopic findings were recorded during histopathologic examination by the pathologist and directly entered into the PathData System. The slides were evaluated during February 2009.

Histologic changes were described, wherever possible, according to distribution, severity and morphologic character. Severity scores were assigned as given under "Explanation of Codes and Symbols".

All microscopic findings are listed in the "Table of Individual Microscopic Findings", along with an explanation of the codes and symbols used. Computer-generated incidence tables derived from these data are also presented as well as the complete narrative of the macroscopic and microscopic findings.

2.4 Peer Review

The following sections were reviewed by _____ (Pathology, at Harlan Laboratories Ltd., Itingen / Switzerland): all organs of animal No. 1, 36, 44 and 73.

The assessment of the study pathologist and reviewing pathologist compared favourable.

3 RESULTS

3.1 Mortality

All animals survived the scheduled study period.

3.2 Organ Weights

There were no differences indicating an effect of the test item. A few statistically significant deviations in average organ weights at the end of treatment period were considered to be incidental, reflecting the usual individual variability.

3.3 Macroscopic Findings

There were no gross lesions that could be attributed to treatment with the test item. All gross lesions recorded were considered to be within the range of normal background alterations.

3.4 Microscopic Findings

The test item Lyso-Phospholipase produced no histological evidence of toxicological properties in the organs and tissues examined. All findings recorded were within the range of normal background lesions, which may be recorded in animals of this strain and age.

4 DISCUSSION AND CONCLUSION

Under the conditions of this experiment, no test item-related macroscopic findings were recorded. The test item, Lyso-Phospholipase produced no histological evidence of toxicological properties in the organs and tissues examined.

**PATHOLOGY REPORT
 SUMMARY TABLES**

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

	SEX :	MALE			
	DOSE GROUP:	01	02	03	04
	NO.ANIMALS:	10	10	10	10
<hr/>					
HEART	:	10	-	-	10
- Mononuclear foci	:	3	-	-	2
<hr/>					
TRACHEA	:	10	-	-	10
- Glandular dilation	:	1	-	-	1
- Inflammat.infiltrate:	:	2	-	-	2
<hr/>					
LIVER	:	10	-	-	10
- Inflammat. cell foci:	:	8	-	-	9
- Fatty change	:	2	-	-	3
- Glycogen increase	:	5	-	-	2
- Hemopoietic foci	:	1	-	-	-
- Peribiliary infilt. :	:	1	-	-	-
<hr/>					
SPLEEN	:	10	-	-	10
- Extram. hemopoiesis :	:	6	-	-	4
- Hemosiderin	:	9	-	-	10
<hr/>					
MESENT. LYMPH NODE	:	10	-	-	10
- Lymphoid hyperplasia:	:	3	-	-	4
- Hemosiderin d	:	3	-	-	3
<hr/>					
KIDNEYS	:	10	-	-	10
- Hyaline droplets	:	3	-	-	3
- Tubular basophilia	:	3	-	-	2
- Tubular casts	:	-	-	-	1
- Tubular dilation	:	-	-	-	1
- Tubular vacuolation :	:	1	-	-	-
- Pelvic dilation	:	-	-	-	1
- Pyelitis	:	-	-	-	1
<hr/>					
STOMACH	:	10	1	1	10
- Glandular dilation	:	-	-	-	2
- Ulcer/erosion, Gld. :	:	-	-	-	1
- No histol. correlate:	:	1	1	1	-

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	MALE			
DOSE GROUP:	01	02	03	04
NO. ANIMALS:	10	10	10	10
PEYERS PATCHES JEJ. :	10	-	-	10
- Mineralization :	3	-	-	5
- Lymphoid hyperplasia:	1	-	-	4
ILEUM :	10	-	-	10
- Congestion :	-	-	-	1
PEYERS PATCHES ILEUM :	10	-	-	10
- Lymphoid hyperplasia:	7	-	-	6
RECTUM :	10	-	-	10
- Luminal dilation :	-	-	-	1
LUNGS :	10	-	-	10
- Vasc. mineralization:	5	-	-	7
- Alveolar macrophages:	4	-	-	6
- Alveolar hemorrhage :	5	-	-	1
- Osseous metaplasia :	1	-	-	-
- No histol. correlate:	-	-	-	1
THYMUS :	10	3	-	10
- Atrophy / involution:	5	3	-	7
- Cyst(s) :	4	1	-	3
- Hemorrhage :	-	2	-	-
- Hemosiderin deposits:	-	1	-	-
- Congestion :	1	-	-	1
TESTES :	10	-	-	10
- Tubular atrophy :	-	-	-	1
EPIDIDYMIDES :	10	-	-	10
- Mononuclear foci :	3	-	-	1
- Vacuolation, epithel.:	2	-	-	2
MANDIBULAR GLANDS :	10	-	-	10
- Acinar vacuolation :	2	-	-	1

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	MALE			
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
SUBLINGUAL GLANDS :	10	-	-	10
- Parotid gland ectopia :	-	-	-	1
MANDIB.LYMPH NODES :	10	-	1	10
- Hemosiderin deposits:	-	-	-	1
- Congestion :	-	-	1	-
THYROID GLAND :	10	-	-	10
- Ultimobranchial cyst:	-	-	-	1
ADRENAL CORTICES :	10	-	-	10
- Vacuolation, Z.fasc.:	3	-	-	1
SKIN/SUBCUTIS :	10	-	1	10
- No histol. correlate:	-	-	1	-
EYES :	10	-	-	10
- Retro-orb.hemorrhage:	8	-	-	6
HARDERIAN GLANDS :	10	-	-	10
- Porphyrin deposits :	8	-	-	9
- Mononuclear Infiltr.:	1	-	-	2
SKELETAL MUSCLE :	10	-	-	10
- Mononuclear infiltr.:	2	-	-	2
TONGUE :	10	-	-	10
- Mononuclear infilt. :	1	-	-	-
PROSTATE GLAND :	10	-	-	10
- Inflammation :	-	-	-	1
BONE MARROW, FEMUR :	10	-	-	10
- Fatty replacement :	8	-	-	9

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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	MALE			
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
LACRIMAL GLANDS,EXO. :	10	-	-	10
- Harderian gland.change:	3	-	-	3
- Cyto/karyomegaly :	5	-	-	3
- Mononuclear Infiltr.:	1	-	-	2
PITUITARY GLAND :	10	-	-	9
- Cyst :	2	-	-	2
SPINAL CORD, CERVIC. :	10	-	-	10
- Hemorrhage :	1	-	-	-
SPINAL CORD, THORAC. :	10	-	-	10
- Hemorrhage :	-	-	-	1
BONE, STERNUM :	10	-	-	10
- Chondromucin.degen.:	-	-	-	1
LARYNX :	10	-	-	10
- Inflammat. exudates :	1	-	-	-
- Inflammat.infilt. :	5	-	-	3
- Desiccated secretion:	1	-	-	1
NASAL CAVITIES :	10	-	-	10
- Hyaline inclusion :	1	-	-	1
PHARYNX :	10	-	-	10
- Mononuclear Infiltr.:	2	-	-	1
- Inflammat.infilt. :	-	-	-	1

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NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	FEMALE			
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
HEART :	10	-	-	10
- Mononuclear foci :	-	-	-	1
TRACHEA :	10	-	-	10
- Glandular dilation :	2	-	-	-
- Inflammat.infiltrate:	1	-	-	1
LIVER :	10	-	-	10
- Inflammat. cell foci:	7	-	-	5
- Fatty change :	1	-	-	3
- Glycogen increase :	4	-	-	4
- Congestion :	-	-	-	1
- Kupffer C.Siderosis.:	-	-	-	1
- Focal necrosis :	-	-	-	1
- Peribiliary infilt. :	1	-	-	1
SPLEEN :	10	1	-	10
- Extram. hemopoiesis :	4	1	-	3
- Hemosiderin :	10	1	-	10
MESENT. LYMPH NODE :	10	-	-	10
- Lymphoid hyperplasia:	3	-	-	3
- Hemosiderin d :	-	-	-	1
KIDNEYS :	10	1	-	10
- Tubular basophilia :	1	-	-	2
- Pelvic dilation :	-	-	-	1
- Papillary mineraliz.:	1	-	-	1
- Corticomed.mineral. :	1	-	-	-
- Hypoplasia :	-	1	-	-
STOMACH :	10	-	-	10
- Glandular dilation :	2	-	-	1
- Vacuolation :	1	-	-	-
- Hyperkeratosis :	1	-	-	-
- No histol. correlate:	-	-	-	1

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 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	FEMALE			
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
PEYERS PATCHES JEJ. :	10	-	-	10
- Mineralization :	3	-	-	4
- Lymphoid hyperplasia:	2	-	-	-
PEYERS PATCHES ILEUM :	10	-	-	10
- Lymphoid hyperplasia:	9	-	-	8
LUNGS :	10	-	-	10
- Vasc. mineralization:	6	-	-	5
- Alveolar macrophages:	7	-	-	4
- Alveolar hemorrhage :	1	-	-	1
- Microgranuloma :	1	-	-	-
THYMUS :	10	-	-	10
- Atrophy / involution:	7	-	-	6
- Cyst(s) :	5	-	-	6
OVARIES :	10	-	1	10
- Congestion :	-	-	1	-
SUBLINGUAL GLANDS :	10	-	-	10
- Parotid gland ectopia :	2	-	-	-
- Ductular hyperplasia:	1	-	-	-
PANCREAS :	10	-	-	10
- Acinar cell atrophy :	-	-	-	1
- Acinar C.Vacuolation:	3	-	-	2
- Mononuclear Infiltr.:	1	-	-	1
- Ductular hyperplasia:	-	-	-	1
MANDIB.LYMPH NODES :	10	1	-	10
- Lymphoid hyperplasia:	1	-	-	2
- Hemosiderin deposits:	-	1	-	-
- Congestion :	1	1	-	-

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	FEMALE			
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
THYROID GLAND :	10	-	-	10
- Ultimobranchial cyst:	1	-	-	1
- Thymic remnant :	1	-	-	-
PARATHYROID GLANDS :	8	-	-	9
- Thymic remnant :	1	-	-	-
ADRENAL CORTICES :	10	-	-	10
- Vacuolation, Z.fasc.:	-	-	-	1
- Subcaps.C.hyperplas.:	1	-	-	-
- Congestion :	1	-	-	-
SCIATIC NERVES :	10	-	-	10
- Axonal degeneration :	-	-	-	1
SKIN/SUBCUTIS :	10	1	-	10
- Epidermal cyst :	1	-	-	-
- No histol. correlate:	-	1	-	-
EYES :	10	-	-	10
- Retro-orb.hemorrhage:	8	-	-	9
- Peri-orbit.inflam. :	2	-	-	2
HARDERIAN GLANDS :	10	-	-	10
- Porphyrin deposits :	6	-	-	5
- Mononuclear Infiltr.:	1	-	-	2
SKELETAL MUSCLE :	10	-	-	10
- Mononuclear infiltr.:	1	-	-	3
- Myodegeneration :	2	-	-	1
UTERUS :	10	-	-	10
- Luminal dilation :	3	-	-	3
CERVIX :	10	-	-	10
- Epidermal cyst :	1	-	-	-

**PATHOLOGY REPORT
 SUMMARY TABLES**

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 Harlan Laboratories B99180

TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

	SEX :					FEMALE
	DOSE GROUP:	01	02	03	04	
	NO.ANIMALS:	10	10	10	10	
VAGINA	:	10	-	-	10	
- Proestrus	:	3	-	-	2	
- Estrus	:	3	-	-	4	
- Metestrus	:	2	-	-	-	
- Diestrus	:	2	-	-	4	
BONE MARROW, FEMUR	:	10	-	-	10	
- Fatty replacement	:	9	-	-	9	
- Hemosiderin deposits:	:	1	-	-	2	
LACRIMAL GLANDS, EXO.	:	10	-	-	10	
- Harderian gland change:	:	1	-	-	-	
- Mononuclear Infiltr.:	:	1	-	-	-	
PITUITARY GLAND	:	10	-	-	10	
- Cyst	:	3	-	-	2	
LARYNX	:	10	-	-	10	
- Inflammation infiltr.	:	4	-	-	5	
- Desiccated secretion:	:	-	-	-	1	
NASAL CAVITIES	:	10	-	-	10	
- Hyaline inclusion	:	1	-	-	1	
BODY CAVITIES	:	-	-	-	1	
- Fat Necrosis	:	-	-	-	1	

