REPORT No. 2500114
Regulatory Document

DSM

Document Date:	20-Sep-2005
Author(s):	Weber E (DSM) & Ramesh E (Testing Facility)
Title:	REPEATED DOSE (28-DAY) ORAL TOXICITY STUDY WITH CALCIUM LIGNOSULFONATE IN WISTAR RATS (Testing Facility: Rallis / Advinus, Study Number: 4091/04)
Project No.	6309
Compound No.	LSFG DP955 (FGR-004)

Summary

The test item Lignosulfonate, manufactured by Borregaard Industries Ltd, Post Box 162, N-1701 SARPSBORG, Norway and supplied by DSM Nutritional Products Ltd, Wurmisweg 576, CH-4303 Kaiseraugst, SWITZERLAND was tested for its toxic potential in a "Repeated dose (28-day) oral toxicity study in Wistar rats".

The test item was mixed with the Ssniff rats/mice powder food to administer specified test item dose levels of 500, 1500 and 4000 mg/kg Bwt/day to low (G2), mid (G3) and high (G4) dose groups, respectively. A concurrent control group (G1) received Ssniff rats/mice powder food without the test item admixture. All the four groups consisted of 6 male and 6 female rats per group.

(Summary continued on page II)

This report consists of Pages I – II and 1-140

Distribution
B. Mussler (pdf-file of report)

Approved

Name	Signature	Date
Main Author E. Weber		03-Oct-2005
Principal Scientist / Competence Mgr J. Bausch		6 Oct 05
Research Center Head L. Pasamontes		13.10.05
Project Manager B. Mussler		18/10/05

Summary (continued)

Observations were made for unscheduled mortality, clinical signs, ophthalmologic findings, physical abnormalities, body weight changes, feed consumption. Laboratory investigations (haematology and clinical chemistry parameters), organ weights and their ratios and gross pathology were performed at sacrifice. Histopathological examination was carried out on the preserved organs and tissues (including gross lesions) of the control and high dose groups. All gross lesions in the lower dose groups (both males and females) and rectum in the low and mid dose males were examined.

Under the experimental conditions described in the material and method section, the following results were observed:

- At 500 and 1500 mg/kg Bwt/day the test item did not affect the general health status, growth and food consumption, haematological and clinical chemistry parameters, fasting body weights, organ weights and their ratios, gross and histopathology in male and female rats.

- At 4000 mg/kg Bwt/day the test item did not affect the general health status, growth and food consumption, haematological and clinical chemistry parameters, fasting body weights, organ weights and their ratios and gross pathology in male and female rats. Microscopically, rectum showed chronic inflammation of minimal severity in males, which is considered treatment related change.

NO OBSERVED EFFECT LEVEL (NOEL):

In view of the results discussed above, as no treatment-related changes were noted in animals that received a dose of 1500 mg/kg Bwt/day of Lignosulfonate, this level is considered to be the No Observed Effect Level (NOEL) of Lignosulfonate in Wistar rats, under the test conditions and doses employed.

CONCLUSIONS:

The results of this study indicated that the oral administration of Lignosulfonate in male and female Wistar rats at doses of up to 4000 mg/kg Bwt/day did not affect the general health status, growth and food consumption, haematological and clinical chemistry parameters, fasting body weights, organ weights and their ratios, and gross pathology. The only treatment-related finding was a chronic inflammation in the rectum of high dose males.

In view of the results discussed above, as no treatment-related changes were noted in animals that received a dose of 1500 mg/kg Bwt/day of Lignosulfonate, this level is considered to be the No Observed Effect Level (NOEL) of Lignosulfonate in Wistar rats, under the test conditions and doses employed.

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STUDY TITLE

REPEATED DOSE (28-DAY) ORAL TOXICITY STUDY WITH CALCIUM LIGNOSULFONATE IN WISTAR RATS

DATA REQUIREMENTS

1. OECD 407, adopted 27th July 1995 (OECD, 1995)

STUDY DIRECTOR AND AUTHOR: Mr. E. RAMESH

STUDY COMPLETED ON: 20.09.2005

SPONSOR

DSM NUTRITIONAL PRODUCTS LTD
WURMISWEG 576
4303 KAISERAUGST, SWITZERLAND

PERFORMING LABORATORY

TOXICOLOGY DEPARTMENT
ADVINUS THERAPEUTICS PRIVATE LIMITED
POST BOX No. 5813, PLOT Nos. 21 & 22
PEENYA II PHASE, BANGALORE - 560 058
INDIA

LABORATORY PROJECT ID

STUDY No.: 4091/04

(COPY No. 1/3)

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 1/140

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STATEMENT OF CONFIDENTIALITY

The report contains **confidential** and **proprietary** information of DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland which would not be disclosed to anyone except the employees of this company or to persons authorised by law or judicial judgement without an expressed or a written approval of DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland.

STATEMENT OF GLP COMPLIANCE

The study was performed in compliance with the OECD Principles of Good Laboratory Practice (GLP) for the testing of chemicals [OECD, {C(97) 186/Final} adopted on 26th November, 1997] and in accordance with the Standard Operating Procedures and the Study Plan.

This study was conducted with OECD Guideline No. 407 for the testing of chemicals, "Repeated Dose 28-Day Oral Toxicity Study in Rodents" adopted on 27th July, 1995.

DECLARATION

The Study Director hereby declares that the work was performed under his supervision and in accordance with the described procedures. It is assured that the reported results faithfully represent the raw data obtained during the experimental work. No circumstances have been left unreported which may have affected the quality or integrity of the data or which might have a potential bearing on the validity and reproducibility of this study.

The Study Director accepts overall responsibility for the technical conduct of the study as well as the interpretation, analysis, documentation and reporting of the results except for the data related to the results of concentration, homogeneity and stability of test item in food which are the responsibility of the study sponsor.

Mr. E. RAMESH
Study Director

20.09.2005
Date

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 2/140

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QUALITY ASSURANCE STATEMENT

The Study No.: 4091/04, entitled " Repeated dose (28-day) oral toxicity study with Calcium Lignosulfonate in Wistar rats" has been inspected in accordance with the OECD Principles of Good Laboratory Practice [C(97) 186/Final].

This study was inspected and findings reported to Management and to the Study Director on the dates shown below:

Inspection Date	Study Phase	Reporting date
	INITIATION PHASE	
24.12.2004	Study plan review	24.12.2004
24.01.2005	Review of Amendment No. 1 to study plan	24.01.2005
18.08.2005	Review of Amendment No. 2 to study plan	18.08.2005
	IN-LIFE PHASE	
19.01.2005	Body weights, feed mixing and feed input	25.01.2005
16.02.2005	Preparation of blood smears	21.02.2005
17.02.2005	Terminal sacrifice – main groups	21.02.2005
	REPORTING PHASE	
11.04.2005 to 19.04.2005	Draft report review	19.04.2005
25.08.2005 & 26.08.2005	Final report review	26.08.2005

Inspections were performed according to the Standard Operating Procedures of the test facility's Quality Assurance Unit. The report was inspected against the approved study plan and pertinent raw data and accurately reflects the raw data.

Date: 20/09/2005

Satish Murthy. V

(Mr.SATISH MURTHY. V)
Head, Quality Assurance Unit
Advinus Therapeutics Private Limited,
Bangalore

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 3/140

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LIST OF COMMONLY USED ABBREVIATIONS AND SYMBOLS

Alb	Albumin
Alp	Alkaline phosphatase
ALT	Alanine aminotransferase
App	Appendix / Appendices
Approx.	Approximately
AST	Aspartate aminotransferase
Baso	Basophils
BUN	Blood Urea Nitrogen
Bwt	Body weight
Chol	Total Cholesterol
Creat	Creatinine
Cm	Centimetre
Eosi	Eosinophil
EDTA	Ethylene Diamine Tetra Acetic Acid
Epididym	Epididymides
F	Female
fl	Femto litre
g	gram
G	Giga
G.	Group
GGT	Gamma Glutamyl Transpeptidase
Glu	Fasting glucose
H	Height
Hb	Haemoglobin
Hct	Haematocrit
K	Potassium
kg	kilogram
L	Length
l	litre
Lymp	Lymphocyte
m	meter
M	Male
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
mEq	milli Equivalent
mg	milligram
min	minute
mmol	millimole
Mono	Monocytes
NA	Not Applicable
Na	Sodium
NAD	No Abnormality Detected
Neut	Neutrophil
nm	nanometer
No.	Number
pg	picogram
Plat	Platelets
P.T.	Prothrombin time
RBC	Red Blood Corpuscles
rpm	revolutions per minute
Ref.App.	Reference Appendix
s	seconds
SD	Standard Deviation
T	Tera
Tot.Pro	Total plasma protein
U	Units
UV	Ultra violet
W	Width
WBC	White Blood Corpuscles
%	per cent
µmol	micromole
°C	Degree Celsius

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 4/140

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TABLE OF CONTENTS

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

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1. SUMMARY

The test item Lignosulfonate, manufactured by Borregaard Industries Ltd, Post Box 162, N-1701 SARPSBORG, Norway and supplied by DSM Nutritional Products Ltd, Wurmisweg 576, CH-4303 Kaiseraugst, SWITZERLAND was tested for its toxic potential in a "Repeated dose (28-day) oral toxicity study in Wistar rats".

The test item was mixed with the Ssniff rats/mice powder food to administer specified test item dose levels of 500, 1500 and 4000 mg/kg Bwt/day to low (G2), mid (G3) and high (G4) dose groups, respectively. A concurrent control group (G1) received Ssniff rats/mice powder food without the test item admixture. All the four groups consisted of 6 male and 6 female rats per group.

Observations were made for unscheduled mortality, clinical signs, ophthalmologic findings, physical abnormalities, body weight changes, feed consumption. Laboratory investigations (haematology and clinical chemistry parameters), organ weights and their ratios and gross pathology were performed at sacrifice. Histopathological examination was carried out on the preserved organs and tissues (including gross lesions) of the control and high dose groups. All gross lesions in the lower dose groups (both males and females) and rectum in the low and mid dose males were examined.