**PATHOLOGY REPORT
 SUMMARY TABLES**

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	MALE			
DOSE GROUP:	01	02	03	04
NO. ANIMALS:	10	10	10	10
<hr/>				
HEART :	10	-	-	10
- Mononuclear foci				
GRADE 1 :	2	-	-	1
GRADE 2 :	1	-	-	1
TOTAL AFFECTED :	3	-	-	2
MEAN SEVERITY :	1.3	-	-	1.5
<hr/>				
TRACHEA :	10	-	-	10
- Glandular dilation				
GRADE 1 :	1	-	-	1
TOTAL AFFECTED :	1	-	-	1
MEAN SEVERITY :	1.0	-	-	1.0
<hr/>				
- Inflammat.infiltrate				
GRADE 1 :	2	-	-	2
TOTAL AFFECTED :	2	-	-	2
MEAN SEVERITY :	1.0	-	-	1.0
<hr/>				
LIVER :	10	-	-	10
- Inflammat. cell foci				
GRADE 1 :	7	-	-	9
GRADE 2 :	1	-	-	-
TOTAL AFFECTED :	8	-	-	9
MEAN SEVERITY :	1.1	-	-	1.0
<hr/>				
- Fatty change				
GRADE 1 :	2	-	-	3
TOTAL AFFECTED :	2	-	-	3
MEAN SEVERITY :	1.0	-	-	1.0
<hr/>				

**PATHOLOGY REPORT
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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

	SEX :					MALE
DOSE GROUP:		01	02	03	04	
NO. ANIMALS:		10	10	10	10	
<hr/>						
LIVER	CONT'D.	10	-	-	10	
- Glycogen increase						
GRADE 1 :		4	-	-	2	
GRADE 2 :		1	-	-	-	
TOTAL AFFECTED :		5	-	-	2	
MEAN SEVERITY :		1.2	-	-	1.0	
.....						
- Hemopoietic foci						
GRADE 1 :		1	-	-	-	
TOTAL AFFECTED :		1	-	-	-	
MEAN SEVERITY :		1.0	-	-	-	
.....						
- Peribiliary infilt.						
GRADE 1 :		1	-	-	-	
TOTAL AFFECTED :		1	-	-	-	
MEAN SEVERITY :		1.0	-	-	-	
<hr/>						
SPLEEN		10	-	-	10	
- Extram. hemopoiesis						
GRADE 1 :		6	-	-	4	
TOTAL AFFECTED :		6	-	-	4	
MEAN SEVERITY :		1.0	-	-	1.0	
.....						
- Hemosiderin						
GRADE 1 :		9	-	-	10	
TOTAL AFFECTED :		9	-	-	10	
MEAN SEVERITY :		1.0	-	-	1.0	

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	MALE			
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
<hr/>				
MESENT. LYMPH NODE :	10	-	-	10
- Lymphoid hyperplasia				
GRADE 1 :	1	-	-	4
GRADE 2 :	2	-	-	-
TOTAL AFFECTED :	3	-	-	4
MEAN SEVERITY :	1.7	-	-	1.0
.....				
- Hemosiderin d				
GRADE 1 :	3	-	-	3
TOTAL AFFECTED :	3	-	-	3
MEAN SEVERITY :	1.0	-	-	1.0
<hr/>				
KIDNEYS :	10	-	-	10
- Hyaline droplets				
GRADE 1 :	3	-	-	3
TOTAL AFFECTED :	3	-	-	3
MEAN SEVERITY :	1.0	-	-	1.0
.....				
- Tubular basophilia				
GRADE 1 :	3	-	-	2
TOTAL AFFECTED :	3	-	-	2
MEAN SEVERITY :	1.0	-	-	1.0
.....				
- Tubular casts				
GRADE 1 :	-	-	-	1
TOTAL AFFECTED :	-	-	-	1
MEAN SEVERITY :	-	-	-	1.0
.....				
- Tubular dilation				
GRADE 1 :	-	-	-	1
TOTAL AFFECTED :	-	-	-	1
MEAN SEVERITY :	-	-	-	1.0
.....				

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 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :					MALE
DOSE GROUP:	01	02	03	04	
NO.ANIMALS:	10	10	10	10	
<hr/>					
PEYERS PATCHES JEJ. :	10	-	-	10	
- Lymphoid hyperplasia					
GRADE 1 :	1	-	-	4	
TOTAL AFFECTED :	1	-	-	4	
MEAN SEVERITY :	1.0	-	-	1.0	
<hr/>					
PEYERS PATCHES ILEUM :	10	-	-	10	
- Lymphoid hyperplasia					
GRADE 1 :	6	-	-	6	
GRADE 2 :	1	-	-	-	
TOTAL AFFECTED :	7	-	-	6	
MEAN SEVERITY :	1.1	-	-	1.0	
<hr/>					
LUNGS :	10	-	-	10	
- Vasc. mineralization					
GRADE 1 :	5	-	-	7	
TOTAL AFFECTED :	5	-	-	7	
MEAN SEVERITY :	1.0	-	-	1.0	
<hr/>					
- Alveolar macrophages					
GRADE 1 :	4	-	-	5	
GRADE 2 :	-	-	-	1	
TOTAL AFFECTED :	4	-	-	6	
MEAN SEVERITY :	1.0	-	-	1.2	
<hr/>					
- Alveolar hemorrhage					
GRADE 1 :	5	-	-	1	
TOTAL AFFECTED :	5	-	-	1	
MEAN SEVERITY :	1.0	-	-	1.0	
<hr/>					

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

	SEX :	MALE			
	DOSE GROUP:	01	02	03	04
	NO.ANIMALS:	10	10	10	10
<hr/>					
MANDIB.LYMPH NODES	:	10	-	1	10
- Congestion					
GRADE 1 :		-	-	1	-
TOTAL AFFECTED :		-	-	1	-
MEAN SEVERITY :		-	-	1.0	-
<hr/>					
ADRENAL CORTICES	:	10	-	-	10
- Vacuolation, Z.fasc.					
GRADE 1 :		2	-	-	1
GRADE 2 :		1	-	-	-
TOTAL AFFECTED :		3	-	-	1
MEAN SEVERITY :		1.3	-	-	1.0
<hr/>					
EYES	:	10	-	-	10
- Retro-orb.hemorrhage					
GRADE 1 :		8	-	-	5
GRADE 2 :		-	-	-	1
TOTAL AFFECTED :		8	-	-	6
MEAN SEVERITY :		1.0	-	-	1.2
<hr/>					
HARDERIAN GLANDS	:	10	-	-	10
- Porphyrin deposits					
GRADE 1 :		6	-	-	9
GRADE 2 :		2	-	-	-
TOTAL AFFECTED :		8	-	-	9
MEAN SEVERITY :		1.3	-	-	1.0

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 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

	SEX :	MALE			
	DOSE GROUP:	01	02	03	04
	NO. ANIMALS:	10	10	10	10
<hr/>					
SPINAL CORD, CERVIC. :		10	-	-	10
- Hemorrhage					
GRADE 1 :		1	-	-	-
TOTAL AFFECTED :		1	-	-	-
MEAN SEVERITY :		1.0	-	-	-
<hr/>					
SPINAL CORD, THORAC. :		10	-	-	10
- Hemorrhage					
GRADE 1 :		-	-	-	1
TOTAL AFFECTED :		-	-	-	1
MEAN SEVERITY :		-	-	-	1.0
<hr/>					
BONE, STERNUM :		10	-	-	10
- Chondromucin.degen.					
GRADE 1 :		-	-	-	1
TOTAL AFFECTED :		-	-	-	1
MEAN SEVERITY :		-	-	-	1.0
<hr/>					
LARYNX :		10	-	-	10
- Inflammat. exudates					
GRADE 1 :		1	-	-	-
TOTAL AFFECTED :		1	-	-	-
MEAN SEVERITY :		1.0	-	-	-
<hr/>					
- Inflammat.infilt.					
GRADE 1 :		5	-	-	3
TOTAL AFFECTED :		5	-	-	3
MEAN SEVERITY :		1.0	-	-	1.0
<hr/>					

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

	SEX :					MALE
DOSE GROUP:		01	02	03	04	
NO.ANIMALS:		10	10	10	10	
<hr/>						
LARYNX	CONT'D.	10	-	-	10	
- Desiccated secretion						
	GRADE 1 :	-	-	-	1	
	GRADE 2 :	1	-	-	-	
	TOTAL AFFECTED :	1	-	-	1	
	MEAN SEVERITY :	2.0	-	-	1.0	
<hr/>						
NASAL CAVITIES	:	10	-	-	10	
- Hyaline inclusion						
	GRADE 1 :	1	-	-	1	
	TOTAL AFFECTED :	1	-	-	1	
	MEAN SEVERITY :	1.0	-	-	1.0	
<hr/>						
PHARYNX	:	10	-	-	10	
- Mononuclear Infiltr.						
	GRADE 1 :	2	-	-	1	
	TOTAL AFFECTED :	2	-	-	1	
	MEAN SEVERITY :	1.0	-	-	1.0	
<hr/>						
- Inflammat.infilt.						
	GRADE 1 :	-	-	-	1	
	TOTAL AFFECTED :	-	-	-	1	
	MEAN SEVERITY :	-	-	-	1.0	

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :					FEMALE
DOSE GROUP:	01	02	03	04	
NO.ANIMALS:	10	10	10	10	

LIVER	CONT'D.	10	-	-	10
- Kupffer C.Siderosis.					
GRADE 3 :		-	-	-	1
TOTAL AFFECTED :		-	-	-	1
MEAN SEVERITY :		-	-	-	3.0

.....

- Focal necrosis					
GRADE 3 :		-	-	-	1
TOTAL AFFECTED :		-	-	-	1
MEAN SEVERITY :		-	-	-	3.0

.....

- Peribiliary infilt.					
GRADE 1 :		1	-	-	1
TOTAL AFFECTED :		1	-	-	1
MEAN SEVERITY :		1.0	-	-	1.0

SPLEEN	:	10	1	-	10
- Extram. hemopoiesis					
GRADE 1 :		4	1	-	2
GRADE 2 :		-	-	-	1
TOTAL AFFECTED :		4	1	-	3
MEAN SEVERITY :		1.0	1.0	-	1.3

.....

- Hemosiderin					
GRADE 1 :		1	1	-	1
GRADE 2 :		9	-	-	9
TOTAL AFFECTED :		10	1	-	10
MEAN SEVERITY :		1.9	1.0	-	1.9

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	FEMALE			
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
<hr/>				
MESENT. LYMPH NODE :	10	-	-	10
- Lymphoid hyperplasia				
GRADE 1 :	3	-	-	3
TOTAL AFFECTED :	3	-	-	3
MEAN SEVERITY :	1.0	-	-	1.0
.....				
- Hemosiderin d				
GRADE 1 :	-	-	-	1
TOTAL AFFECTED :	-	-	-	1
MEAN SEVERITY :	-	-	-	1.0
<hr/>				
KIDNEYS :	10	1	-	10
- Tubular basophilia				
GRADE 1 :	1	-	-	2
TOTAL AFFECTED :	1	-	-	2
MEAN SEVERITY :	1.0	-	-	1.0
.....				
- Papillary mineraliz.				
GRADE 1 :	1	-	-	1
TOTAL AFFECTED :	1	-	-	1
MEAN SEVERITY :	1.0	-	-	1.0
.....				
- Corticomed.mineral.				
GRADE 1 :	1	-	-	-
TOTAL AFFECTED :	1	-	-	-
MEAN SEVERITY :	1.0	-	-	-
<hr/>				
STOMACH :	10	-	-	10
- Glandular dilation				
GRADE 1 :	2	-	-	1
TOTAL AFFECTED :	2	-	-	1
MEAN SEVERITY :	1.0	-	-	1.0
.....				

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	FEMALE			
DOSE GROUP:	01	02	03	04
NO. ANIMALS:	10	10	10	10
<hr/>				
STOMACH CONT'D.	10	-	-	10
- Vacuolation				
GRADE 2 :	1	-	-	-
TOTAL AFFECTED :	1	-	-	-
MEAN SEVERITY :	2.0	-	-	-
.....				
- Hyperkeratosis				
GRADE 1 :	1	-	-	-
TOTAL AFFECTED :	1	-	-	-
MEAN SEVERITY :	1.0	-	-	-
<hr/>				
PEYERS PATCHES JEJ. :	10	-	-	10
- Mineralization				
GRADE 1 :	2	-	-	4
GRADE 2 :	1	-	-	-
TOTAL AFFECTED :	3	-	-	4
MEAN SEVERITY :	1.3	-	-	1.0
.....				
- Lymphoid hyperplasia				
GRADE 1 :	2	-	-	-
TOTAL AFFECTED :	2	-	-	-
MEAN SEVERITY :	1.0	-	-	-
<hr/>				
PEYERS PATCHES ILEUM :	10	-	-	10
- Lymphoid hyperplasia				
GRADE 1 :	7	-	-	7
GRADE 2 :	2	-	-	1
TOTAL AFFECTED :	9	-	-	8
MEAN SEVERITY :	1.2	-	-	1.1

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	FEMALE			
DOSE GROUP:	01	02	03	04
NO. ANIMALS:	10	10	10	10
<hr/>				
LUNGS :	10	-	-	10
- Vasc. mineralization				
GRADE 1 :	5	-	-	5
GRADE 2 :	1	-	-	-
TOTAL AFFECTED :	6	-	-	5
MEAN SEVERITY :	1.2	-	-	1.0
.....				
- Alveolar macrophages				
GRADE 1 :	7	-	-	4
TOTAL AFFECTED :	7	-	-	4
MEAN SEVERITY :	1.0	-	-	1.0
.....				
- Alveolar hemorrhage				
GRADE 1 :	1	-	-	1
TOTAL AFFECTED :	1	-	-	1
MEAN SEVERITY :	1.0	-	-	1.0
.....				
- Microgranuloma				
GRADE 1 :	1	-	-	-
TOTAL AFFECTED :	1	-	-	-
MEAN SEVERITY :	1.0	-	-	-
<hr/>				
THYMUS :	10	-	-	10
- Atrophy / involution				
GRADE 1 :	7	-	-	5
GRADE 3 :	-	-	-	1
TOTAL AFFECTED :	7	-	-	6
MEAN SEVERITY :	1.0	-	-	1.3

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	FEMALE			
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
<hr/>				
SUBLINGUAL GLANDS :	10	-	-	10
- Parotid gland ectopia				
GRADE 1 :	2	-	-	-
TOTAL AFFECTED :	2	-	-	-
MEAN SEVERITY :	1.0	-	-	-
.....				
- Ductular hyperplasia				
GRADE 1 :	1	-	-	-
TOTAL AFFECTED :	1	-	-	-
MEAN SEVERITY :	1.0	-	-	-
<hr/>				
PANCREAS :	10	-	-	10
- Acinar cell atrophy				
GRADE 1 :	-	-	-	1
TOTAL AFFECTED :	-	-	-	1
MEAN SEVERITY :	-	-	-	1.0
.....				
- Acinar C.Vacuolation				
GRADE 1 :	3	-	-	2
TOTAL AFFECTED :	3	-	-	2
MEAN SEVERITY :	1.0	-	-	1.0
.....				
- Mononuclear Infiltr.				
GRADE 1 :	1	-	-	1
TOTAL AFFECTED :	1	-	-	1
MEAN SEVERITY :	1.0	-	-	1.0
.....				
- Ductular hyperplasia				
GRADE 1 :	-	-	-	1
TOTAL AFFECTED :	-	-	-	1
MEAN SEVERITY :	-	-	-	1.0

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
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SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	FEMALE			
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
<hr/>				
MANDIB.LYMPH NODES :	10	1	-	10
- Lymphoid hyperplasia				
GRADE 1 :	1	-	-	2
TOTAL AFFECTED :	1	-	-	2
MEAN SEVERITY :	1.0	-	-	1.0
.....				
- Hemosiderin deposits				
GRADE 1 :	-	1	-	-
TOTAL AFFECTED :	-	1	-	-
MEAN SEVERITY :	-	1.0	-	-
.....				
- Congestion				
GRADE 1 :	1	1	-	-
TOTAL AFFECTED :	1	1	-	-
MEAN SEVERITY :	1.0	1.0	-	-
<hr/>				
ADRENAL CORTICES :	10	-	-	10
- Vacuolation, Z.fasc.				
GRADE 1 :	-	-	-	1
TOTAL AFFECTED :	-	-	-	1
MEAN SEVERITY :	-	-	-	1.0
.....				
- Subcaps.C.hyperplas.				
GRADE 1 :	1	-	-	-
TOTAL AFFECTED :	1	-	-	-
MEAN SEVERITY :	1.0	-	-	-
.....				
- Congestion				
GRADE 1 :	1	-	-	-
TOTAL AFFECTED :	1	-	-	-
MEAN SEVERITY :	1.0	-	-	-

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 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	FEMALE			
DOSE GROUP:	01	02	03	04
NO.ANIMALS:	10	10	10	10
SCIATIC NERVES :	10	-	-	10
- Axonal degeneration				
GRADE 1 :	-	-	-	1
TOTAL AFFECTED :	-	-	-	1
MEAN SEVERITY :	-	-	-	1.0
SKIN/SUBCUTIS :	10	1	-	10
- Epidermal cyst				
GRADE 2 :	1	-	-	-
TOTAL AFFECTED :	1	-	-	-
MEAN SEVERITY :	2.0	-	-	-
EYES :	10	-	-	10
- Retro-orb.hemorrhage				
GRADE 1 :	6	-	-	9
GRADE 2 :	2	-	-	-
TOTAL AFFECTED :	8	-	-	9
MEAN SEVERITY :	1.3	-	-	1.0
.....				
- Peri-orbit.inflam.				
GRADE 1 :	1	-	-	2
GRADE 2 :	1	-	-	-
TOTAL AFFECTED :	2	-	-	2
MEAN SEVERITY :	1.5	-	-	1.0
HARDERIAN GLANDS :	10	-	-	10
- Porphyrin deposits				
GRADE 1 :	6	-	-	5
TOTAL AFFECTED :	6	-	-	5
MEAN SEVERITY :	1.0	-	-	1.0
.....				

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 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :					FEMALE
DOSE GROUP:	01	02	03	04	
NO.ANIMALS:	10	10	10	10	
<hr/>					
BONE MARROW, FEMUR :	10	-	-	10	
- Hemosiderin deposits					
GRADE 1 :	1	-	-	2	
TOTAL AFFECTED :	1	-	-	2	
MEAN SEVERITY :	1.0	-	-	1.0	
<hr/>					
LACRIMAL GLANDS,EXO. :	10	-	-	10	
- Harderian gland change					
GRADE 1 :	1	-	-	-	
TOTAL AFFECTED :	1	-	-	-	
MEAN SEVERITY :	1.0	-	-	-	
<hr/>					
- Mononuclear Infiltr.					
GRADE 1 :	1	-	-	-	
TOTAL AFFECTED :	1	-	-	-	
MEAN SEVERITY :	1.0	-	-	-	
<hr/>					
PITUITARY GLAND :	10	-	-	10	
- Cyst					
GRADE 1 :	3	-	-	2	
TOTAL AFFECTED :	3	-	-	2	
MEAN SEVERITY :	1.0	-	-	1.0	
<hr/>					
LARYNX :	10	-	-	10	
- Inflammation infiltr.					
GRADE 1 :	4	-	-	5	
TOTAL AFFECTED :	4	-	-	5	
MEAN SEVERITY :	1.0	-	-	1.0	
<hr/>					

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 TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

SUMMARY INCIDENCE OF GRADINGS BY ORGAN/GROUP/SEX
 STATUS AT NECROPSY: K0

SEX :	FEMALE				
DOSE GROUP:	01	02	03	04	
NO. ANIMALS:	10	10	10	10	
LARYNX	CONT'D.	10	-	-	10
- Desiccated secretion					
GRADE 1 :	-	-	-	1	
TOTAL AFFECTED :	-	-	-	1	
MEAN SEVERITY :	-	-	-	1.0	
NASAL CAVITIES :	10	-	-	10	
- Hyaline inclusion					
GRADE 1 :	1	-	-	1	
TOTAL AFFECTED :	1	-	-	1	
MEAN SEVERITY :	1.0	-	-	1.0	
BODY CAVITIES :	-	-	-	1	
- Fat Necrosis					
GRADE 3 :	-	-	-	1	
TOTAL AFFECTED :	-	-	-	1	
MEAN SEVERITY :	-	-	-	3.0	

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SPONSOR : AB Enzymes GmbH *PathData@System* V6.2b5

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 01, FEMALE

NECROPSY OBSERVATION

CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 45

.....

UTERUS

- 01: BOTH HORNS: DILATION, D=5 MM. - Luminal dilation, (cyclic
change).

.....

ANIMAL NO: 48

.....

MANDIBULAR LYMPH NODES

- 01: DISCOLORATION, DARK RED. - Congestion, bilateral, grade 1.

.....

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CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 02, MALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 13
.....

THYMUS
- 01: FOCUS/FOCI, SEVERAL, D=1 MM, - Hemorrhage, focal, grade 1.
DARK RED.
.....

ANIMAL NO: 14
.....

THYMUS
- 01: FOCUS/FOCI, ISOLATED, D=1 MM, - Hemosiderin deposits, focal,
DARK RED. grade 1.
.....

ANIMAL NO: 15
.....

THYMUS
- 01: FOCUS/FOCI, MANY, D=1 MM, - Hemorrhage, multifocal, grade 1.
DARK RED.
.....

ANIMAL NO: 18
.....

STOMACH
- 01: MUCOSA, FUNDUS: FOCUS/FOCI, - No histological correlate.
ISOLATED, D=3X1 MM, REDDISH.
.....

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 02, FEMALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 51
.....

SKIN/SUBCUTIS

- 01: DORSO-LUMBAR REGION, LEFT
 SIDE: ALOPECIA, D=20 MM,
 MODERATE.

- No histological correlate.

ANIMAL NO: 53
.....

SPLEEN

- 01: ECTOPIC SPLENIC TISSUE, D=
 20X10 MM.

- No abnormality, histologically

MANDIBULAR LYMPH NODES

- 01: FOCUS/FOCI, ISOLATED, D=1 MM,
 DARK RED.

- Congestion, focal, bilateral,
 grade 1.

ANIMAL NO: 57
.....

KIDNEYS

- 01: LEFT SIDE: REDUCED IN SIZE, D=
 8X6 MM.

- Hypoplasia, unilateral.

- 02: LEFT SIDE: DISCOLORATION, TAN.

- Hypoplasia, unilateral.

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 03, MALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 21
.....

SKIN/SUBCUTIS
- 01: TIP OF TAIL: KINKED TAIL. - No histological correlate.
.....

ANIMAL NO: 24
.....

MANDIBULAR LYMPH NODES
- 01: FOCUS/FOCI, SEVERAL, D=1 MM, - Congestion, focal, bilateral,
DARK RED. grade 1.
.....

ANIMAL NO: 25
.....

STOMACH
- 01: MUCOSA, FUNDUS: FOCUS/FOCI, - No histological correlate.
ISOLATED, D=3X1 MM, REDDISH.
.....

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SPONSOR : AB Enzymes GmbH *PathData@System* V6.2b5

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 03, FEMALE

NECROPSY OBSERVATION

CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 67

.....

OVARIES

- 01: RIGHT SIDE: FOCUS/FOCI, D=1 - Congestion, focal, unilateral.
MM, BLACK.

.....

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CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 04, MALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

THYMUS
- 01: FOCUS/FOCI, MANY, D=1 MM, - Congestion.
DARK RED.
.....
ANIMAL NO: 31
.....

KIDNEYS
- 01: RIGHT SIDE: PELVIC DILATION. - Pelvic dilation, unilateral.
.....
ANIMAL NO: 32
.....

LUNGS
- 01: RIGHT CRANIAL LOBE: FOCUS/
FOCI, D=3 MM, REDDISH. - No histological correlate.
.....
ANIMAL NO: 39
.....

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CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 04, FEMALE

NECROPSY OBSERVATION CORRESPONDING MICROSCOPIC FINDING

ANIMAL NO: 72
.....

BODY CAVITIES

- 01: UTERINE ADIPOSE TISSUE, RIGHT - Fat necrosis, focal, grade 3.
 SIDE: NODULE(S), D=13 MM,
 GRAY WHITE, REDDISH, FIRM.

.....
ANIMAL NO: 73
.....

KIDNEYS

- 01: BOTH SIDES: PELVIC DILATION. - Pelvic dilation, bilateral.

.....
ANIMAL NO: 75
.....

STOMACH

- 01: MUCOSA, FUNDUS: FOCUS/FOCI, - No histological correlate.
 ISOLATED, D=2 MM, BLACK.

.....
ANIMAL NO: 79
.....

LIVER

- 01: PAPILLARY PROCESS: - Congestion, focal.
 DISCOLORATION, DARK RED.

.....

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TEST ARTICLE	: LYSO-PHOSPHOLIPASE	PATHOL. NO.:	21029 IHI
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SPONSOR	: AB Enzymes GmbH	PathData@System	V6.2b5

EXPLANATION OF CODES AND SYMBOLS

CODES AND SYMBOLS USED AT ANIMAL LEVEL:

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

CODES AND SYMBOLS USED AT ORGAN LEVEL:

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

CODES AND SYMBOLS USED AT FINDING LEVEL:

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

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 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
 DOSE GROUP : 01, 0 mg/kg

ANIMAL NUMBER :

	1	2	3	4	5	6	7	8	9	10
	MK0	MK0	MK0	MK0	MK0	MK0	MK0	MK0	MK0	MK0
PANCREAS	-	-	-	-	-	-	-	-	-	-
MANDIB.LYMPH NODES	-	-	-	-	-	-	-	-	-	-
THYROID GLAND	-	-	-	(-	-	-	-	-	-	-
PARATHYROID GLANDS	(-	(-	(-	(-	0	(-	(-	(-	(-	(-
ADRENAL CORTICES	+	-	-	+	-	-	-	+	-	-
- Vacuolation, Z.fasc.	1.	.	.	2.	.	.	.	(1.	.	.
ADRENAL MEDULLAS	-	-	-	-	-	-	-	-	-	-
SCIATIC NERVES	-	-	-	-	-	-	-	-	-	-
SKIN/SUBCUTIS	-	-	-	-	-	-	-	-	-	-
MAMMARY GLAND AREA	-	-	-*	-*	-	-	-	-	-	-
EYES	+	+	+	+	+	-	+	-	+	+
- Retro-orb.hemorrhage	(1.	(1.	(1.	(1.	(1.	.	(1.	.	(1.	(1.
OPTIC NERVES	(-	-	-	-	-	-	-	(-	-	-
HARDERIAN GLANDS	+	-	+	+	+	+	+	+	+	+
- Porphyrin deposits	(1.	.	(1.	1.	1.	2.	(1.	(1.	.	2.
- Mononuclear Infiltr.	(1.	.
CEREBRUM	-	-	-	-	-	-	-	-	-	-
CEREBELLUM	-	-	-	-	-	-	-	-	-	-
PONS	-	-	-	-	-	-	-	-	-	-
MEDULLA OBLONGATA	-	-	-	-	-	-	-	-	-	-
SKELETAL MUSCLE	-	+	+	-	-	-	-	-	-	-
- Mononuclear infiltr.	.	1.	1.