Under the experimental conditions described in the material and method section, the following results were observed:

- At 500 and 1500 mg/kg Bwt/day the test item did not affect the general health status, growth and food consumption, haematological and clinical chemistry parameters, fasting body weights, organ weights and their ratios, gross and histopathology in male and female rats.
- At 4000 mg/kg Bwt/day the test item did not affect the general health status, growth and food consumption, haematological and clinical chemistry parameters, fasting body weights, organ weights and their ratios and gross pathology in male and female rats. Microscopically, rectum

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showed chronic inflammation of minimal severity in males, which is considered treatment related change.

NO OBSERVED EFFECT LEVEL (NOEL):

In view of the results discussed above, as no treatment-related changes were noted in animals that received a dose of 1500 mg/kg Bwt/day of Lignosulfonate, this level is considered to be the No Observed Effect Level (NOEL) of Lignosulfonate in Wistar rats, under the test conditions and doses employed.

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2. STUDY DETAILS

Study Title	:	Repeated dose (28-day) oral toxicity study with Calcium Lignosulfonate in Wistar rats
Test Item	:	Calcium Lignosulfonate
Study Number	:	4091/04
Study Director	:	Mr. E. RAMESH
Sponsor	:	DSM Nutritional Products Ltd Wurmisweg 576 4303 Kaiseraugst, Switzerland
Monitoring Scientist	:	Dr. Edgar Weber DSM Nutritional Products Ltd Bldg 205 / Room 315 P.O. Box 3255 CH-4002 Basel Switzerland
Test Facility	:	Toxicology Department Advinus Therapeutics Private Limited Post Box No. 5813, Plot Nos. 21 & 22 Peenya II Phase Bangalore – 560 058 INDIA

Experimental schedule

• Acclimatization	:	Start: 14.01.2005	End: 18.01.2005
• Treatment	:	Start: 19.01.2005	End: 16.02.2005
• Sacrifice	:	17.02.2005	

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3. STUDY PERSONNEL

The following personnel participated in the conduct of the study.

Name, Responsibility, Section / Department	Function	Signature with date
Mr. E. RAMESH M.Sc., Study Director Chronic section	Overall in-charge for the conduct of the study and report preparation.	20.09.2005
Mr. B. N. VISHWANATH M.Sc., Technical co-ordinator Chronic section	Assistance in conduct of the study and report preparation.	01/09/05
Dr. H. KRISHNAPPA M.V.Sc., Study Veterinarian Chronic section	Veterinary services	01/09/05
Mr. M. Y. SUNAGAR M.Sc., Laboratory Investigations Haematology, Clinical Biochemistry and Radioisotope Section	Analyst – Haematology & Clinical chemistry	1/9/05
Mr.P.V. LOKESH M.Sc., Necropsy and Histotechniques Histopathology Section	Group Leader – Necropsy & Slide Preparation	1.9.05
Dr. JOMY JOSE M.V.Sc., Necropsy Histopathology Section	Necropsy and Pathology services	1.9.05
Dr. K. KAMALA M.V.Sc., Pathology Histopathology Section	Pathologist	1/9/2005
Ms.T.M.TEJASWINI B.Sc., Histopathology Data Entry EDP Section	Documentation	1/9/2005
Mr. SANJEEV. V. HULSOOR B.Sc. Data Entry EDP Section	Data Entry	1/9/05
Mr. M. VENKATESULU B.Sc. Data Analysis and Report Compilation, EDP Section	Report preparation & Documentation	1.9.05

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4. OBJECTIVE

The purpose of this Repeated Dose 28 day Oral Toxicity in Rodents study was to assess the toxicological profile of the test item when administered to rats. The animals were observed during the entire treatment period. This study may provide information on major toxic effects, target organs and an estimate of a No Observed Effect Level (NOEL) / No Observed Adverse Effect Level (NOAEL).

5. GUIDELINE

This study was performed in accordance with the following guideline:

- OECD 407 adopted July 27 1995 (OECD, 1995) [As per the request of sponsor this study did not include recovery groups and neurological examination at the end of treatment was not carried out].

This study was also conducted in accordance with the standard operating procedures and the mutually agreed study plan signed by Study Director and Monitoring Scientist on 06.01.2005 and 17.01.2005 respectively. Subsequently the study plan was amended, Amendment No. 1 signed by Study Director on 28.01.2005 and by the Sponsor's Monitoring Scientist on 01.02.2005 and Amendment No. 2 signed by Study Director on 27.08.2005 and by the Sponsor's Monitoring Scientist on 19.09.2005.

6. MATERIAL AND METHOD

6.1 MATERIAL

6.1.1 Test Item Information

(as furnished by the Sponsor)

Name	:	Ultrazine FG-R®
Common Name (active ingredient)	:	Calcium Lignosulfonate
Name to be used in the report	:	Lignosulfonate

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Chemical name (IUPAC)	:	Not applicable
Code by test facility	:	052/8-CLSN
CAS No.	:	8061-52-7
Batch No.	:	004 (DP955)
Manufactured by	:	Borregaard Industries Ltd Post Box 162 N-1701 SARPSBORG, Norway
Supplied by		DSM Nutritional Products Ltd Wurmisweg 576 CH-4303 Kaiseraugst, SWITZERLAND
Date of manufacture	:	January 2004
Date of expiry	:	January 2006
Date of receipt at test facility	:	23.12.2004
Purity to be stated in the report	:	About 85%
Physical appearance	:	Brownish free-flowing powder
Storage conditions	:	Ambient (+18 to +36^0 C), dry
Hazards and precautions	:	Hazards: no specific known Precautions: Standard hygienic procedures (gloves, goggles, face mask)

6.1.2 Equipments

Balances:

- For test item weighing:
  Mettler BB 2400, Capable of weighing 2400 g with the sensitivity of 0.01 g.

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- For animal and feed weighing:
  Sartorius BP 2100S, Capable of weighing 2100 g with the sensitivity of 0.01 g.

  Avery PS6C, Capable of weighing 2500 g with the sensitivity of 0.1 g.

- For organ weighing:
  Mettler Toledo PG 503-S, Capable of weighing 500 g with the sensitivity of 0.001 g.

Ophthalmoscope:
- For ophthalmological examination:
  Welch Allyn.

Sysmex TM K-800:
- For Haematology parameters

BM-HITACHI 704:
- For Clinical chemistry parameters

ST-art-4 coagulation analyzer:
- For Prothrombin time

Easylyte Sodium Potassium analyzer:
- For Sodium and Potassium parameters

Deep freezer:
- For storing experimental feed and plasma samples

6.1.3 Test System

Animals	:	HsdCpb: WU rats-conventionally bred (in-house random bred) Strain: Wistar Substrain: Hsdola (Parent stock obtained from Harlan, UK Limited).
Justification for selection of species	:	Rat is one of the test systems referred by the guideline.
Source	:	Toxicology Department Rallis Research Centre Bangalore - 560 058, INDIA

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No. of groups	:	4 groups: Control, low, mid and high dose groups
No. of rats/group	:	12 rats (6 males + 6 females)
Date of birth	:	11.12.2004 to 13.12.2004
Age at start of treatment	:	5 weeks

Mean body weights (g)
Mean ± SD at the start of treatment :

	Males	Females
G1:	134.53 ± 16.52	108.64 ± 7.30
G2:	135.08 ± 10.90	108.98 ± 8.98
G3:	132.83 ± 7.38	107.25 ± 7.06
G4:	135.70 ± 10.21	107.16 ± 3.35

Identification	:	The animals were individually identified by accession numbers, cage cards and turmeric colour body markings.
Acclimatization	:	After veterinary examination, for ascertaining good health and suitability for the study, the rats were acclimatized for five days before the start of the treatment. Females used in the study were nulliparous and non-pregnant. During acclimatization, animals were temporarily identified using crystal violet solution for body marking.

6.2 METHOD

6.2.1 Principle

To evaluate the potential toxicity of Calcium Lignosulfonate when administered to Wistar rats for a minimum of 28 consecutive days. This study may also be applicable for predicting toxicity in humans as it is a possible route of exposure to humans.

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6.2.2 Performance of the Test

6.2.2.1 Husbandry

Room Number

Laboratory Room No. SC-25

Conditions

- Air conditioned with adequate filtered fresh air supply (12 - 15 air changes/hour),
- Temperature 20 - 23°C,
- Relative humidity 30 - 70%,
- Photo period: 12 hour light and 12 hour dark cycle.

Housing

Two rats per sex per cage were housed in sterilized standard polypropylene mesh bottom cages (size: L 410 x W 282 x H 150 mm) with stainless steel top grill having facilities for holding powder food in hopper and for drinking water in glass bottle with a stainless steel sipper tube.

Diet:

The animals were provided with *ad libitum* Ssniff rats/mice powder food-maintenance meal - low in germs manufactured by Ssniff Spezialdiäten GmbH., Ferdinand-Gabriel-Weg 16, D-59494 Söest, GERMANY. Analysis report and contaminant analysis report for Ssniff rats/mice diet – maintenance meal are given in Annexures 3 and 4, respectively.

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Water

The animals were provided with *ad libitum* water i.e., deep borewell water passed through activated charcoal filter and exposed to UV rays in Aquaguard on-line water filter-cum-purifier manufactured by Eureka Forbes Ltd., Mumbai - 400 001, INDIA. Analysis report and contaminant analysis report for water sample are given in Annexures 5 and 6, respectively.

6.2.2.2 Dose Selection

Three dose levels of 500, 1500 and 4000 mg/kg/day were selected as suggested by the sponsor.

6.2.2.3 Grouping

Grouping was done on day 1 of acclimatization period by in-house method of body weight stratification and distribution as follows:
The rats procured for the study were weighed and segregated depending upon body weight ranges. The body weights ranged between 61 - 100 g for males and 41 - 80 g for females. Animals with body weight ranges, 71-80, 81–90 g for males and 51-60, 61-70, 71-80 g for females were selected and rats within each body weight range were randomly distributed to all groups to attain group mean body weights not varying by more than 20%. The rats which were not selected or with extreme body weights were discarded. The selected male and female rats were assigned to control and different treatment groups as shown under "Group Allocation and Number of animals".