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TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
 DOSE GROUP : 01, 0 mg/kg

ANIMAL NUMBER :

	1	2	3	4	5	6	7	8	9	10
	MK0									
NASAL CAVITIES	-	-	-	-	-	-	-	-	-	+
- Hyaline inclusion	1.
.....										
PHARYNX	+	-	-	+	-	-	-	-	-	-
- Mononuclear Infiltr.	1.	.	.	1.
.....										

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 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
 DOSE GROUP : 01, 0 mg/kg

ANIMAL NUMBER :

	41	42	43	44	45	46	47	48	49	50
	FK0									
MANDIB.LYMPH NODES	-	-	-	-	-	-	-	+G	+	-
- Lymphoid hyperplasia	1.	.
- Congestion	1.	.	.
.....										
THYROID GLAND	-	-	-	-	-	-	-	+	+	-
- Ultimobranchial cyst	(P.	.
- Thymic remnant	(P.	.	.
.....										
PARATHYROID GLANDS	(-	(-	(-	(-	0	(+	0	-	(-	(-
- Thymic remnant	(P.
.....										
ADRENAL CORTICES	-	-	-	-	-	-	-	+	-	+
- Subcaps.C.hyperplas.	(1.	.	.
- Congestion	(1.
.....										
ADRENAL MEDULLAS	-	-	-	-	-	-	-	-	-	-
.....										
SCIATIC NERVES	-	-	-	-	-	-	-	-	-	-
.....										
SKIN/SUBCUTIS	-	-	+	-	-	-	-	-	-	-
- Epidermal cyst	.	.	2.
.....										
MAMMARY GLAND AREA	-	-	-	-	-	-	-	-	-	-
.....										
EYES	+	+	+	+	+	+	+	+	+	+
- Retro-orb.hemorrhage	(2.	(1.	(1.	(1.	(1.	(1.	.	(2.	.	(1.
- Peri-orbit.inflam.	(1.	.	(2.	.
.....										
OPTIC NERVES	(-	-	-	(-	-	-	-	-	-	-
.....										
HARDERIAN GLANDS	-	+	+	+	+	+	+	+	-	-
- Porphyrin deposits	.	1.	.	(1.	(1.	1.	(1.	1.	.	.
- Mononuclear Infiltr.	.	.	1.
.....										
CEREBRUM	-	-	-	-	-	-	-	-	-	-
.....										
CEREBELLUM	-	-	-	-	-	-	-	-	-	-
.....										
PONS	-	-	-	-	-	-	-	-	-	-
.....										

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TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
 DOSE GROUP : 01, 0 mg/kg

ANIMAL NUMBER :

	41	42	43	44	45	46	47	48	49	50
	FK0									
BONE, FEMUR	-	-	-	-	-	-	-	-	-	-
.....										
CARTILAGE	-	-	-	-	-	-	-	-	-	-
.....										
LARYNX	-	-	+	-	+	-	-	+	+	-
- Inflammat.infilt.	.	.	1.	.	1.	.	.	1.	1.	.
.....										
NASAL CAVITIES	+	-	-	-	-	-	-	-	-	-
- Hyaline inclusion	1.
.....										
PHARYNX	-	-	-	-	-	-	-	-	-	-
.....										

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TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
 DOSE GROUP : 02, 100 mg/kg

ANIMAL NUMBER :

	11	12	13	14	15	16	17	18	19	20
	MK0									

STOMACH	'	'	'	'	'	'	'	'	+G	'	'
- No histol. correlate									P.		
.....											
THYMUS	'	'	+G	+G	+G	'	'	'	'	'	'
- Atrophy / involution			1.	1.	1.						
- Cyst(s)			.	P.	.						
- Hemorrhage			1.	.	1.						
- Hemosiderin deposits			.	1.	.						
.....											

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TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)

DOSE GROUP : 02, 100 mg/kg

ANIMAL NUMBER :

	51	52	53	54	55	56	57	58	59	60
	FK0	FK0	FK0	FK0						
SPLEEN	'	'	+G	'	'	'	'	'	'	'
- Extram. hemopoiesis			1.							
- Hemosiderin			1.							
.....										
KIDNEYS	'	'	'	'	'	'	+G	'	'	'
- Hypoplasia							(P.			
.....										
MANDIB. LYMPH NODES	'	'	+G	'	'	'	'	'	'	'
- Hemosiderin deposits			1.							
- Congestion			1.							
.....										
SKIN/SUBCUTIS	+G	'	'	'	'	'	'	'	'	'
- No histol. correlate	P.									
.....										

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TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 03, 300 mg/kg

ANIMAL NUMBER :

	21	22	23	24	25	26	27	28	29	30
	MK0									
STOMACH	'	'	'	'	+G	'	'	'	'	'
- No histol. correlate					P.					
.....										
MANDIB.LYMPH NODES	'	'	'	+G	'	'	'	'	'	'
- Congestion				1.						
.....										
SKIN/SUBCUTIS	+G	'	'	'	'	'	'	'	'	'
- No histol. correlate	P.									
.....										

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 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
 DOSE GROUP : 04, 1000 mg/kg

ANIMAL NUMBER :

	31	32	33	34	35	36	37	38	39	40
	MK0	MK0	MK0	MK0	MK0	MK0	MK0	MK0	MK0	MK0
DUODENUM	-	-	-	-	-	-	-	-	-	-
.....										
JEJUNUM	-	-	-	-	-	-	-	-	-	-
.....										
PEYERS PATCHES JEJ.	+	+	+	+	+	-	-	+	+	+
- Mineralization	1.	.	.	2.	1.	.	.	1.	.	1.
- Lymphoid hyperplasia	1.	1.	1.	1.	.
.....										
ILEUM	-	-	+	-	-	-	-	-	-	-
- Congestion	.	.	P.
.....										
PEYERS PATCHES ILEUM	+	-	+	-	+	+	-	+	+	-
- Lymphoid hyperplasia	1.	.	1.	.	1.	1.	.	1.	1.	.
.....										
CECUM	-	-	-	-	-	-	-	-	-	-
.....										
COLON	-	-	-	-	-	-	-	-	-	-
.....										
RECTUM	-	-	-	-	-	-	-	-	-	+
- Luminal dilation	P.
.....										
LUNGS	+	+	-	+	+	+	+	+	+G	+
- Vasc. mineralization	1.	1.	.	.	1.	.	1.	1.	1.	1.
- Alveolar macrophages	1.	2.	.	1.	.	1.	.	1.	.	1.
- Alveolar hemorrhage	1.
- No histol. correlate	P.	.
.....										
THYMUS	+G	+	+	-	-	+	+	+	+	+
- Atrophy / involution	.	1.	1.	.	.	1.	1.	1.	1.	1.
- Cyst(s)	P.	P.	P.
- Congestion	P.
.....										
TESTES	-	-	-	+	-	-	-	-	-	-
- Tubular atrophy	.	.	.	(1.
.....										
EPIDIDYMIDES	-	-	+	+	-	+	-	-	-	-
- Mononuclear foci	.	.	(1.
- Vacuolation, epithel.	.	.	(1.	.	(1.
.....										

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 SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
 DOSE GROUP : 04, 1000 mg/kg

ANIMAL NUMBER :

	71	72	73	74	75	76	77	78	79	80
	FK0									
MANDIB.LYMPH NODES	-	-	+	-	+	-	-	-	-	-
- Lymphoid hyperplasia	.	.	1.	.	1.
.....										
THYROID GLAND	-	-	-	-	-	-	-	-	-	+
- Ultimobranchial cyst	(P.
.....										
PARATHYROID GLANDS	(-	0	(-	(-	-	(-	(-	-	(-	(-
.....										
ADRENAL CORTICES	-	-	-	-	-	-	+	-	-	-
- Vacuolation, Z.fasc.	(1.	.	.	.
.....										
ADRENAL MEDULLAS	-	-	-	-	-	-	-	-	-	-
.....										
SCIATIC NERVES	-	-	-	-	-	-	-	+	-	-
- Axonal degeneration	1.	.	.
.....										
SKIN/SUBCUTIS	-	-	-	-	-	-	-	-	-	-
.....										
MAMMARY GLAND AREA	-	-	-	-	-	-	-	-	-	-
.....										
EYES	+	+	+	+	+	+	+	+	+	+
- Retro-orb.hemorrhage	(1.	(1.	(1.	(1.	(1.	.	(1.	(1.	(1.	(1.
- Peri-orbit.inflam.	(1.	.	.	(1.	.
.....										
OPTIC NERVES	-	-	-	-	-	0	-	-	(-	(-
.....										
HARDERIAN GLANDS	+	+	+	+	-	-	+	-	+	-
- Porphyrin deposits	1.	1.	(1.	.	.	.	1.	.	1.	.
- Mononuclear Infiltr.	(1.	.	.	(1.
.....										
CEREBRUM	-	-	-	-	-	-	-	-	-	-
.....										
CEREBELLUM	-	-	-	-	-	-	-	-	-	-
.....										
PONS	-	-	-	-	-	-	-	-	-	-
.....										
MEDULLA OBLONGATA	-	-	-	-	-	-	-	-	-	-
.....										

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 41

PITUITARY GLAND:
-Cyst, single, pars distalis, grade 1
NASAL CAVITIES:
-Hyaline inclusion, nasal septum, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 42

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-Inflammatrory cell focus/foci, grade 1
SPLEEN:
-Extramedullary hemopoiesis, grade 1
-Hemosiderin storage, grade 2
MESENTERIC LYMPH NODE:
-Lymphoid hyperplasia, grade 1
STOMACH:
-Hyperkeratosis, focal, limitting ridge, grade 1
PEYER'S PATCHES (JEJUNUM):
-Mineralization, grade 2
LUNGS:
-Alveolar macrophages, multifocal, grade 1
THYMUS:
-Atrophy / involution, grade 1
-Cyst(s), focal/multifocal

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 42

MANDIBULAR GLANDS:

Only one of paired organs examined/present

PARATHYROID GLANDS:

Only one of paired organs examined/present

EYES:

-Retro-orbital hemorrhage, unilateral, grade 1

HARDERIAN GLANDS:

-Porphyrin deposits, bilateral, grade 1

VAGINA:

-Diestrus

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0

DAYS ON TEST : 90

* ANIMAL NO. : 43

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

TRACHEA:

-Inflammatory cell infiltrate, submucosa, focal, grade 1

SPLEEN:

-Hemosiderin storage, grade 2

KIDNEYS:

-Tubular basophilia, focal/multifocal, unilateral, grade 1

PEYER'S PATCHES (ILEUM):

-Lymphoid hyperplasia, grade 1

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 43

LUNGS:
-Microgranuloma, single, grade 1
THYMUS:
-Atrophy / involution, grade 1
-Cyst(s), focal/multifocal
MANDIBULAR GLANDS:
Only one of paired organs examined/present
PARATHYROID GLANDS:
Only one of paired organs examined/present
SKIN/SUBCUTIS:
-Epidermal cyst, grade 2
EYES:
-Retro-orbital hemorrhage, unilateral, grade 1
HARDERIAN GLANDS:
-Mononuclear infiltration, focal, bilateral, grade 1
SKELETAL MUSCLE:
-Mononuclear infiltration, focal, grade 1
VAGINA:
-Metestrus
LARYNX:
-Inflammatory cell infiltrate, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 44

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 44

* MICROSCOPIC FINDINGS

LIVER:
-Inflammatrory cell focus/foci, grade 1
SPLEEN:
-Hemosiderin storage, grade 2
MESENTERIC LYMPH NODE:
-Lymphoid hyperplasia, grade 1
STOMACH:
-Mucosal gland dilation, grade 1
-Vacuolation, epithelium, limiting ridge, grade 2
PEYER'S PATCHES (ILEUM):
-Lymphoid hyperplasia, grade 1
LUNGS:
-Alveolar macrophages, multifocal, grade 1
THYMUS:
-Atrophy / involution, grade 1
-Cyst(s), focal/multifocal
MANDIBULAR GLANDS:
Only one of paired organs examined/present
SUBLINGUAL GLANDS:
Only one of paired organs examined/present
-Ectopic parotid gland acini, unilateral, grade 1
PANCREAS:
-Acinar cell vacuolation, focal, grade 1
-Mononuclear infiltration, focal, grade 1
PARATHYROID GLANDS:
Only one of paired organs examined/present
EYES:
-Retro-orbital hemorrhage, unilateral, grade 1
OPTIC NERVES:
Only one of paired organs examined/present
HARDERIAN GLANDS:
-Porphyrin deposits, unilateral, grade 1
VAGINA:
-Metestrus

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 44

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

LACRIMAL GLANDS, EXORBITAL:

-Mononuclear infiltration, focal, unilateral, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0

DAYS ON TEST : 90

* ANIMAL NO. : 45

* NECROPSY FINDINGS

UTERUS:

01: BOTH HORNS: DILATION, D=5 MM.

NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

AURICULES:

Tissue not present for histologic examination

TRACHEA:

-Glandular dilation, submucosa, grade 1

LIVER:

-Inflammatrory cell focus/foci, grade 1

-Fatty change, focal, grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 2

STOMACH:

-Mucosal gland dilation, grade 1

PEYER'S PATCHES (JEJUNUM):

-Mineralization, grade 1

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 45

PEYER'S PATCHES (ILEUM):

-Lymphoid hyperplasia, grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 2

MANDIBULAR GLANDS:

Only one of paired organs examined/present

SUBLINGUAL GLANDS:

-Ductular hyperplasia, focal, unilateral, grade 1

PANCREAS:

-Acinar cell vacuolation, focal, grade 1

PARATHYROID GLANDS:

Tissue not present for histologic examination

EYES:

-Retro-orbital hemorrhage, unilateral, grade 1

HARDERIAN GLANDS:

-Porphyrin deposits, unilateral, grade 1

UTERUS:

-Luminal dilation, (cyclic change)

This finding corresponds to necropsy observation no: 01.

VAGINA:

-Estrus

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

-Hemosiderin deposits, grade 1

LARYNX:

-Inflammatory cell infiltrate, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 46
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-Inflammatrory cell focus/foci, grade 1
-Increased hepatocytic glycogen deposits, grade 1
SPLEEN:
-Hemosiderin storage, grade 1
KIDNEYS:
-Papillary mineralization, focal/multifocal, unilateral,
grade 1
PEYER'S PATCHES (JEJUNUM):
-Lymphoid hyperplasia, grade 1
PEYER'S PATCHES (ILEUM):
-Lymphoid hyperplasia, grade 1
LUNGS:
-Vascular mineralization, focal/multifocal, grade 1
-Alveolar macrophages, multifocal, grade 1
MANDIBULAR GLANDS:
Only one of paired organs examined/present
PARATHYROID GLANDS:
Only one of paired organs examined/present
-Thymic remnant, unilateral
EYES:
-Retro-orbital hemorrhage, unilateral, grade 1
HARDERIAN GLANDS:
-Porphyrin deposits, bilateral, grade 1
VAGINA:
-Proestrus
BONE MARROW (FEMUR):
-Fatty replacement, grade 1

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 46

PITUITARY GLAND:
-Cyst, single, pars distalis, grade 1
SPINAL CORD (CERVICAL SEGMENT):
Tissue not present for histologic examination
SPINAL CORD (THORACIC SEGMENT):
Tissue not present for histologic examination
SPINAL CORD (LUMBAR SEGMENT):
Tissue not present for histologic examination
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 47

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-Inflammatrory cell focus/foci, grade 1
-Increased hepatocytic glycogen deposits, grade 1
-Peribiliary cell infiltrate, grade 1
SPLEEN:
-Hemosiderin storage, grade 2
MESENTERIC LYMPH NODE:
-Lymphoid hyperplasia, grade 1
PEYER'S PATCHES (ILEUM):
-Lymphoid hyperplasia, grade 1
LUNGS:
-Vascular mineralization, focal/multifocal, grade 1
-Alveolar macrophages, multifocal, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 47

THYMUS:

- Atrophy / involution, grade 1
- Cyst(s), focal/multifocal

MANDIBULAR GLANDS:

Only one of paired organs examined/present

PARATHYROID GLANDS:

Tissue not present for histologic examination

EYES:

- Peri-orbital Inflammation, unilateral, grade 1

HARDERIAN GLANDS:

- Porphyrin deposits, unilateral, grade 1

UTERUS:

- Luminal dilation, (cyclic change)

VAGINA:

- Proestrus

BONE MARROW (FEMUR):

- Fatty replacement, grade 1

PITUITARY GLAND:

- Cyst, single, pars distalis, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0

DAYS ON TEST : 90

* ANIMAL NO. : 48

* NECROPSY FINDINGS

MANDIBULAR LYMPH NODES:

01: DISCOLORATION, DARK RED.

NO OTHER NECROPSY OBSERVATIONS NOTED

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 48

* MICROSCOPIC FINDINGS

LIVER:

- Inflammatrory cell focus/foci, grade 1
- Increased hepatocytic glycogen deposits, grade 1

SPLEEN:

- Extramedullary hemopoiesis, grade 1
- Hemosiderin storage, grade 2

PEYER'S PATCHES (ILEUM):

- Lymphoid hyperplasia, grade 2

LUNGS:

- Vascular mineralization, focal/multifocal, grade 1
- Alveolar macrophages, multifocal, grade 1

THYMUS:

- Atrophy / involution, grade 1

MANDIBULAR GLANDS:

Only one of paired organs examined/present

SUBLINGUAL GLANDS:

Only one of paired organs examined/present

MANDIBULAR LYMPH NODES:

- Congestion, bilateral, grade 1
- This finding corresponds to necropsy observation no: 01.

THYROID GLAND (BOTH LOBES):

- Thymic remnant, unilateral

ADRENAL CORTICES:

- Subcapsular cell hyperplasia, unilateral, grade 1

EYES:

- Retro-orbital hemorrhage, unilateral, grade 2

HARDERIAN GLANDS:

- Porphyrin deposits, bilateral, grade 1

SKELETAL MUSCLE:

- Myodegeneration, focal, grade 1

VAGINA:

- Estrus

BONE MARROW (FEMUR):

- Fatty replacement, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 48

LARYNX:

-Inflammatory cell infiltrate, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 49

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

TRACHEA:

-Glandular dilation, submucosa, grade 1

SPLEEN:

-Hemosiderin storage, grade 2

KIDNEYS:

-Corticomedullary mineralization, focal/multifocal, unilateral,
grade 1

PEYER'S PATCHES (ILEUM):

-Lymphoid hyperplasia, grade 2

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

-Alveolar hemorrhage, focal/multifocal, grade 1

MANDIBULAR GLANDS:

Only one of paired organs examined/present

SUBLINGUAL GLANDS:

-Ectopic parotid gland acini, unilateral, grade 1

MANDIBULAR LYMPH NODES:

-Lymphoid hyperplasia, bilateral, grade 1

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 49

.....
THYROID GLAND (BOTH LOBES):
-Ultimobranchial cyst(s), focal/multifocal, unilateral
PARATHYROID GLANDS:
Only one of paired organs examined/present
EYES:
-Peri-orbital Inflammation, unilateral, grade 2
VAGINA:
-Estrus
BONE MARROW (FEMUR):
-Fatty replacement, grade 1
LARYNX:
-Inflammatory cell infiltrate, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

.....
* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 50
.....

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
LIVER:
-Increased hepatocytic glycogen deposits, grade 1
SPLEEN:
-Hemosiderin storage, grade 2
PEYER'S PATCHES (JEJUNUM):
-Mineralization, grade 1
-Lymphoid hyperplasia, grade 1

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 01, 0 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 50

PEYER'S PATCHES (ILEUM):

-Lymphoid hyperplasia, grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

-Alveolar macrophages, multifocal, grade 1

THYMUS:

-Atrophy / involution, grade 1

MANDIBULAR GLANDS:

Only one of paired organs examined/present

SUBLINGUAL GLANDS:

Only one of paired organs examined/present

PARATHYROID GLANDS:

Only one of paired organs examined/present

ADRENAL CORTICES:

-Congestion, unilateral, grade 1

EYES:

-Retro-orbital hemorrhage, unilateral, grade 1

SKELETAL MUSCLE:

-Myodegeneration, focal, grade 1

UTERUS:

-Luminal dilation, (cyclic change)

CERVIX:

-Epidermal cyst, grade 2

VAGINA:

-Proestrus

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

ANIMAL HEADING DATA

DOSE GROUP : 02, 100 mg/kg

ANIMAL NUMBER	SEX M/F	DEFINED AND STATE	FINAL OF NECROPSY	TEST DAYS	FIRST DAY	LAST DAY UNDER TEST	DATE OF NECROPSY
11	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
12	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
13	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
14	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
15	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
16	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
17	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
18	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
19	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
20	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
51	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
52	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
53	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
54	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
55	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
56	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
57	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
58	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
59	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
60	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 mg/kg MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 91 * ANIMAL NO. : 13
.....

* NECROPSY FINDINGS

THYMUS:
01: FOCUS/FOCI, SEVERAL, D=1 MM, DARK RED.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

THYMUS:
-Atrophy / involution, grade 1
-Hemorrhage, focal, grade 1
This finding corresponds to necropsy observation no: 01.

* STATE AT NECROPSY: K0
DAYS ON TEST : 91 * ANIMAL NO. : 14
.....

* NECROPSY FINDINGS

THYMUS:
01: FOCUS/FOCI, ISOLATED, D=1 MM, DARK RED.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

THYMUS:
-Atrophy / involution, grade 1
-Cyst(s), focal/multifocal
-Hemosiderin deposits, focal, grade 1
This finding corresponds to necropsy observation no: 01.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 mg/kg FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 51
.....

* NECROPSY FINDINGS

SKIN/SUBCUTIS:
01: DORSO-LUMBAR REGION, LEFT SIDE: ALOPECIA, D=20 MM, MODERATE.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

SKIN/SUBCUTIS:
-No histological correlate
This finding corresponds to necropsy observation no: 01.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 52
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 mg/kg FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 53
.....

* NECROPSY FINDINGS

SPLEEN:
01: ECTOPIC SPLENIC TISSUE, D=20X10 MM.
MANDIBULAR LYMPH NODES:
01: FOCUS/FOCI, ISOLATED, D=1 MM, DARK RED.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

SPLEEN:
No abnormality, histologically
-Extramedullary hemopoiesis, grade 1
-Hemosiderin storage, grade 1
MANDIBULAR LYMPH NODES:
-Hemosiderin deposits, bilateral, grade 1
-Congestion, focal, bilateral, grade 1
This finding corresponds to necropsy observation no: 01.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 54
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 54

.....
* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: K0

DAYS ON TEST : 90 * ANIMAL NO. : 55

.....
* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: K0

DAYS ON TEST : 90 * ANIMAL NO. : 56

.....
* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 56

.....
* MICROSCOPIC FINDINGS

NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: K0

DAYS ON TEST : 90 * ANIMAL NO. : 57

.....
* NECROPSY FINDINGS

KIDNEYS:
01: LEFT SIDE: REDUCED IN SIZE, D=8X6 MM.
02: LEFT SIDE: DISCOLORATION, TAN.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

KIDNEYS:
-Hypoplasia, unilateral
This finding corresponds to necropsy observations nos: 01,02.

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 02, 100 mg/kg FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 58
.....

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 59
.....

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

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TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

ANIMAL HEADING DATA

DOSE GROUP : 03, 300 mg/kg

ANIMAL NUMBER	SEX M/F	DEFINED AND STATE	FINAL OF NECROPSY	TEST DAYS	FIRST DAY	LAST DAY UNDER TEST	DATE OF NECROPSY
21	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
22	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
23	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
24	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
25	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
26	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
27	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
28	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
29	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
30	M	K0	K0	91	08-OCT-08	06-JAN-09	07-JAN-09
61	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
62	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
63	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
64	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
65	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
66	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
67	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
68	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
69	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09
70	F	K0	K0	90	08-OCT-08	05-JAN-09	06-JAN-09

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 mg/kg FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 61
.....

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 62
.....

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 mg/kg FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 63
.....

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 64
.....

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

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TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 03, 300 mg/kg FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 69
.....

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 70
.....

* NECROPSY FINDINGS
NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS
NO EXAMINATION REQUIRED.

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TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 91 * ANIMAL NO. : 31
.....

* NECROPSY FINDINGS

THYMUS:
01: FOCUS/FOCI, MANY, D=1 MM, DARK RED.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

SPLEEN:
-Hemosiderin storage, grade 1
KIDNEYS:
-Hyaline droplets, proximal tubulus epithelium, multifocal,
unilateral, grade 1
STOMACH:
-Mucosal gland dilation, focal, grade 1
PEYER'S PATCHES (JEJUNUM):
-Mineralization, grade 1
-Lymphoid hyperplasia, grade 1
PEYER'S PATCHES (ILEUM):
-Lymphoid hyperplasia, grade 1
LUNGS:
-Vascular mineralization, focal/multifocal, grade 1
-Alveolar macrophages, multifocal, grade 1
THYMUS:
-Congestion
This finding corresponds to necropsy observation no: 01.
MANDIBULAR GLANDS:
Only one of paired organs examined/present
-Acinar vacuolation, focal, unilateral, grade 1
SUBLINGUAL GLANDS:
Only one of paired organs examined/present
PARATHYROID GLANDS:
Only one of paired organs examined/present

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg MALE

CONT./FF. ANIMAL NO. : 31

EYES:

-Retro-orbital hemorrhage, unilateral, grade 1

HARDERIAN GLANDS:

-Porphyrin deposits, unilateral, grade 1

LACRIMAL GLANDS, EXORBITAL:

-Harderian glandular change, unilateral, grade 1

SPINAL CORD (THORACIC SEGMENT):

-Hemorrhage, focal, grade 1

LARYNX:

-Desiccated secretion, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0

DAYS ON TEST : 91

* ANIMAL NO. : 32

* NECROPSY FINDINGS

KIDNEYS:

01: RIGHT SIDE: PELVIC DILATION.

NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

LIVER:

-Inflammatrory cell focus/foci, grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 1

KIDNEYS:

-Tubular basophilia, focal/multifocal, bilateral, grade 1

-Pelvic dilation, unilateral

This finding corresponds to necropsy observation no: 01.

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg MALE

CONT./FF. ANIMAL NO. : 32

STOMACH:

- Mucosal gland dilation, grade 1
- Ulcer/erosion, Glandular stomach, focal, grade 2

PEYER'S PATCHES (JEJUNUM):

- Lymphoid hyperplasia, grade 1

LUNGS:

- Vascular mineralization, focal/multifocal, grade 1
- Alveolar macrophages, multifocal, grade 2

THYMUS:

- Atrophy / involution, grade 1

MANDIBULAR GLANDS:

Only one of paired organs examined/present

PARATHYROID GLANDS:

Only one of paired organs examined/present

MAMMARY GLAND AREA:

mammary gland was missing

HARDERIAN GLANDS:

- Porphyrin deposits, bilateral, grade 1
- Mononuclear infiltration, focal, unilateral, grade 2

SKELETAL MUSCLE:

- Mononuclear infiltration, focal, grade 2

BONE MARROW (FEMUR):

- Fatty replacement, grade 2

LACRIMAL GLANDS, EXORBITAL:

- Harderian glandular change, unilateral, grade 1
- Cyto/karyomegaly, bilateral, grade 1
- Mononuclear infiltration, focal, unilateral, grade 1

LARYNX:

- Inflammatory cell infiltrate, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 91 * ANIMAL NO. : 33
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

TRACHEA:
-Inflammatory cell infiltrate, submucosa, grade 1
LIVER:
-Inflammatrory cell focus/foci, grade 1
-Fatty change, focal, grade 1
SPLEEN:
-Hemosiderin storage, grade 1
MESENTERIC LYMPH NODE:
-Lymphoid hyperplasia, grade 1
PEYER'S PATCHES (JEJUNUM):
-Lymphoid hyperplasia, grade 1
ILEUM:
-Congestion
PEYER'S PATCHES (ILEUM):
-Lymphoid hyperplasia, grade 1
THYMUS:
-Atrophy / involution, grade 1
EPIDIDYMIDES:
-Mononuclear cell focus/foci, interstitial, unilateral, grade 1
MANDIBULAR GLANDS:
Only one of paired organs examined/present
SUBLINGUAL GLANDS:
Only one of paired organs examined/present
PARATHYROID GLANDS:
Only one of paired organs examined/present
EYES:
-Retro-orbital hemorrhage, unilateral, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg MALE

CONT./FF. ANIMAL NO. : 33

OPTIC NERVES:

Only one of paired organs examined/present

HARDERIAN GLANDS:

-Porphyrin deposits, bilateral, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 2

PITUITARY GLAND:

-Cyst, single, pars distalis, grade 2

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0

DAYS ON TEST : 91

* ANIMAL NO. : 34

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

TRACHEA:

-Inflammatory cell infiltrate, submucosa, grade 1

LIVER:

-Inflammatroy cell focus/foci, grade 1

-Fatty change, grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 1

MESENTERIC LYMPH NODE:

-Lymphoid hyperplasia, grade 1

-Hemosiderin deposits, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg MALE

CONT./FF. ANIMAL NO. : 34

.....
PEYER'S PATCHES (JEJUNUM):
-Mineralization, grade 2
LUNGS:
-Alveolar macrophages, multifocal, grade 1
TESTES:
-Tubular atrophy, focal, unilateral, grade 1
EPIDIDYMIDES:
-Vacuolation, epithelium, unilateral, grade 1
MANDIBULAR GLANDS:
Only one of paired organs examined/present
PARATHYROID GLANDS:
Only one of paired organs examined/present
EYES:
-Retro-orbital hemorrhage, bilateral, grade 1
HARDERIAN GLANDS:
-Porphyrin deposits, bilateral, grade 1
BONE MARROW (FEMUR):
-Fatty replacement, grade 2
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

.....
* STATE AT NECROPSY: K0
DAYS ON TEST : 91 * ANIMAL NO. : 35
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg MALE

CONT./FF. ANIMAL NO. : 35

* MICROSCOPIC FINDINGS

TRACHEA:

-Glandular dilation, submucosa, grade 1

LIVER:

-Inflammatrory cell focus/foci, grade 1

SPLEEN:

-Hemosiderin storage, grade 1

MESENTERIC LYMPH NODE:

-Lymphoid hyperplasia, grade 1

-Hemosiderin deposits, grade 1

KIDNEYS:

-Tubular dilation, cystic, focal, papilla, bilateral, grade 1

PEYER'S PATCHES (JEJUNUM):

-Mineralization, grade 1

PEYER'S PATCHES (ILEUM):

-Lymphoid hyperplasia, grade 1

LUNGS:

-Vascular mineralization, focal/multifocal, grade 1

MANDIBULAR GLANDS:

Only one of paired organs examined/present

SUBLINGUAL GLANDS:

-Ectopic parotid gland acini, unilateral, grade 1

THYROID GLAND (BOTH LOBES):

-Ultimobranchial cyst(s), focal/multifocal, unilateral

EYES:

-Retro-orbital hemorrhage, unilateral, grade 1

HARDERIAN GLANDS:

-Porphyrin deposits, bilateral, grade 1

COAGULATING GLANDS (ANTERIOR PROSTATE):

Only one of paired organs examined/present

BONE MARROW (FEMUR):

-Fatty replacement, grade 2

LACRIMAL GLANDS, EXORBITAL:

-Cyto/karyomegaly, bilateral, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg MALE

CONT./FF. ANIMAL NO. : 35

PITUITARY GLAND:

Tissue not present for histologic examination
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0
DAYS ON TEST : 91 * ANIMAL NO. : 36

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

HEART:

-Mononuclear cell focus/foci, grade 2

LIVER:

-Inflammatrory cell focus/foci, grade 1

-Fatty change, focal, grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 1

KIDNEYS:

-Hyaline droplets, proximal tubulus epithelium, multifocal,
unilateral, grade 1

-Tubular basophilia, focal/multifocal, unilateral, grade 1

PEYER'S PATCHES (ILEUM):

-Lymphoid hyperplasia, grade 1

LUNGS:

-Alveolar macrophages, multifocal, grade 1

THYMUS:

-Atrophy / involution, grade 1

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg MALE

CONT./FF. ANIMAL NO. : 36

EPIDIDYMIDES:

-Vacuolation, epithelium, unilateral, grade 1

MANDIBULAR GLANDS:

Only one of paired organs examined/present

PARATHYROID GLANDS:

Only one of paired organs examined/present

MAMMARY GLAND AREA:

mammary gland was missing

EYES:

-Retro-orbital hemorrhage, unilateral, grade 2

HARDERIAN GLANDS:

-Mononuclear infiltration, focal, unilateral, grade 1

SKELETAL MUSCLE:

-Mononuclear infiltration, focal, grade 1

PROSTATE GLAND:

-Inflammation, focal, acute, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

LACRIMAL GLANDS, EXORBITAL:

-Harderian glandular change, unilateral, grade 1

-Cyto/karyomegaly, bilateral, grade 1

-Mononuclear infiltration, focal, unilateral, grade 1

BONE (STERNUM):

-Chondromucinous degeneration, grade 1

LARYNX:

-Inflammatory cell infiltrate, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg MALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 91 * ANIMAL NO. : 39
.....

* NECROPSY FINDINGS

LUNGS:
01: RIGHT CRANIAL LOBE: FOCUS/FOCI, D=3 MM, REDDISH.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

LIVER:
-Inflammatroy cell focus/foci, grade 1
-Increased hepatocytic glycogen deposits, grade 1
SPLEEN:
-Hemosiderin storage, grade 1
MESENTERIC LYMPH NODE:
-Lymphoid hyperplasia, grade 1
-Hemosiderin deposits, grade 1
KIDNEYS:
-Hyaline droplets, proximal tubulus epithelium, multifocal,
bilateral, grade 1
-Tubular casts, focal/multifocal, bilateral, grade 1
PEYER'S PATCHES (JEJUNUM):
-Lymphoid hyperplasia, grade 1
PEYER'S PATCHES (ILEUM):
-Lymphoid hyperplasia, grade 1
LUNGS:
-Vascular mineralization, focal/multifocal, grade 1
-No histological correlate
This finding corresponds to necropsy observation no: 01.
THYMUS:
-Atrophy / involution, grade 1
-Cyst(s), focal/multifocal
MANDIBULAR GLANDS:
Only one of paired organs examined/present

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TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg MALE

CONT./FF. ANIMAL NO. : 39

PARATHYROID GLANDS:

Only one of paired organs examined/present

EYES:

-Retro-orbital hemorrhage, unilateral, grade 1

OPTIC NERVES:

Only one of paired organs examined/present

HARDERIAN GLANDS:

-Porphyrin deposits, bilateral, grade 1

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

NASAL CAVITIES:

-Hyaline inclusion, nasal septum, grade 1

PHARYNX:

-Mononuclear infiltration, focal, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0

DAYS ON TEST : 91

* ANIMAL NO. : 40

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-Inflammatrory cell focus/foci, grade 1

SPLEEN:

-Hemosiderin storage, grade 1

KIDNEYS:

-Pyelitis, acute, unilateral, grade 2

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg MALE

CONT./FF. ANIMAL NO. : 40

.....

PEYER'S PATCHES (JEJUNUM):
-Mineralization, grade 1
RECTUM:
-Luminal dilation
LUNGS:
-Vascular mineralization, focal/multifocal, grade 1
-Alveolar macrophages, multifocal, grade 1
-Alveolar hemorrhage, focal/multifocal, grade 1
THYMUS:
-Atrophy / involution, grade 1
-Cyst(s), focal/multifocal
MANDIBULAR GLANDS:
Only one of paired organs examined/present
MANDIBULAR LYMPH NODES:
-Hemosiderin deposits, bilateral, grade 1
PARATHYROID GLANDS:
Only one of paired organs examined/present
HARDERIAN GLANDS:
-Porphyrin deposits, bilateral, grade 1
COAGULATING GLANDS (ANTERIOR PROSTATE):
Only one of paired organs examined/present
BONE MARROW (FEMUR):
-Fatty replacement, grade 1
PITUITARY GLAND:
-Cyst, multiple, pars distalis, grade 2
LARYNX:
-Inflammatory cell infiltrate, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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INDIVIDUAL ANIMAL DATA

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 71
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-Inflammatrory cell focus/foci, grade 1
-Fatty change, focal, grade 1
SPLEEN:
-Hemosiderin storage, grade 2
MESENTERIC LYMPH NODE:
-Hemosiderin deposits, grade 1
KIDNEYS:
-Tubular basophilia, focal/multifocal, unilateral, grade 1
-Papillary mineralization, focal/multifocal, unilateral,
grade 1
PEYER'S PATCHES (ILEUM):
-Lymphoid hyperplasia, grade 1
LUNGS:
-Vascular mineralization, focal/multifocal, grade 1
-Alveolar macrophages, multifocal, grade 1
MANDIBULAR GLANDS:
Only one of paired organs examined/present
SUBLINGUAL GLANDS:
Only one of paired organs examined/present
PANCREAS:
-Acinar cell vacuolation, focal, grade 1
PARATHYROID GLANDS:
Only one of paired organs examined/present
EYES:
-Retro-orbital hemorrhage, unilateral, grade 1
HARDERIAN GLANDS:
-Porphyrin deposits, bilateral, grade 1
-Mononuclear infiltration, focal, unilateral, grade 1

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 71

SKELETAL MUSCLE:
-Mononuclear infiltration, focal, grade 1
VAGINA:
-Diestrus
BONE MARROW (FEMUR):
-Fatty replacement, grade 1
LARYNX:
-Inflammatory cell infiltrate, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 72

* NECROPSY FINDINGS

BODY CAVITIES:
01: UTERINE ADIPOSE TISSUE, RIGHT SIDE: NODULE(S), D=13 MM,
GRAY WHITE, REDDISH, FIRM.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

TRACHEA:
-Inflammatory cell infiltrate, submucosa, grade 1
LIVER:
-Inflammatrory cell focus/foci, grade 1
-Peribiliary cell infiltrate, grade 1
SPLEEN:
-Extramedullary hemopoiesis, grade 2
-Hemosiderin storage, grade 2

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 72

.....