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6.2.2.4 Group Allocation and Number of Animals

The selected male and female rats were assigned to control and different treatment groups as shown below:

Group No.	Group	Colour of cage card	Dose (mg/kg Bwt/day)	No. of rats	Sex	Rat Numbers From	Rat Numbers To
G1	Control	White	0	6	M	Rf5971	Rf5976
				6	F	Rf5977	Rf5982
G2	Low dose	Yellow	500	6	M	Rf5983	Rf5988
				6	F	Rf5989	Rf5994
G3	Mid dose	Green	1500	6	M	Rf5995	Rf6000
				6	F	Rf6001	Rf6006
G4	High dose	Pink	4000	6	M	Rf6007	Rf6012
				6	F	Rf6013	Rf6018

6.2.2.5 Route of Administration

Oral through food, doses expressed as mg test item per kg body weight per day.

6.2.2.6 Diet Preparation

The experimental food were prepared once in 7 days separately for male and female sexes except for control group.
Experimental food was prepared in quantities of 4 kg for control group on all occasions and 2.5 kg for the treatment groups during the initial mixing and 2.0 kg for the subsequent mixing session of treatment groups.

Dietary concentrations were adjusted to administer specified test item dose levels of 500,1500 and 4000 mg/kg Bwt/day. To achieve this each time when the diet was prepared, adjustments were made based on body weights and food consumption data from preceding interval and the new concentration were calculated which corresponds to the dose levels of 500,1500 and 4000 mg/kg Bwt/day.

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Accordingly the concentrations of the test item in food prepared for the 4 weeks of the study are as given below (Refer Appendices 3, 4, 9 & 10, Table 4 for the body weight and food consumption data used to arrive at the dietary concentration):

Group & Sex	Weeks			
	1	2	3	4
	Dose (ppm)	Dose (ppm)	Dose (ppm)	Dose (ppm)
G1M&F	0	0	0	0
G2M	3259	4065	4578	5052
G2F	3370	3951	4362	4671
G3M	10029	11729	13578	14985
G3F	9735	12084	13365	14424
G4M	26960	30267	34803	38759
G4F	25866	31662	33681	36132

The procedure followed to prepare 2.5 kg of experimental food for the treatment groups with dietary concentrations for week 1 as given in the above table and 4.0 kg for control group is as given below:

The required quantities of test item were weighed (G2M: 8.15 g, G2F: 8.43 g, G3M: 25.07 g, G3F: 24.34 g, G4M: 67.40 g and G4F: 64.67 g) and mixed in a mixer grinder with approximately 0.5 kg of Ssniff powdered food for approximately 2 minutes to prepare the premix. This premix was mixed in stainless steel drum with approximately 0.5 kg of Ssniff powdered food for approximately 2 minutes and then added in portions to the remaining bulk food and mixed in ribbon mixer for 20 minutes.

For control group, 4 kg of Ssniff powder food was mixed in a ribbon mixer for 20 minutes.

No solvent/vehicle was used in the preparation of the experimental food.

Similar procedure as said above was followed for the subsequent mixing sessions however with the varying test item concentration the

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amount of test item adjusted to get the required test item concentration.

The diet preparations were stored in polyethylene bags within labelled stainless steel drums in the experimental room.

6.2.2.7 Chemical analysis of diet preparations

For the assessment of the concentration of the test item in food, samples from all preparations (Groups G1-G4, males and females, weeks 1-4 of treatment) were taken and stored in a deep freezer (- 21.4 to -25.0°C).

To assess the homogeneity of the prepared feed batches, five individual sub samples from different locations of the blender (top, top/mid, mid, mid/bottom, bottom) from the first batch of feed prepared (Groups G1-G4, males and females, week 1) were collected and stored in a deep freezer (- 21.4 to -25.0°C).

To investigate the stability of the test item, aliquots (stability samples) of the high and mid dose groups of the first feed batches (Groups G3 and G4, males and females, week 1) were stored in the experimental room for 10 days and subsequently stored in a deep freezer (- 21.4 to -25.0°C).

At the end of the treatment period, all the deep frozen samples were shipped on dry ice to the following address:

DSM Nutritional Products Ltd
R&D, Analytics
Sample Registration Desk
Attn. Mr. Daniele Avellina
Building 205 Room 6
Wurmisweg 576
4303 Kaiseraugst, Switzerland
Phone: +41 61 688 56 34
Fax: +41 61 688 0563
E-Mail: sample-reg-arc.kaiseraugst@dsm.com

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All analyses were performed under non-GLP conditions.

The results of the concentration, homogeneity and stability are provided in Annexure 2.

6.2.2.8 Treatment

Each test group received food specifically prepared for that group/sex. The treatment was 7 days a week for 4 weeks.

6.3 OBSERVATIONS

6.3.1 Veterinary, Clinical and Ophthalmological Examinations, General Clinical Signs and Pre-terminal deaths

a. Veterinary/Physical examination

Veterinary/physical examination was done prior to initiation of treatment and weekly thereafter during treatment period.

b. Clinical examination

Clinical examination was done prior to initiation of treatment and once weekly during treatment period.

c. Ophthalmological examination:

Ophthalmological examination of all animals was carried out with an ophthalmoscope prior to initiation of treatment and at the end of treatment period, prior to sacrifice. Mydriasis was induced before examination using 1% Tropicamide.

d. General Clinical signs and pre-terminal deaths

Clinical signs were observed once daily. All animals were observed for morbidity and pre-terminal deaths twice daily.

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6.3.2 Body Weights

Individual body weights were recorded before the administration of test item i.e., day 1 and weekly thereafter.

In addition, to arrive at the nominal dietary level of the test item for the corresponding week the body weights were also recorded on day 4 of acclimatization and day 7 of each week thereafter during the treatment period.

6.3.3 Food Intake

The following method was adopted for measurement of weekly food consumption.

Day 1[a]: Food input 1500 g (inclusive of mesh, hopper and cage card weight)	Food output on day 8 (inclusive of mesh, hopper and cage card weight)

The cagewise food consumption was calculated by adding the food consumed in 7 days and by dividing the total by the number of animals per cage to determine the food intake/rat/week. The visual estimation of food spillage was recorded at each food output recording session and during litter paper change and was taken into consideration (i.e., the food spillage data/cage/week was added to food output data) for the calculation of weekly food consumption. The weekly consumption/rat was divided by the number of days (7) to obtain food consumption (g)/rat/day. This was repeated throughout the treatment period.

In addition, to arrive at the nominal dietary level of the test item for the corresponding week the following method was adopted to measure the food consumption.

Acclimatization period:

Day 1: Food input 1500 g (inclusive of mesh, hopper and cage card weight)	Food output on day 4 (inclusive of mesh, hopper and cage card weight)

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Treatment period:

Day 1[a]: Food input 1500 g (inclusive of mesh, hopper and cage card weight)	Food output on day 7 (inclusive of mesh, hopper and cage card weight)

a: Day '1' denotes food input at the start of each week.

The cagewise food consumption was calculated by adding the food consumed in 4 or 6 days and by dividing the total by the number of animals per cage to determine the food intake/rat/week. The visual estimation of food spillage was recorded at each food output recording session and during litter paper change and was taken into consideration (i.e., the food spillage data/cage/week was added to food output data) for the calculation of weekly food consumption. The weekly food consumption/rat was divided by the number of days (4 or 6) to obtain food consumption (g)/rat/day. This was repeated throughout.

6.3.4 Clinical Laboratory Investigations

a. Blood smear:

Blood smears were made one day prior to sacrifice by tail clipping method and were stained by Wright's stain (solution) and the Differential Leucocyte Count was determined by conventional microscopy.

b. Blood collection:

At the end of the treatment period, all animals were fasted overnight (water allowed) and blood was collected from abdominal aorta under ether anaesthesia. An aliquot of blood was collected in tubes containing 3.8% sodium citrate solution for determination of prothrombin time and the remaining blood was collected into EDTA and heparinized tubes for haematology and clinical chemistry respectively.

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An aliquot of plasma (from the preparation for clinical chemistry) was deep frozen and shipped on dry ice to the sponsor (address: see section 6.2.2.7) for optional biochemical investigations which was not carried out by the sponsor.

c. Haematology:

Blood was analysed for the following haematological parameters using Sysmex TM K-800 Automated Haematology Analyzer (TOA Medical Electronics Co., Kobe, JAPAN).

1. Haemoglobin
2. Red Blood Corpuscles
3. White Blood Corpuscles
4. Haematocrit
5. Platelets

The following calculated RBC associated indices were recorded from the haematology analyser.

1. Mean Corpuscular Volume
2. Mean Corpuscular Haemoglobin
3. Mean Corpuscular Haemoglobin Concentration

Prothrombin time analysis was carried out using STart4 coagulation analyser (Diagnostica stago).

d. Clinical chemistry:

Plasma was separated in a refrigerated centrifuge at 5000 rpm for 15 minutes and analysed using BM-HITACHI 704 (Boehringer Mannheim, Mannheim, GERMANY), Automatic Analyser for the following parameters:

1. Fasting Glucose (Glu) mmol/l:
2. Blood Urea Nitrogen (BUN) mmol/l:
3. Urea (mmol/l):

$$\text{Urea} = \frac{\text{Bun value}}{0.467}$$

4. Total Plasma Protein (Tot.Pro.) g/l:
5. Aspartate Amino transferase (AST) U/l:

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

6. Alanine Amino transferase (ALT) U/l:
7. Alkaline Phosphatase (Alp) U/l :
8. Gamma Glutamyl Transpeptidase (GGT) U/l:
9. Creatinine (Creat) µmol/l:
10. Albumin (Alb) g/l:
11. Total Cholesterol (Chol) mmol/l:

The Easylyte Sodium Potassium analyser (Medica corporation U.S.A) was used for the assay of the following:
1. Sodium (Na): mEq/l 2. Potassium (K): mEq/l
The instrument (Easylyte Sodium Potassium analyzer) measures Na^+ and K^+ ions and the unit mEq/l refers to the number of ionic equivalents of Na^+ and K^+ present per liter of plasma. For Na^+ and K^+ mEq/l is same as mmol/l as both Na and K are monovalent.

6.3.5 Pathology

a. Gross necropsy:

All rats in the study were subjected to gross necropsy and the findings recorded. The animals to be sacrificed at term were fasted overnight (water allowed), anaesthetised (in randomized sequence), weighed, exsanguinated and were subjected to detailed necropsy by the Pathologist.

b. Tissue collection

The following organs and tissues were collected from all rats and preserved in 10% buffered neutral formalin:

1. All gross lesions
2. Brain (Cerebrum, Cerebellum and medulla/pons)
3. Spinal cord - 3 levels (cervical, mid thoracic and lumbar)
4. Stomach
5. Duodenum
6. Jejunum
7. Ileum (with Peyer's patches)
8. Cecum
9. Colon
10. Rectum
11. Liver
12. Kidneys
13. Adrenals
14. Spleen
15. Heart
16. Thymus
17. Thyroid
18. Trachea
19. Lungs (inflated with fixative and then immersed in formalin)
20. Testes
21. Epididymides
22. Ovaries
23. Uterus
24. Seminal vesicles
25. Coagulating glands
26. Prostate
27. Urinary bladder
28. Axillary lymph nodes
29. Mesenteric lymph nodes
30. Sciatic nerve
31. Bone marrow smear from femur

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

c. Organ weights:

The following organs were weighed from all animals: liver, kidneys, adrenals, gonads, epididymides, thymus, spleen, brain and heart. The organ weight ratios as percentage of body weight were also determined and presented in the report.

d. Histopathology:

Histopathological examination was carried out on the preserved organs and tissues (including gross lesions) of the control and high dose groups. All gross lesions in the lower dose groups (both males and females) and rectum in the low and mid dose males were examined.

The tissues were processed for routine paraffin embedding and 5 micron sections were stained with Mayer's Haematoxylin Eosin stain. Unused tissues were archived.

6.4 STATISTICAL ANALYSES

Using specific computer programmes, body weights, food consumption and laboratory investigations (haematology and clinical chemistry) data were compared by Bartlett's test for homogeneity of intragroup variances. When the variances proved to be heterogeneous, the data were transformed using appropriate transformation. The data with homogeneous intragroup variances were subjected to one-way analyses of variance (ANOVA - Snedecor and Cochran, 1987). Following ANOVA, if 'F' was found significant, Dunnett's pairwise comparison (Scheffe, 1953) of means of treated groups with control group mean was done.

All analyses and comparisons were evaluated at the 5% ($P \leq 0.05$) level.

Organ weight and organ weight ratio data was analysed by Student 't' test and Pathology data related to rectum was analysed by 'Z' test.

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

Statistically significant differences ($P \leq 0.05$), indicated by the aforementioned tests were designated by the superscripts throughout the report as stated below:

+/-: Significantly higher (+)/lower (-) than the control group

7. RESULTS AND DISSCUSSION

Details of experimental layout, treatment, laboratory investigations and sacrifice schedule are furnished in Table 1.

7.1 ANALYSES

7.1.1 Analysis of Diet Preparation

The analysis of diet preparation consisted of monitoring the content, homogeneity and stability of lignosulfonate in feed preparations. Reasonable recoveries of 94 to 110% have been found in treatment groups G2 and G4, whereas for treatment group G3 recoveries of around 90% and lower have been found. The distribution of lignosulfonate in feed was found to be homogeneous and the stability of lignosulfonate in this type of feed can be confirmed.

7.2 IN-LIFE DATA

7.2.1 Veterinary, Clinical and Ophthalmological Examinations, General Clinical Signs and Pre-Terminal Deaths

Ref. Tables 2 & 3, App. 1 & 2

Clinical Signs, Veterinary Examination, Clinical Examination and Pre-terminal deaths:

Observation during veterinary and clinical examinations, cage change or cage side observation did not reveal any clinical signs during the course of the treatment period.

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

All animals were observed for moribidity and pre-terminal deaths twice daily and there were no pre-terminal deaths in any of the groups.

Ophthalmological Examination:

Ophthalmological examination did not reveal any abnormalities in the eyes of the experimental animals.

7.2.2 Body Weights and Net Body Weight Gains

Ref. Tables 5 - 8, App. 5 - 8, Figures 1 & 2

No significant changes were observed in the mean body weights and in the net weight gains at any of the tested doses in both sexes.

7.2.3 Food Intake

Ref. Tables 9 & 10, App. 11 & 12, Figures 3 & 4

No significant changes were observed in the food consumptions at any of the tested doses in both sexes.

7.2.4 Test Item Intake

Ref. Tables 11, App. 5, 7, 11 & 12

The calculated mean daily test item intake (mg/kg Bwt/day) was:

Group: G2M

Week	W1	W2	W3	W4
Dose(ppm)	3259	4065	4578	5052
Test Item Intake (mg/kg Bwt/day)	387.6	428.4	446.1	444.5

Group: G3M

Week	W1	W2	W3	W4
Dose(ppm)	10029	11729	13578	14985
Test Item Intake (mg/kg Bwt/day)	1239.2	1248.5	1350.9	1363.8

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Group: G4M

Week	W1	W2	W3	W4
Dose(ppm)	26960	30267	34803	38759
Test Item Intake (mg/kg Bwt/day)	3493.2	3398.5	3560.1	3528.6

Group: G2F

Week	W1	W2	W3	W4
Dose(ppm)	3370	3951	4362	4671
Test Item Intake (mg/kg Bwt/day)	419.6	453.4	465.7	474.8

Group: G3F

Week	W1	W2	W3	W4
Dose(ppm)	9735	12084	13365	14424
Test Item Intake (mg/kg Bwt/day)	1190.2	1368.8	1386.7	1451.4

Group: G4F

Week	W1	W2	W3	W4
Dose(ppm)	25866	31662	33681	36132
Test Item Intake (mg/kg Bwt/day)	3224.8	3742.1	3709.3	3759.3

7.2.5 Laboratory Investigations

Haematology: Ref. Tables 12 & 13, App. 13 & 14

Males:

The following significant changes were observed:

Lower: RBC counts and Hct levels at the mid dose.

Higher: Hb, MCH and MCHC levels at the low, mid,and high doses.

Significantly higher Hb levels with corresponding higher MCH and MCHC levels are considered incidental because of no dose relation and the increase observed was mainly due to lower control values. Similarly lower RBC counts with lower Hct levels at the mid dose is also considered incidental finding due to lack of dose-relation.

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Females:

The following significant change was observed:

Higher: Prothrombin time at the high dose.

Higher prothrombin time without any significant change in the platelet counts is considered incidental and not of any biological significance. Further the higher protrombin time was also within the historical control range.

Clinical chemistry: Ref. Tables 14 & 15, App. 15 & 16

Males:

The following significant change was observed:

Higher: Cholesterol levels at the mid dose.

The higher cholesterol levels is considered incidental due to lack of dose-relation and also the values were within the historical control range.

Females:

No significant changes were observed in any of the parameters analysed.

7.2.6 Terminal Fasting Body Weights, Organ Weights and Organ Weight Ratios

Ref. Tables 16 & 17, App. 17 & 18

Males:

There were no significant intergroup differences in the terminal fasting body weights, organ weights and organ weight ratios. .

Females:

A significant increase in the absolute weight of ovaries and thymus at low dose and heart and brain in the mid dose group animals was

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

observed. These changes were not considered treatment related as there was no change in the organ weights at high dose. Further the changes in the organ weights were also within the historical control range.

7.2.7 Gross and Histopathology

Ref. Tables 18 & 19, App. 19 & 20

Gross pathology:

There were no treatment related gross findings. The few cases of kidneys-pelvis dilated were confirmed microscopically. One incidence of testes unilateral flabby was observed in a low dose male. Microscopically, this was found to be atrophy of seminiferous tubules (unilateral). The discolouration-red observed in the cecum in a mid dose male was microscopically found to be congestion. The incidences of uterus-dilatation-focal were considered physiological and not treatment related.

The other findings were also considered incidental as only single incidences were observed.

Histopathology:

Higher incidence of chronic inflammation was observed in the rectum in high dose males and hence this tissue was examined in the low and mid dose males. In low and mid dose groups this change was not observed.

The chronic inflammation in the rectum in high dose males was of minimal severity and the distribution was focal/multifocal. This lesion comprised minimal fibrosis with a few inflammatory cells infiltration.

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

The occurrence of this finding in high dose males was considered to be treatment-related.

All the other changes were considered incidental and not treatment related as the incidences were similar in control and high dose groups.

8. CONCLUSIONS

The results of this study indicated that the oral administration of Lignosulfonate in male and female Wistar rats at doses of up to 4000 mg/kg Bwt/day did not affect the general health status, growth and food consumption, haematological and clinical chemistry parameters, fasting body weights, organ weights and their ratios and gross pathology. The only treatment-related finding was a chronic inflammation in the rectum of high dose males.

In view of the results discussed above, as no treatment-related changes were noted in animals that received a dose of 1500 mg/kg Bwt/day of Lignosulfonate, this level is considered to be the No Observed Effect Level (NOEL) of Lignosulfonate in Wistar rats, under the test conditions and doses employed.

9. REFERENCES

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ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

10. ARCHIVING

Advinus will archive at the archives of the test facility the following for 15 years after completion of the study: study plan, raw data, draft and final reports. A sample of the test item has been sent from the test item stores to the archives after the receipt of test item. This sample shall be stored for a period of 2 years from the date of this final report or till next GLP inspection, whichever is later, however not beyond 30 years. All tissue specimens will be archived for 5 years; blocks and slides will be archived for 12 years after which these will be handed over to the sponsor or preserved longer at the cost of the sponsor.

11. REPORT DISTRIBUTION

Sponsor : Two signed final reports in original (Copy Nos. 1/3 to 2/3).
Archives : One signed final report in original (Copy No. 3/3).