PEYER'S PATCHES (JEJUNUM):
-Mineralization, with giant cell, grade 1
PEYER'S PATCHES (ILEUM):
-Lymphoid hyperplasia, grade 1
LUNGS:
-Vascular mineralization, focal/multifocal, grade 1
THYMUS:
-Atrophy / involution, grade 3
MANDIBULAR GLANDS:
Only one of paired organs examined/present
SUBLINGUAL GLANDS:
Only one of paired organs examined/present
PARATHYROID GLANDS:
Tissue not present for histologic examination
EYES:
-Retro-orbital hemorrhage, unilateral, grade 1
HARDERIAN GLANDS:
-Porphyrin deposits, bilateral, grade 1
UTERUS:
-Luminal dilation, (cyclic change)
VAGINA:
-Estrus
BONE MARROW (FEMUR):
-Fatty replacement, grade 1
BODY CAVITIES:
-Fat necrosis, focal, grade 3
This finding corresponds to necropsy observation no: 01.
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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INDIVIDUAL ANIMAL DATA

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 73
.....

* NECROPSY FINDINGS

KIDNEYS:
01: BOTH SIDES: PELVIC DILATION.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

HEART:
-Mononuclear cell focus/foci, grade 1
SPLEEN:
-Extramedullary hemopoiesis, grade 1
-Hemosiderin storage, grade 2
KIDNEYS:
-Pelvic dilation, bilateral
This finding corresponds to necropsy observation no: 01.
STOMACH:
-Mucosal gland dilation, grade 1
PEYER'S PATCHES (ILEUM):
-Lymphoid hyperplasia, grade 1
LUNGS:
-Vascular mineralization, focal/multifocal, grade 1
-Alveolar macrophages, multifocal, grade 1
THYMUS:
-Atrophy / involution, grade 1
MANDIBULAR GLANDS:
Only one of paired organs examined/present
PANCREAS:
-Acinar cell atrophy, focal, grade 1
-Mononuclear infiltration, focal, grade 1
-Ductular hyperplasia, focal, grade 1
MANDIBULAR LYMPH NODES:
-Lymphoid hyperplasia, bilateral, grade 1

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 73

PARATHYROID GLANDS:

Only one of paired organs examined/present

EYES:

-Retro-orbital hemorrhage, unilateral, grade 1

HARDERIAN GLANDS:

-Porphyrin deposits, unilateral, grade 1

UTERUS:

-Luminal dilation, (cyclic change)

VAGINA:

-Estrus

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

LARYNX:

-Inflammatory cell infiltrate, grade 1

NASAL CAVITIES:

-Hyaline inclusion, nasal septum, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0

DAYS ON TEST : 90

* ANIMAL NO. : 74

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-Fatty change, focal, grade 1

SPLEEN:

-Hemosiderin storage, grade 1

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TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 74

MESENTERIC LYMPH NODE:

-Lymphoid hyperplasia, grade 1

PEYER'S PATCHES (ILEUM):

-Lymphoid hyperplasia, grade 1

THYMUS:

-Atrophy / involution, grade 1

-Cyst(s), focal/multifocal

MANDIBULAR GLANDS:

Only one of paired organs examined/present

PARATHYROID GLANDS:

Only one of paired organs examined/present

EYES:

-Retro-orbital hemorrhage, unilateral, grade 1

HARDERIAN GLANDS:

-Mononuclear infiltration, focal, unilateral, grade 1

SKELETAL MUSCLE:

-Myodegeneration, focal, grade 1

VAGINA:

-Diestrus

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

LARYNX:

-Inflammatory cell infiltrate, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 75
.....

* NECROPSY FINDINGS

STOMACH:
01: MUCOSA, FUNDUS: FOCUS/FOCI, ISOLATED, D=2 MM, BLACK.
NO OTHER NECROPSY OBSERVATIONS NOTED

* MICROSCOPIC FINDINGS

SPLEEN:
-Hemosiderin storage, grade 2
STOMACH:
-No histological correlate
This finding corresponds to necropsy observation no: 01.
PEYER'S PATCHES (ILEUM):
-Lymphoid hyperplasia, grade 2
LUNGS:
-Vascular mineralization, focal/multifocal, grade 1
THYMUS:
-Atrophy / involution, grade 1
-Cyst(s), focal/multifocal
MANDIBULAR GLANDS:
Only one of paired organs examined/present
PANCREAS:
-Acinar cell vacuolation, focal, grade 1
MANDIBULAR LYMPH NODES:
-Lymphoid hyperplasia, bilateral, grade 1
EYES:
-Retro-orbital hemorrhage, unilateral, grade 1
VAGINA:
-Estrus
LARYNX:
-Inflammatory cell infiltrate, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 76
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-Inflammatrory cell focus/foci, grade 1
-Increased hepatocytic glycogen deposits, grade 1
SPLEEN:
-Hemosiderin storage, grade 2
PEYER'S PATCHES (JEJUNUM):
-Mineralization, grade 1
PEYER'S PATCHES (ILEUM):
-Lymphoid hyperplasia, grade 1
LUNGS:
-Alveolar macrophages, multifocal, grade 1
THYMUS:
-Atrophy / involution, grade 1
-Cyst(s), focal/multifocal
MANDIBULAR GLANDS:
Only one of paired organs examined/present
PARATHYROID GLANDS:
Only one of paired organs examined/present
EYES:
-Peri-orbital Inflammation, unilateral, grade 1
OPTIC NERVES:
Tissue not present for histologic examination
UTERUS:
-Luminal dilation, (cyclic change)
VAGINA:
-Proestrus
BONE MARROW (FEMUR):
-Fatty replacement, grade 1

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 76

LARYNX:

-Desiccated secretion, focal, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0

DAYS ON TEST : 90

* ANIMAL NO. : 77

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-Inflammatroy cell focus/foci, grade 1

-Increased hepatocytic glycogen deposits, grade 1

SPLEEN:

-Hemosiderin storage, grade 2

MESENTERIC LYMPH NODE:

-Lymphoid hyperplasia, grade 1

THYMUS:

-Atrophy / involution, grade 1

-Cyst(s), focal/multifocal

MANDIBULAR GLANDS:

Only one of paired organs examined/present

SUBLINGUAL GLANDS:

Only one of paired organs examined/present

PARATHYROID GLANDS:

Only one of paired organs examined/present

ADRENAL CORTICES:

-Vacuolation, zona fasciculata/reticularis, focal, unilateral,
grade 1

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TEST SYSTEM : RAT, 90-Day, Oral (Gavage) DATE : 13-MAY-09
SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 77

EYES:

-Retro-orbital hemorrhage, unilateral, grade 1

HARDERIAN GLANDS:

-Porphyrin deposits, bilateral, grade 1

SKELETAL MUSCLE:

-Mononuclear infiltration, focal, grade 1

VAGINA:

-Estrus

BONE MARROW (FEMUR):

-Fatty replacement, grade 1

PITUITARY GLAND:

-Cyst, single, pars distalis, grade 1

ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0

DAYS ON TEST : 90

* ANIMAL NO. : 78

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:

-Inflammatrory cell focus/foci, grade 1

SPLEEN:

-Extramedullary hemopoiesis, grade 1

-Hemosiderin storage, grade 2

PEYER'S PATCHES (ILEUM):

-Lymphoid hyperplasia, grade 1

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 78

LUNGS:
-Alveolar hemorrhage, focal/multifocal, grade 1
THYMUS:
-Cyst(s), focal/multifocal
MANDIBULAR GLANDS:
Only one of paired organs examined/present
SCIATIC NERVES:
-Axonal degeneration, secondary, focal/multifocal, bilateral,
grade 1
EYES:
-Retro-orbital hemorrhage, unilateral, grade 1
VAGINA:
-Diestrus
BONE MARROW (FEMUR):
-Fatty replacement, grade 1
-Hemosiderin deposits, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 79

* NECROPSY FINDINGS

LIVER:
01: PAPILLARY PROCESS: DISCOLORATION, DARK RED.
NO OTHER NECROPSY OBSERVATIONS NOTED

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 79

* MICROSCOPIC FINDINGS

LIVER:

- Fatty change, focal, grade 1
- Increased hepatocytic glycogen deposits, grade 1
- Congestion, focal
This finding corresponds to necropsy observation no: 01.
- Kupffer cell siderosis, focal, grade 3
- Focal necrosis, grade 3

SPLEEN:

- Hemosiderin storage, grade 2

PEYER'S PATCHES (JEJUNUM):

- Mineralization, grade 1

LUNGS:

- Alveolar macrophages, multifocal, grade 1

MANDIBULAR GLANDS:

Only one of paired organs examined/present

PARATHYROID GLANDS:

Only one of paired organs examined/present

EYES:

- Retro-orbital hemorrhage, unilateral, grade 1
- Peri-orbital Inflammation, unilateral, grade 1

OPTIC NERVES:

Only one of paired organs examined/present

HARDERIAN GLANDS:

- Porphyrin deposits, bilateral, grade 1

SKELETAL MUSCLE:

- Mononuclear infiltration, grade 1

VAGINA:

- Diestrus

BONE MARROW (FEMUR):

- Fatty replacement, grade 1
- Hemosiderin deposits, grade 1

LARYNX:

- Inflammatory cell infiltrate, grade 1

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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 79

.....
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

* STATE AT NECROPSY: K0
DAYS ON TEST : 90 * ANIMAL NO. : 80
.....

* NECROPSY FINDINGS

NO NECROPSY OBSERVATIONS NOTED.

* MICROSCOPIC FINDINGS

LIVER:
-Increased hepatocytic glycogen deposits, grade 1
SPLEEN:
-Hemosiderin storage, grade 2
MESENTERIC LYMPH NODE:
-Lymphoid hyperplasia, grade 1
KIDNEYS:
-Tubular basophilia, focal/multifocal, unilateral, grade 1
PEYER'S PATCHES (JEJUNUM):
-Mineralization, grade 1
PEYER'S PATCHES (ILEUM):
-Lymphoid hyperplasia, grade 1
LUNGS:
-Vascular mineralization, focal/multifocal, grade 1
THYMUS:
-Cyst(s), focal/multifocal
MANDIBULAR GLANDS:
Only one of paired organs examined/present
SUBLINGUAL GLANDS:
Only one of paired organs examined/present

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TEST ARTICLE : LYSO-PHOSPHOLIPASE PATHOL. NO.: 21029 IHI
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SPONSOR : AB Enzymes GmbH PathData@System V6.2b5

TEXT OF GROSS AND MICROSCOPIC FINDINGS
DOSE GROUP : 04, 1000 mg/kg FEMALE

CONT./FF. ANIMAL NO. : 80

.....

THYROID GLAND (BOTH LOBES):
-Ultimobranchial cyst(s), focal/multifocal, unilateral
PARATHYROID GLANDS:
 Only one of paired organs examined/present
EYES:
 -Retro-orbital hemorrhage, unilateral, grade 1
OPTIC NERVES:
 Only one of paired organs examined/present
VAGINA:
 -Proestrus
BONE MARROW (FEMUR):
 -Fatty replacement, grade 1
PITUITARY GLAND:
 -Cyst, single, pars distalis, grade 1
ALL OTHER PROTOCOL TISSUES WITHOUT PATHOLOGIC FINDINGS.

**An application to amend the
Australia New Zealand Food
Standards Code with a Triacylglycerol
lipase preparation produced by a
genetically modified *Trichoderma
reesei***

AB Enzymes GmbH

Appendix 13 – CCI version

May 29, 2018

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Elements in Appendix 13 that are to be treated as **confidential commercial information** (CCI) are marked in **highlighted text** in this CCI version (the corresponding text will be marked as in the non-CCI version).

II. The host/receipient organism

The recipient strain used for the genetic modifications in constructing RF10625 was *Trichoderma reesei* strain [REDACTED], a genetically modified derivative of [REDACTED] mutant strain.

a. Taxonomy

Trichoderma reesei is a hypercellulolytic fungus which was found on deteriorating military fabrics such as tents and clothing.