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12. TABLES

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TABLE 1. Details of Experimental Layout, Treatment, Laboratory Investigations and Sacrifice Schedule

Group No.	Dose (mg/kg Bwt/ day)	No. of rats per group		Treatment period (days)	Laboratory investigations		Pathology			Sacrifice Schedule
		M	F		Haema-tology	Clinical Chemistry	Gross Pathology	Organ Weights	Histo-pathology	30th day
G1	0	6	6	28	+	+	+	+	+	+
G2	500	6	6	28	+	+	+	+	a	+
G3	1500	6	6	28	+	+	+	+	a	+
G4	4000	6	6	28	+	+	+	+	+	+

+: Yes; M: Males; F: Females; a: Lesions only;

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 38/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

TABLE 2. Summary of Veterinary/Physical Examination, Clinical Signs, Ophthalmological Examination and Pre-Terminal Deaths

Ref.App.: 1 & 2

PARAMETERS	Sex	Males				Females			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
	Dose (mg/kg Bwt/day)	0	500	1500	4000	0	500	1500	4000
	No. of rats	6	6	6	6	6	6	6	6
1. GENERAL EFFECTS		0	0	0	0	0	0	0	0
2. NEUROLOGICAL EFFECTS		0	0	0	0	0	0	0	0
3. RESPIRATORY EFFECTS		0	0	0	0	0	0	0	0
4. EYE EFFECTS		0	0	0	0	0	0	0	0
5. GASTRO INTESTINAL EFFECTS		0	0	0	0	0	0	0	0
6. SKIN EFFECTS		0	0	0	0	0	0	0	0
7. UROGENITAL EFFECTS		0	0	0	0	0	0	0	0
8. PRE-TERMINAL DEATHS		0	0	0	0	0	0	0	0

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 39/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

Ref.App.: 1 & 2

TABLE 3. Summary of Clinical Examination

PARAMETERS	Sex	Males				Females			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
	Dose (mg/kg Bwt/day)	0	500	1500	4000	0	500	1500	4000
	No. of rats	6	6	6	6	6	6	6	6
1. Skin and Fur		0	0	0	0	0	0	0	0
2. Eyes		0	0	0	0	0	0	0	0
3. Mucous membrane		0	0	0	0	0	0	0	0
4. Occurrence of secretions and excretions									
a. Salivation		0	0	0	0	0	0	0	0
b. Urine staining		0	0	0	0	0	0	0	0
c. Fecal staining or diarrhoea		0	0	0	0	0	0	0	0
d. Nasal discharge		0	0	0	0	0	0	0	0
5. Autonomic activity									
a. Lacrimation		0	0	0	0	0	0	0	0
b. Piloerection		0	0	0	0	0	0	0	0
c. Pupil size or Pupillary response		0	0	0	0	0	0	0	0
d. Unusual respiratory pattern		0	0	0	0	0	0	0	0
6. Response to handling		0	0	0	0	0	0	0	0
7. Changes in gait		0	0	0	0	0	0	0	0
8. Posture		0	0	0	0	0	0	0	0
9. Clonic or Tonic movements		0	0	0	0	0	0	0	0
10. Stereotypies									
a. Repetitive circling		0	0	0	0	0	0	0	0
b. Excessive grooming		0	0	0	0	0	0	0	0
11. Bizarre behaviour		0	0	0	0	0	0	0	0
a. Self mutilation		0	0	0	0	0	0	0	0
b. Walking backwards		0	0	0	0	0	0	0	0

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 40/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

Ref.App.: 3, 4, 9 & 10

TABLE 4. Dietary Concentration in Food

Males							Females						
Target Dose (mg/kg/day) ---------->				500	1500	4000	Target Dose (mg/kg/day) ---------->				500	1500	4000
	Bwt (g)	FC (g)	FCR (g/kg)	TAC (ppm)	TAC (ppm)	TAC (ppm)		Bwt (g)	FC (g)	FCR (g/kg)	TAC (ppm)	TAC (ppm)	TAC (ppm)
WEEK 0							WEEK 0						
G2M	126.43	19.4	153.4	3259			G2F	103.12	15.3	148.4	3370		
G3M	124.36	18.6	149.6		10029		G3F	102.54	15.8	154.1		9735	
G4M	126.04	18.7	148.4			26960	G4F	102.17	15.8	154.6			25866
WEEK 1							WEEK 1						
G2M	179.69	22.1	123.0	4065			G2F	130.39	16.5	126.5	3951		
G3M	174.37	22.3	127.9		11729		G3F	128.90	16.0	124.1		12084	
G4M	181.60	24.0	132.2			30267	G4F	128.23	16.2	126.3			31662
WEEK 2							WEEK 2						
G2M	227.96	24.9	109.2	4578			G2F	152.67	17.5	114.6	4362		
G3M	223.59	24.7	110.5		13578		G3F	150.58	16.9	112.2		13365	
G4M	231.44	26.6	114.9			34803	G4F	149.04	17.7	118.8			33681
WEEK 3							WEEK 3						
G2M	269.79	26.7	99.0	5052			G2F	171.90	18.4	107.0	4671		
G3M	267.73	26.8	100.1		14985		G3F	170.20	17.7	104.0		14424	
G4M	274.22	28.3	103.2			38759	G4F	167.11	18.5	110.7			36132

FC: Food consumption; FCR: Food consumption ratio; TAC: Test article concentration

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 41/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

TABLE 5. Summary of Body Weights (g) - Males

Values: Mean ± SD — Ref.App.: 3

Group No. Dose (mg/kg Bwt/day)	No. of rats	Day/Week 1/$	8/1	15/2	22/3	29/4
G1 0	6	134.53 16.52	185.77 22.31	238.85 24.96	281.58 29.48	318.63 33.79
G2 500	6	135.08 10.90	186.36 13.83	238.49 15.95	276.37 15.64	309.90 20.64
G3 1500	6	132.83 7.38	181.29 11.94	232.99 15.82	271.71 19.45	306.55 24.86
G4 4000	6	135.70 10.21	187.03 13.97	236.90 17.96	281.55 17.12	317.45 21.75

S: Initial week before administration of test item

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TABLE 6. Summary of Cumulative Net Body Weight Gains (g) - Males

Values: Mean ± SD — Ref.App.: 4

Group No. Dose (mg/kg Bwt/day)	No. of rats	Day/Week 8/1	15/2	22/3	29/4
G1 0	6	51.24 7.34	104.32 10.10	147.05 15.19	184.10 19.74
G2 500	6	51.29 3.53	103.42 8.51	141.29 8.46	174.82 14.01
G3 1500	6	48.45 5.84	100.16 10.09	138.87 15.12	173.72 20.42
G4 4000	6	51.33 5.89	101.20 11.42	145.85 14.07	181.75 19.13

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TABLE 7. Summary of Body Weights (g) - Females

Values: Mean ± SD — Ref.App.: 5

Group No. Dose (mg/kg Bwt/day)	No. of rats	Day/Week 1/$	8/1	15/2	22/3	29/4
G1 0	6	108.64 7.30	126.65 8.68	148.19 8.76	162.89 12.85	175.87 14.51
G2 500	6	108.98 8.98	133.07 9.32	156.58 9.58	173.90 11.50	188.88 12.73
G3 1500	6	107.25 7.06	132.51 9.56	153.90 9.62	172.20 10.23	185.18 14.72
G4 4000	6	107.16 3.35	132.08 2.45	151.17 6.17	169.50 10.24	179.41 9.73

$: Initial week before administration of test item

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TABLE 8. Summary of Cumulative Net Body Weight Gains (g) - Females

Values: Mean ± SD

Group No. Dose (mg/kg Bwt/day)	No. of rats	Ref.App.: 6 Day/Week 8/1	15/2	22/3	29/4
G1 0	6	18.01 5.96	39.56 8.75	54.25 13.88	67.23 15.35
G2 500	6	24.09 3.17	47.60 4.95	64.92 7.68	79.90 9.93
G3 1500	6	25.26 5.05	46.65 5.79	64.95 8.13	77.93 13.76
G4 4000	6	24.92 5.21	44.01 9.03	62.34 13.00	72.26 12.40

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TABLE 9. Summary of Cagewise Average Food Intake (g/rat/day) - Males

Values: Mean ± SD — Ref.App.: 9

Group No. Dose (mg/kg Bwt/day)	No. of cages	No. of rats / cage	Weeks 1	2	3	4
G1 0	3	2	22.3 1.12	25.7 1.60	27.9 1.75	28.1 1.36
G2 500	3	2	22.2 0.85	25.1 0.96	26.9 0.55	27.3 0.23
G3 1500	3	2	22.4 1.23	24.8 1.68	27.0 1.63	27.9 1.22
G4 4000	3	2	24.2 1.20	26.6 1.77	28.8 1.15	28.9 0.96

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TABLE 10. Summary of Cagewise Average Food Intake (g/rat/day) - Females

Values: Mean ± SD — Ref.App.: 10

Group No. Dose (mg/kg Bwt/day)	No. of cages	No. of rats / cage	Weeks 1	2	3	4
G1 0	3	2	16.6 0.25	19.1 1.12	18.5 1.17	18.6 1.30
G2 500	3	2	16.6 0.74	18.0 0.70	18.6 0.61	19.2 0.78
G3 1500	3	2	16.2 1.44	17.4 1.23	17.9 1.10	18.6 0.65
G4 4000	3	2	16.5 1.07	17.9 0.42	18.7 1.30	18.7 0.75

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Ref.App.: 5, 7, 11 & 12

TABLE 11. Mean Food and Test Item Intake

MALES

Group No.	G1				G2				G3				G4			
Week	W1	W2	W3	W4	W1	W2	W3	W4	W1	W2	W3	W4	W1	W2	W3	W4
Dose (ppm)	0	0	0	0	3259	4065	4578	5052	10029	11729	13578	14985	26960	30267	34803	38759
FOOD INTAKE																
g/animal/7 days	156.3	179.9	195.3	196.5	155.2	175.9	188.5	190.9	156.8	173.6	189.2	195.3	169.6	186.2	201.6	202.3
g/animal/day	22.3	25.7	27.9	28.1	22.2	25.1	26.9	27.3	22.4	24.8	27.0	27.9	24.2	26.6	28.8	28.9
g/kg Bwt/7 days	841.5	753.2	693.6	616.6	832.6	737.7	682.2	615.9	864.9	745.1	696.5	637.1	907.0	786	716	637.3
g/kg Bwt/day	120.2	107.6	99.1	88.1	118.9	105.4	97.5	88.0	123.6	106.4	99.5	91.0	129.6	112.3	102.3	91
TEST ITEM INTAKE																
mg/kg Bwt/7 days	0	0	0	0	2805.9	2914.6	2975.7	2876.9	8674.4	8739.2	9456.6	9546.7	24452.7	23789.8	24920.4	24700.2
mg/kg Bwt/day	0	0	0	0	400.8	416.4	425.1	411.0	1239.2	1248.5	1350.9	1363.8	3493.2	3398.5	3560.1	3528.6