Taxonomic studies have shown that the species *Trichoderma reesei* consists only of a single isolate QM6a and its derivatives (Nevalainen et al. 1994).

The taxonomic classification of *T. reesei* is: *Hypocreaceae*, *Hypocreales*, *Hypocreomycetidae*, *Sordariomycetes*, *Pezizomycotina*, *Ascomycota*, *Fungi*, according to *Index Fungorum* database.

T. reesei can be identified by PCR-fingerprinting assay and sequence analyses of the nuclear ribosomal DNA region containing the internal transcribed spacers (ITS-1 and ITS-2) and the 5.8S rRNA gene (Kuhls et al. 1996).

Synonyms¹: *Trichoderma reesei* is the species name given to the anamorphic form (the form which reproduces asexually) of the fungus whose teleomorphic form (the form which reproduces sexually) is now understood to be *Hypocrea jecorina* (Kuhls et al. 1996; Seidl et al. 2008).

Trichoderma reesei was formerly known as *Trichoderma longibrachiatum*. Therefore, it is of relevance to note that enzymes have been approved that are produced by *T. reesei* under the name of *T. longibrachiatum*².

The *T. reesei* parental strain [REDACTED] was characterized by the Centraalbureau voor Schimmelcultures (CBS) in the Netherlands as *Trichoderma reesei*. It was identified based on the

¹ Reference: *Mycobank taxonomic database* (see: <http://www.mycobank.org/Biolomics.aspx?Table=Mycobank&Page=200&ViewMode=Basic>).

² see: <http://amfep.drupalgardens.com/sites/amfep.drupalgardens.com/files/Amfep-List-of-Commercial-Enzymes.pdf>

sequences of Internal Transcribed Spacer 1 and 2 and the 5.8S gene and Translation Elongation Factor 1 α . *T. reesei* [REDACTED] was deposited as a CBS culture (safe deposit) as CBS 114041.

The classification of [REDACTED] (also referred to as [REDACTED]³) as *Trichoderma reesei* has been confirmed by the Centraalbureau voor Schimmelcultures (CBS) in the Netherlands ([Appendix #13.1](#)).

Therefore the recipient can be described as followed:

Genus:	<i>Trichoderma</i>
Species:	<i>Trichoderma reesei</i>
Subspecies (if appropriate):	not applicable
Generic name of the strain:	[REDACTED]
Previous or other name(s) (if applicable):	none
Commercial name:	Not applicable. The organism is not sold as such.

Synonyms⁴: *Trichoderma reesei* is the species name given to the anamorphic form (the form which reproduces asexually) of the fungus whose teleomorphic form (the form which reproduces sexually) is now understood to be *Hypocrea jecorina*.

Trichoderma reesei was formerly known as *Trichoderma longibrachiatum*.

b. Construction of the host

The *Trichoderma reesei* host strain is a classical mutant derived from *T. reesei* QM6a.

Trichoderma reesei [REDACTED] was developed from the wild type strain QM6a by conventional mutagenesis.

The genetically modified strain [REDACTED] used as a recipient in construction of RF10625 derives from [REDACTED]. For a summary of the genetic construction steps from [REDACTED] see [Appendix #13.2](#).

³ Both numbers are indifferently referring to the same strain, depending on ROAL or AB Enzymes reference system. For easy reading, the RF reference number will be use most of the time throughout the dossier.

⁴ Reference: Mycobank taxonomic database (see: <http://www.mycobank.org/Biolomics.aspx?Table=Mycobank&Page=200&ViewMode=Basic>).

III. Origin and donor of vector and inserts

a. The enzyme gene

Origin

The *Fusarium oxysporum* lipase gene for lipase protein overproduced by RF10625 was designed and synthesized using the preferred codon usage for *Trichoderma reesei*. A codon-optimized *Fusarium oxysporum* lipase [REDACTED] encoding sequence was designed based on the *Hypocrea jecorina* preferred codon usage (<http://www.kazusa.or.jp/codon/cgi-bin/showcodon.cgi?species=51453>) and synthesized by Eurofins (Germany). The lipase DNA sequence, with ATG (Met) codon at position +1 comprises an open reading frame of [REDACTED]. The codon-optimized lipase sequence expressed in *T. reesei* showed 86% identity to the original lipase sequence from *Fusarium oxysporum*. **The amino acid sequence remained unchanged.**

Allergenicity

In order to specifically evaluate the risk that the lipase enzyme would cross react with known allergens and induce a reaction in an already sensitized individual, sequence homology testing to known allergens was performed. This test used a 80 amino acid (aa) sliding window search as well as conventional FASTA alignment (overall homology), with the threshold of 35% homology as recommended in the most recent literature (Food and Agriculture Organization of the United Nations January/2001; Ladics et al. 2007; Goodman et al. 2008).

A sequence homology comparison test was then performed using a database of allergens from the Food Allergy Research and Resource Program (FARRP), University of Nebraska, Allergen Database (Version 14, January 20, 2014), which contains the amino acid sequences of known and putative allergenic proteins.

The resulting alignments of the full-length lipase protein sequence to any allergenic proteins in the allergen database showed no sequences with $E() < 1.000000$. In addition, the lipase protein sequence

showed no matches of greater than 35% to the known allergens when searching for 80 amino acid alignments and no perfect match when searching for a stretch of eight amino acids.

See [Appendix #13.3](#) for further information.

Conclusion:

Based on the results obtained from the bioinformatics approach to estimate potential allergenicity on relatedness to known allergens and taking into account the most recent scientific recommendations on the interpretation of such data, and based on the fact that the enzyme is typically denatured during the food manufacturing process and that any residual enzyme still present in the final food will be subject to digestion in the gastro-intestinal system, it is not likely that the lipase produced by *Trichoderma reesei* RF10625 under evaluation will cause allergic reactions after ingestion of food containing the residues of these enzymes.

b. Vector

The *Fusarium oxysporum* lipase [REDACTED] encoding sequence was designed and synthesized using the preferred codon usage for *Trichoderma reesei*. The lipase gene contains an *AvrII* site four nucleotides upstream of the ATG and a *PacI* site downstream of the stop-codon. The lipase gene was cloned into the pCR4-TOPO vector, resulting in the plasmid Lip-FO.

The plasmid Lip-FO was digested with *AvrII* and *PacI*. The *AvrII-PacI* fragment containing the lipase gene was ligated into the *SpeI* and *PacI* sites of the plasmid pAB140SP ([Appendix #13.4](#)) resulting in the plasmid pAB140SP-LipFO. In this plasmid the *Fusarium oxysporum* lipase gene was placed under the control of the *Trichoderma reesei* [REDACTED] promoter and [REDACTED]-terminator.

The plasmid pAB140SP-LipFO was characterized by restriction with endonucleases and the construct was confirmed by DNA sequencing. The expression plasmid pAB140SP-LipFO is shown in more detail in [Appendix #13.5](#).

The description of the plasmid Lip-FO used in the construction of the plasmid pAB140SP-LipFO is included in [Appendix #13.6](#).

The plasmid pAB140SP-LipFO was digested with *NotI* and the expression cassette containing the lipase gene was isolated ([Appendix #13.7](#)). The purified expression cassette was used for transformation of *T. reesei* [REDACTED].

c. Promoter

The lipase is expressed under the strong [REDACTED] promoter.

IV. Introduced genetic sequence

Standard molecular biology methods were used in the construction of the expression plasmid. The expression cassette fragment used in fungal transformation does not contain any vector derived sequences as it is isolated from the expression plasmid by restriction digestion and purification from an agarose gel. It is free from any harmful sequences and contains the following genetic materials:

- ***Fusarium oxysporum lipase gene***: The lipase gene was synthesized using the preferred codon usage for *Trichoderma reesei*. [REDACTED]
[REDACTED]. The sequence of the lipase gene and the deduced amino acid sequence of the encoded protein are included [Appendix #14.8](#). For the construction of the expression vector, the gene is fused at its 5'-end to the [REDACTED] promoter. This promoter is strong and is used to drive *lipase* expression, to obtain high yields of lipase enzyme.
- **Linker**: synthetic DNA sequence contained *PacI* and *BamHI* restriction sites
- [REDACTED] **terminator**: To ensure termination of transcription the native [REDACTED] terminator is used.
- **Linker**: synthetic DNA sequence with *StuI* restriction site

- ***Aspergillus nidulans amdS* gene**: the gene has been isolated from *Aspergillus nidulans* VH1-TRSX6 (Kelly, Hynes 1985). *Aspergillus nidulans* is closely related to *Aspergillus niger*, which is used in industrial production of food enzymes. The gene codes for an acetamidase that enables the strain to grow on acetamide as a sole nitrogen source. This characteristic has been used for selecting the transformants. The product of the *amdS* gene, acetamidase, can degrade acetamide and is not harmful or dangerous. The *amdS* marker gene has been widely used as a selection marker in fungal transformations without any disadvantage for more than 20 years.

Of the above genetic materials, the lipase gene and *Aspergillus nidulans amdS* gene are not naturally present in the host genome.

The DNA fragments that have been transformed to *T. reesei* host strain are well characterized, the sequences of the genes are known, and the fragments are free from any harmful sequences.

V. Construction of the recombinant production organism

The transformation of *T. reesei* host strain with the expression cassettes was performed as described by Penttilä et al. (1987) with the modifications described in Karhunen et al. (1993).

Southern blot analyses were performed to the genome of the production strain RF10625. Results indicated that [REDACTED] of the expression cassettes were integrated in the genome of strain RF10625 (Appendix #13.9).

VI. Description of the production organism

a. Identity and taxonomy

The transformed production strain containing the lipase gene is ***Trichoderma reesei* strain RF10625** which is deposited in the "Centraalbureau voor Schimmelcultures" (CBS) in the Netherlands with the deposit number CBS 134213.

The taxonomic classification of the *T. reesei* is: *Hypocreaceae*, *Hypocreales*, *Hypocreomycetidae*, *Sordariomycetes*, *Pezizomycotina*, *Ascomycota*, Fungi, according to Index *Fungorum* database. See [section II.a.](#) for more taxonomy details.

b. Stability of the genetic traits in the GMM

T. reesei strains are widely used in biotechnological processes because of their known stability.

The production strain RF10625 is stable in terms of genetic traits. The genetic materials in the expression cassettes have been integrated as part of the genome and are as stable as any natural gene. The integrated genetic materials are not acting as mobilisable elements and they do not contain mobilisable elements.

Potential changes in the genome of the production strain could theoretically occur during the propagation in the fermentation process. Therefore, Southern blot analysis was performed after fermentation process of the RF10625 strain (see [Appendix #13.10](#)). The results revealed that the lipase gene stays genetically stable in *T. reesei* genome over necessary time that is needed for industrial fermentation process of the RF10625 production strain.

Additionally, the stability is also followed as equal production of the lipase in a number of fermentation batches performed for the *T. reesei* strain RF10625. The activity measurements from parallel successful fermentations showed that the productivity of the RF10625 strain remains unchanged.

c. Mobilisation and transfer capacity

The inserted DNA does not include any mobile genetic element. Additionally, it should be highlighted that *T. reesei* genome lacks a significant repetitive DNA component and no extant functional transposable elements have been found in the genome (Kubicek et al. 2011; Martinez et al. 2008). This results to low risk of transfer of genetic material.

d. Presence of acquired antimicrobial resistance genes

The review article by Nevalainen et al. (1994) reveals that some species belonging to *Trichoderma* genus are able to secrete various types of antibiotics in laboratory cultures. However, strains of *T. reesei* used in industrial applications are proven to be absent of antibiotic activities (Hjortkjaer et al. 1986; Coenen et al. 1995). The absence of antibiotic activities, according to the specifications recommended by JECFA was also confirmed.

Additionally, no genes have been introduced during the genetic construction that encode antimicrobial resistance.

VII. Information on any Significant Similarity between the Amino Acid Sequence of the Enzyme and that of Known Protein Toxins

A study was conducted to assess the toxicity of the *Fusarium oxysporum* lipase using bioinformatics tools.

A homology search was performed from the non-redundant protein sequences database (nr) using the BLAST-P (protein – protein BLAST) program, v. 2.6.1+ (Altschul *et al.*, 1997; <http://blast.ncbi.nlm.nih.gov/>). The amino acid sequence of the lipase (██████████) was used as the query sequence in the searches. For the purpose of toxicity analysis, additional search criterion was used to limit the search to sequences that are related to toxins. The word “toxin” was given as the Entrez Query.

For detailed methods and results, see [Appendix #13.11](#).

According to the results obtained from the searches performed it can be concluded that the lipase protein does not shown significant homology to any protein sequence identified or known to be a toxin.

VIII. Appendices

13.1. Centraalbureau voor Schimmelcultures (CBS) of host strain - Confidential

13.2. [Redacted]

13.3 [Redacted]

13.4 [Redacted]

13.5 [Redacted]

13.6 [Redacted]

13.7 [Redacted]

13.8 [Redacted]

13.9. [Redacted]

13.10) [Redacted]

13.11. [Redacted]

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