FEMALES

Group No.	G1				G2				G3				G4			
Week	W1	W2	W3	W4	W1	W2	W3	W4	W1	W2	W3	W4	W1	W2	W3	W4
Dose (ppm)	0	0	0	0	3370	3951	4362	4671	9735	12084	13365	14424	25866	31662	33681	36132
FOOD INTAKE																
g/animal/7 days	116.4	133.9	129.3	130.2	116.0	125.8	130.0	134.4	113.4	122.0	125.1	130.4	115.3	125.1	130.7	130.7
g/animal/day	16.6	19.1	18.5	18.6	16.6	18.0	18.6	19.2	16.2	17.4	17.9	18.6	16.5	17.9	18.7	18.7
g/kg Bwt/7 days	919.3	903.8	793.6	740.3	871.5	803.2	747.4	711.6	855.8	792.9	726.3	704.4	872.7	827.3	770.9	728.3
g/kg Bwt/day	131.3	129.1	113.4	105.8	124.5	114.7	106.8	101.7	122.3	113.3	103.8	100.6	124.7	118.2	110.1	104
TEST ITEM INTAKE																
mg/kg Bwt/7 days	0	0	0	0	2936.9	3173.6	3260.1	3323.7	8331.2	9581.8	9706.9	10159.8	22573.6	26194.8	25965.3	26314.9
mg/kg Bwt/day	0	0	0	0	419.6	453.4	465.7	474.8	1190.2	1368.8	1386.7	1451.4	3224.8	3742.1	3709.3	3759.3

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 48/140

CONFIDENTIAL

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

TABLE 12. Summary of Haematological Values at Termination - Males

Values: Mean ± SD

Ref App.: 11

Group No. / Dose (mg/kg Bwt/day)	No. of rats	WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV fl	MCH pg	MCHC g/l	Plat G/l	P.T. s	Neut %	Lymp %	Eosi %	Mono %	Baso %
G1	6	4.9	7.10	146	0.415	58.5	20.6	353	1005	15.6	5.5	94.3	0.2	0.0	0.0
0		0.89	0.33	2.93	0.014	2.55	0.85	15.99	72.42	2.58	1.38	1.21	0.41	0.00	0.00
G2	6	5.2	7.09	+ 157	0.416	58.8	+ 22.1	+ 376	961	15.6	6.5	92.7	0.7	0.2	0.0
500		0.97	0.32	2.95	0.017	2.55	0.82	10.54	88.62	1.46	2.07	2.58	0.82	0.41	0.00
G3	6	4.6	- 6.54	+ 156	- 0.387	59.2	+ 23.9	+ 403	1010	15.7	7.2	92.3	0.3	0.2	0.0
1500		1.00	0.45	7.40	0.025	2.54	1.15	7.25	66.72	0.75	2.14	2.66	0.82	0.41	0.00
G4	6	4.6	7.04	+ 155	0.413	58.7	+ 22.0	+ 375	1003	16.4	6.2	93.2	0.5	0.2	0.0
4000		0.93	0.23	3.06	0.017	1.49	0.29	10.50	59.42	2.62	1.47	2.14	0.84	0.41	0.00

+/- Significantly higher(+)/lower(-) than the control group

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 49/140

CONFIDENTIAL

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

TABLE 13. Summary of Haematological Values at Termination - Females

Values: Mean ± SD

Ref App.: 12

Group No. / Dose (mg/kg Bwt/day)	No. of rats	WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV fl	MCH pg	MCHC g/l	Plat G/l	P.T. s	Neut %	Lymp %	Eosi %	Mono %	Baso %
G1	6	3.1	7.04	153	0.404	57.4	21.8	379	984	15.7	5.7	93.3	0.5	0.5	0.0
0		0.68	0.41	6.16	0.010	2.15	1.06	11.82	66.87	1.12	1.37	2.16	0.84	0.84	0.00
G2	6	3.8	6.68	156	0.386	57.9	23.4	404	936	14.6	7.3	92.2	0.3	0.2	0.0
500		1.37	0.41	3.43	0.015	2.14	1.03	9.06	91.41	1.03	2.73	2.64	0.52	0.41	0.00
G3	6	5.3	7.03	153	0.398	56.8	21.9	386	918	15.2	5.3	93.8	0.7	0.2	0.0
1500		3.53	0.55	6.77	0.020	2.96	2.33	32.08	261.33	0.37	1.75	2.23	0.82	0.41	0.00
G4	6	4.1	6.94	155	0.396	57.2	22.4	392	1009	17.5 +	7.2	92.3	0.2	0.3	0.0
4000		0.94	0.35	3.54	0.012	2.85	1.09	6.25	95.57	1.26	2.48	2.73	0.41	0.82	0.00

+: Significantly higher(+) than the control group

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 50/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

TABLE 14. Summary of Clinical Chemistry Values at Termination - Males

Values: Mean ± SD

Ref App.: 13

Group No. / Dose (mg/kg Bwt/day)	No. of rats	Glu mmol/l	BUN mmol/l	Urea mmol/l	Tot.Pro g/l	AST U/l	ALT U/l	Alp U/l	GGT U/l	Creat µmol/l	Alb g/l	Chol mmol/l	Na mEq/l	K mEq/l
G1	6	7.80	2.18	4.67	63.2	68	39	257	3	38	35.7	1.96	143.3	4.56
0		0.52	0.38	0.82	1.77	4.59	3.61	21.22	2.83	1.51	1.56	0.26	0.84	0.67
G2	6	7.56	2.22	4.75	63.0	69	38	249	5	38	36.1	2.12	143.3	4.03
500		1.04	0.23	0.49	1.24	12.10	7.99	29.56	2.14	1.26	1.25	0.24	0.91	0.55
G3	6	7.87	2.16	4.63	64.1	64	36	242	8	37	36.6	2.42 +	143.7	3.95
1500		0.90	0.41	0.88	1.99	6.84	5.34	22.46	4.12	2.95	1.63	0.20	0.46	0.21
G4	6	7.51	2.13	4.57	62.9	65	35	239	7	40	36.0	1.91	143.8	4.09
4000		0.51	0.29	0.63	1.31	6.86	3.60	21.59	6.11	7.13	0.75	0.19	1.19	0.33

+: Significantly higher(+) than the control group

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

TABLE 15. Summary of Clinical Chemistry Values at Termination - Females

Values: Mean ± SD

Ref.App. 14

Group No. / Dose (mg/kg Bwt/day)	No. of rats	Glu mmol/l	BUN mmol/l	Urea mmol/l	Tot.Pro g/l	AST U/l	ALT U/l	Alp U/l	GGT U/l	Creat µmol/l	Alb g/l	Chol mmol/l	Na mEq/l	K mEq/l
G1	6	6.31	2.64	5.65	63.1	71	33	187	3	41	36.3	2.05	142.7	4.08
0		1.05	0.53	1.14	2.30	4 12	1.38	35.03	3.20	3 54	1.34	0.26	0 85	0.56
G2	6	5.98	2.66	5.69	63.9	69	32	176	5	44	36.7	2.14	142.8	4.05
500		0.51	0.54	1.15	0.94	0.98	1.72	16.95	3.19	5.86	1.18	0.28	0.92	0.24
G3	6	6.38	2.37	5.07	63.7	78	34	182	4	41	36.3	2.15	143.0	3.95
1500		0.84	0.27	0.58	1.09	13.86	4.69	35.89	2.07	2.32	0.81	0.31	1.44	0.41
G4	6	6.28	2.79	5.98	63.2	66	29	152	6	42	36.3	2.10	144.0	4.16
4000		1.08	0.60	1.27	1.51	5.98	3.62	16.42	3.69	4.07	1.33	0.30	1.01	0.50

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 52/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

TABLE 16. Summary of Terminal Fasting Body Weights, Organ Weights and Organ Weight Ratios - Males

Values: Mean ± SD

Ref.App.: 17

Group No. / Dose (mg/kg Bwt/day)	No. of rats	Fasting Bwt (g)	Organ weights(g)										Organ weight ratios(%)								
			Adrenals	Testes	Kidneys	Liver	Heart	Brain	Epididym	Thymus	Spleen	Adrenals	Testes	Kidneys	Liver	Heart	Brain	Epididym	Thymus	Spleen
G1	6	292.09	0.054	3.220	2.263	9.580	1.074	1.849	0.842	0.651	0.552	0.019	1.105	0.773	3.277	0.367	0.636	0.290	0.223	0.191
0		29.05	0.008	0.300	0.320	1.135	0.127	0.112	0.112	0.128	0.102	0.003	0.074	0.044	0.132	0.016	0.051	0.039	0.038	0.043
G2	6	286.23	0.052	3.326	2.163	9.101	1.070	1.862	0.814	0.644	0.619	0.018	1.165	0.754	3.179	0.375	0.653	0.285	0.227	0.216
500		19.84	0.007	0.207	0.240	0.728	0.057	0.059	0.097	0.072	0.215	0.003	0.082	0.037	0.118	0.035	0.036	0.033	0.037	0.072
G3	6	282.36	0.049	3.307	2.216	9.088	1.087	1.806	0.783	0.677	0.597	0.017	1.180	0.784	3.216	0.386	0.643	0.278	0.243	0.213
1500		23.70	0.004	0.229	0.249	0.889	0.117	0.084	0.050	0.132	0.116	0.002	0.152	0.045	0.076	0.034	0.054	0.018	0.063	0.043
G4	6	291.45	0.051	3.000	2.269	9.343	1.079	1.853	0.782	0.644	0.502	0.018	1.033	0.778	3.204	0.371	0.638	0.270	0.222	0.173
4000		20.24	0.007	0.259	0.253	0.836	0.059	0.052	0.059	0.078	0.034	0.002	0.099	0.050	0.156	0.015	0.037	0.030	0.031	0.007

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 53/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

Ref.App.: 18

TABLE 17. Summary of Terminal Fasting Body Weights, Organ Weights and Organ Weight Ratios - Females

Values: Mean ± SD

Group No.	No. of	Fasting	Organ weights(g)								Organ weight ratios(%)							
Dose (mg/kg Bwt/day)	rats	Bwt (g)	Adrenals	Ovaries	Kidneys	Liver	Heart	Brain	Thymus	Spleen	Adrenals	Ovaries	Kidneys	Liver	Heart	Brain	Thymus	Spleen
G1	6	163.49	0.060	0.105	1.257	5.110	0.669	1.670	0.442	0.350	0.037	0.064	0.770	3.127	0.411	1.027	0.271	0.215
0		11.65	0.005	0.013	0.084	0.414	0.040	0.034	0.046	0.031	0.002	0.006	0.035	0.151	0.036	0.088	0.028	0.021
G2	6	175.09	0.064	0.121 +	1.311	5.523	0.712	1.755	0.519 +	0.412	0.037	0.069	0.751	3.155	0.407	1.006	0.297	0.234
500		12.53	0.007	0.009	0.084	0.410	0.058	0.089	0.062	0.078	0.003	0.005	0.061	0.104	0.025	0.083	0.035	0.036
G3	6	172.80	0.062	0.116	1.316	5.644	0.740 +	1.743 +	0.517	0.418	0.036	0.067	0.761	3.262	0.428	1.012	0.298	0.241
1500		10.29	0.007	0.018	0.086	0.506	0.060	0.066	0.094	0.069	0.005	0.007	0.015	0.108	0.024	0.071	0.040	0.027
G4	6	166.30	0.064	0.115	1.287	5.442	0.694	1.740	0.542	0.389	0.038	0.069	0.775	3.271	0.418	1.047	0.325	0.234
4000		9.89	0.007	0.011	0.080	0.397	0.058	0.086	0.105	0.072	0.004	0.004	0.033	0.074	0.027	0.030	0.054	0.037

+: Significantly higher(+) than the control group

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 54/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

TABLE 18. Summary of Gross Pathology Findings

Ref. App.: 15 & 16

PARAMETERS	Sex	Males				Females			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
	Dose (mg/kg Bwt/day)	0	500	1500	4000	0	500	1500	4000
	No. of rats	6	6	6	6	6	6	6	6
1. No. dead during treatment		0	0	0	0	0	0	0	0
2. No. of moribund sacrifice		0	0	0	0	0	0	0	0
3. No. finally sacrificed		6	6	6	6	6	6	6	6
4. No. examined for gross pathology		6	6	6	6	6	6	6	6
5. No. showing gross pathology		2	1	3	1	0	0	2	2
A. No. showing external pathology		0	0	0	0	0	0	0	0
B. No. showing visceral organ pathology		2	1	3	1	0	0	2	2
i. Kidney unilateral/bilateral – pelvis dilated		1	0	2	1	0	0	2	1
ii. Cecum – discoloration-red		0	0	1	0	0	0	0	0
iii. Thymus – discoloration-red		1	0	0	0	0	0	0	0
iv. Spleen – enlarged		0	1	0	0	0	0	0	0
v. Testes unilateral - flabby		0	1	0	0	NA	NA	NA	NA
vi. Uterus - dilatation - focal		NA	NA	NA	NA	0	0	1	2

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 55/140

CONFIDENTIAL

21 & 22, Peenya, Phase II, Bangalore 560 058, India

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TABLE 19. SUMMARY OF HISTOPATHOLOGICAL (MICROSCOPIC) FINDINGS

Number in (): No. of tissues evaluated/group — Ref.App.: 19 & 20

Sex	MALES				FEMALES			
Group No.	G1	G2	G3	G4	G1	G2	G3	G4
TISSUE AND Dose (mg/kg Bwt/day)	0	500	1500	4000	0	500	1500	4000
OBSERVATION No. of rats	6	6	6	6	6	6	6	6
No. of rats examined	6	6	6	6	6	0	2	6
1. STOMACH	(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
Cystic gland(s)	1	-	-	0	0	-	-	0
2. DUODENUM	(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
3. JEJUNUM	(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
4. ILEUM WITH PEYER'S PATCH	(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
5. CECUM	(6)	(-)	(1)	(6)	(6)	(-)	(-)	(6)
Congestion	0	-	1	0	0	-	-	0
6. COLON	(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
7. RECTUM	(6)	(6)	(6)	(6)	(6)	(-)	(-)	(6)
Inflammation-chronic	0	0	0	4+	0	-	-	1
Parasite(s)	0	0	2	0	0	-	-	0
8. LIVER	(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
Lymphocytic infiltration	0	-	-	0	0	-	-	1
Necrobiotic focus(i)	4	-	-	2	5	-	-	4
9. LUNGS	(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
10. TRACHEA	(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)

+: Significantly higher(+) than the control group

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TOXI-4891/04
052/0-CLSM/28-OR
PAGE No. 56/148

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

TABLE 19 contd. SUMMARY OF HISTOPATHOLOGICAL (MICROSCOPIC) FINDINGS

Number in (): No. of tissues evaluated/group — Ref.App.: 19 & 20

Sex	MALES				FEMALES			
Group No.	G1	G2	G3	G4	G1	G2	G3	G4
TISSUE AND Dose (mg/kg Bwt/day)	0	500	1500	4000	0	500	1500	4000
OBSERVATION No. of rats	6	6	6	6	6	6	6	6
No. of rats examined	6	6	6	6	6	6	2	6
11. SPLEEN	(6)	(1)	(-)	(6)	(6)	(-)	(-)	(6)
12. MESENTERIC LYMPH NODES	(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
13. AXILLARY LYMPH NODE	(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
14. KIDNEYS	(6)	(-)	(2)	(6)	(6)	(-)	(2)	(6)
Mineralisation	0	-	0	0	1	-	0	0
Dilatation of pelvis	1	-	2	1	0	-	2	1
Papillary necrosis	1	-	0	0	0	-	0	0
Tubulointerstitial nephritis	1	-	0	0	0	-	0	0
Urothelial hyperplasia	0	-	1	0	0	-	0	0
Basophilic tubules	1	-	2	0	0	-	1	1
Proteinaceous material in tubules	1	-	0	0	0	-	0	0
Hyaline droplets-tubular epithelium	4	-	0	4	0	-	0	0
15. URINARY BLADDER	(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
Epithelial hyperplasia	1	-	-	0	0	-	-	0
16. TESTES	(6)	(1)	(-)	(6)	NA	NA	NA	NA
Atrophy-seminiferous tubules	0	1	-	0	NA	NA	NA	NA
17. EPIDIDYMIDES	(6)	(-)	(-)	(6)	NA	NA	NA	NA
Lymphocytic infiltration	1	-	-	0	NA	NA	NA	NA

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TOXI-4491/04
052/0-CLSH/28-OR
PAGE No. 57/140

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

TABLE 19 contd. SUMMARY OF HISTOPATHOLOGICAL (MICROSCOPIC) FINDINGS

Number in (): No. of tissues evaluated/group — Ref.App.: 19 & 20

	Sex	MALES				FEMALES			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
TISSUE AND	Dose (mg/kg Bwt/day)	0	500	1500	4000	0	500	1500	4000
OBSERVATION	No. of rats	6	6	6	6	6	6	6	6
	No. of rats examined	6	6	6	6	6	0	2	6
18. PROSTATE		(6)	(-)	(-)	(6)	NA	NA	NA	NA
19. SEMINAL VESICLES		(6)	(-)	(-)	(6)	NA	NA	NA	NA
20. COAGULATING GLANDS		(6)	(-)	(-)	(6)	NA	NA	NA	NA
21. OVARIES		NA	NA	NA	NA	(6)	(-)	(-)	(6)
22. UTERUS		NA	NA	NA	NA	(6)	(-)	(1)	(6)
Dilatation		NA	NA	NA	NA	0	-	1	2
23. THYROIDS		(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
Ultimobranchial cyst		1	-	-	0	0	-	-	0
Ectopic thymus		1	-	-	2	0	-	-	0
24. ADRENALS		(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
25. BRAIN-CEREBRUM		(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
26. BRAIN-CEREBELLUM		(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
27. BRAIN-MEDULLA/PONS		(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)

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TOXI-4091/04
052/B-CLSH/28-OR
PAGE No. 58/140

CONFIDENTIAL

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

TABLE 19 contd. SUMMARY OF HISTOPATHOLOGICAL (MICROSCOPIC) FINDINGS

Number in (): No. of Tissues evaluated/group — Ref.App.: 19 & 20

	Sex	MALES				FEMALES			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
TISSUE AND	Dose (mg/kg Bwt/day)	0	500	1500	4000	0	500	1500	4000
OBSERVATION	No. of rats	6	6	6	6	6	6	6	6
	No. of rats examined	6	6	6	6	6	0	2	6
28. SPINAL CORD		(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
29. SCIATIC NERVES		(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
30. THYMUS		(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)
Hemorrhage		1	-	-	0	0	-	-	0
31. BONE MARROW (SMEAR)		(6)	(-)	(-)	(6)	(6)	(-)	(-)	(6)

TOXI-4091/04
052/0-CLSM/20-OR
PAGE No. 59/140

ADVINUS

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13. FIGURES

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FIGURE 1. Body Weight and Growth Curves – Males

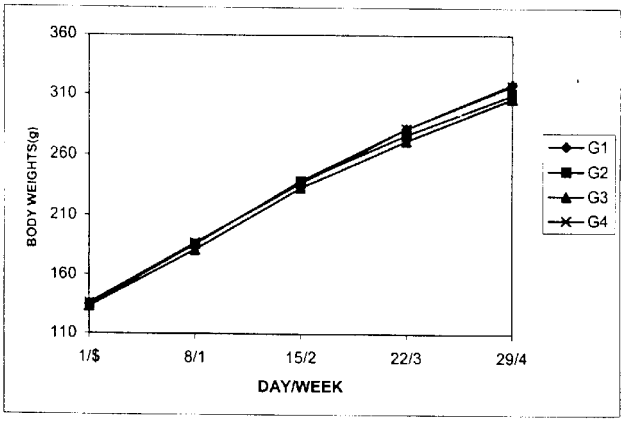
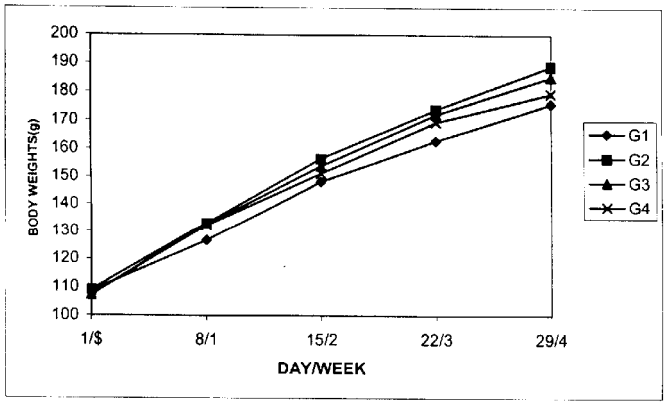


FIGURE 2. Body Weight and Growth Curves – Females



TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 61/140

CONFIDENTIAL

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

FIGURE 3. Food Consumption Curves – Males

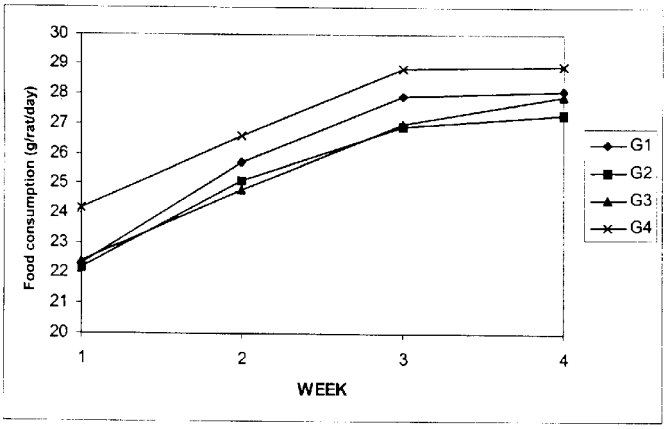
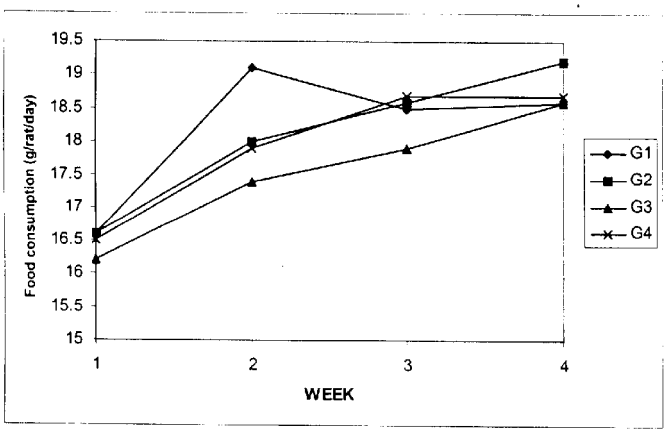


FIGURE 4. Food Consumption Curves – Females



TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 62/140

CONFIDENTIAL

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

14. APPENDICES

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 1. Individual Veterinary/Physical and Clinical Examinations, Clinical Signs, Ophthalmological Examination and Pre-Terminal Deaths – Males

Group No. Dose (mg/kg Bwt/day)	Rat No.	Veterinary/Physical examination & clinical signs	Clinical examination	Ophthalmological findings	
				Prior to treatment	End of treatment
G1	Rf5971	NAD	NAD	NAD	NAD
0	Rf5972	NAD	NAD	NAD	NAD
	Rf5973	NAD	NAD	NAD	NAD
	Rf5974	NAD	NAD	NAD	NAD
	Rf5975	NAD	NAD	NAD	NAD
	Rf5976	NAD	NAD	NAD	NAD
G2	Rf5983	NAD	NAD	NAD	NAD
500	Rf5984	NAD	NAD	NAD	NAD
	Rf5985	NAD	NAD	NAD	NAD
	Rf5986	NAD	NAD	NAD	NAD
	Rf5987	NAD	NAD	NAD	NAD
	Rf5988	NAD	NAD	NAD	NAD
G3	Rf5995	NAD	NAD	NAD	NAD
1500	Rf5996	NAD	NAD	NAD	NAD
	Rf5997	NAD	NAD	NAD	NAD
	Rf5998	NAD	NAD	NAD	NAD
	Rf5999	NAD	NAD	NAD	NAD
	Rf6000	NAD	NAD	NAD	NAD
G4	Rf6007	NAD	NAD	NAD	NAD
4000	Rf6008	NAD	NAD	NAD	NAD
	Rf6009	NAD	NAD	NAD	NAD
	Rf6010	NAD	NAD	NAD	NAD
	Rf6011	NAD	NAD	NAD	NAD
	Rf6012	NAD	NAD	NAD	NAD

NAD: No Abnormality Detected

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APPENDIX 2. Individual Veterinary/Physical and Clinical Examinations, Clinical Signs, Ophthalmological Examination and Pre-Terminal Deaths – Females

Group No. Dose (mg/kg Bwt/day)	Rat No.	Veterinary/Physical examination & clinical signs	Clinical examination	Ophthalmological findings	
				Prior to treatment	End of treatment
G1 0	Rf5977	NAD	NAD	NAD	NAD
	Rf5978	NAD	NAD	NAD	NAD
	Rf5979	NAD	NAD	NAD	NAD
	Rf5980	NAD	NAD	NAD	NAD
	Rf5981	NAD	NAD	NAD	NAD
	Rf5982	NAD	NAD	NAD	NAD
G2 500	Rf5989	NAD	NAD	NAD	NAD
	Rf5990	NAD	NAD	NAD	NAD
	Rf5991	NAD	NAD	NAD	NAD
	Rf5992	NAD	NAD	NAD	NAD
	Rf5993	NAD	NAD	NAD	NAD
	Rf5994	NAD	NAD	NAD	NAD
G3 1500	Rf6001	NAD	NAD	NAD	NAD
	Rf6002	NAD	NAD	NAD	NAD
	Rf6003	NAD	NAD	NAD	NAD
	Rf6004	NAD	NAD	NAD	NAD
	Rf6005	NAD	NAD	NAD	NAD
	Rf6006	NAD	NAD	NAD	NAD
G4 4000	Rf6013	NAD	NAD	NAD	NAD
	Rf6014	NAD	NAD	NAD	NAD
	Rf6015	NAD	NAD	NAD	NAD
	Rf6016	NAD	NAD	NAD	NAD
	Rf6017	NAD	NAD	NAD	NAD
	Rf6018	NAD	NAD	NAD	NAD

NAD: No Abnormality Detected

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APPENDIX 3. Individual Body Weights (g) [To Calculate Dietary Concentration for the next week]- Males

Group No.	Rat No.	Day			
		1#	7	14	21
G1	Rf5971	137.70	191.02	250.10	308.28
	Rf5972	101.87	148.09	193.67	241.81
	Rf5973	140.24	197.00	246.37	292.08
	Rf5974	109.99	156.91	198.77	242.83
	Rf5975	128.53	192.68	242.70	298.14
	Rf5976	127.45	182.65	231.20	279.50
G2	Rf5983	118.05	167.79	217.21	251.76
	Rf5984	131.24	182.59	236.42	287.60
	Rf5985	133.57	186.08	231.28	275.47
	Rf5986	112.55	161.62	212.61	258.85
	Rf5987	122.95	178.43	220.92	260.80
	Rf5988	140.24	201.62	249.29	284.25
G3	Rf5995	114.65	156.66	199.20	238.38
	Rf5996	130.17	179.49	223.76	260.84
	Rf5997	128.12	179.27	234.86	282.68
	Rf5998	116.16	164.52	211.26	256.24
	Rf5999	132.92	186.48	236.06	283.68
	Rf6000	124.11	179.81	236.37	284.56
G4	Rf6007	141.25	203.79	263.35	298.69
	Rf6008	130.46	181.04	225.44	266.51
	Rf6009	128.88	186.28	240.63	281.22
	Rf6010	124.77	174.93	220.23	262.29
	Rf6011	118.31	173.49	225.78	277.30
	Rf6012	112.55	170.05	213.19	259.33

#: Day 4 of acclimatization period

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 4. Individual Body Weights (g) [To Calculate Dietary Concentration for the next week]- Females

Group No.	Rat No.	Day 1#	Day 7	Day 14	Day 21
G1	Rf5977	100.18	112.39	125.53	134.07
	Rf5978	94.26	122.57	149.25	161.68
	Rf5979	107.53	131.93	149.98	161.05
	Rf5980	95.17	118.61	145.67	163.16
	Rf5981	111.64	133.29	152.90	169.87
	Rf5982	102.96	130.59	143.87	160.86
G2	Rf5989	99.69	125.99	141.69	162.42
	Rf5990	105.37	137.34	163.57	180.09
	Rf5991	123.41	143.65	163.74	185.48
	Rf5992	98.25	124.33	146.41	165.79
	Rf5993	96.13	124.95	156.03	180.70
	Rf5994	95.87	126.09	144.58	156.89
G3	Rf6001	91.31	117.90	140.42	155.64
	Rf6002	100.09	118.79	141.62	162.83
	Rf6003	100.48	135.65	158.84	182.60
	Rf6004	101.02	128.00	151.51	179.90
	Rf6005	107.05	132.34	150.02	163.36
	Rf6006	115.29	140.70	161.04	176.89
G4	Rf6013	100.69	129.03	150.86	173.03
	Rf6014	103.71	126.98	146.49	152.94
	Rf6015	106.89	130.45	146.27	170.06
	Rf6016	100.95	132.78	151.09	170.19
	Rf6017	96.84	127.10	157.76	182.23
	Rf6018	103.95	123.03	141.77	154.22

#: Day 4 of acclimatization period

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 5. Individual Body Weights (g) - Males

Group No. Dose (mg/kg Bwt/day)	Rat No.	Day/Week 1/$	8/1	15/2	22/3	29/4
G1	Rf5971	148.75	199.05	261.25	315.17	362.33
0	Rf5972	111.56	155.05	206.20	243.75	281.97
	Rf5973	152.20	206.63	255.82	294.68	335.60
	Rf5974	117.64	160.68	209.20	247.67	277.75
	Rf5975	140.06	202.44	257.94	302.77	340.36
	Rf5976	136.96	190.77	242.67	285.43	313.74
G2	Rf5983	127.36	176.62	223.68	257.89	282.96
500	Rf5984	137.44	190.59	250.68	290.48	335.18
	Rf5985	142.55	193.12	236.27	284.73	318.16
	Rf5986	119.31	168.19	223.19	263.79	294.19
	Rf5987	133.78	182.07	233.37	266.20	300.16
	Rf5988	150.01	207.57	263.75	295.12	328.73
G3	Rf5995	124.60	162.63	208.10	244.03	269.23
1500	Rf5996	138.25	185.34	234.52	262.66	295.31
	Rf5997	136.55	187.22	244.88	283.85	320.76
	Rf5998	123.23	170.87	219.75	258.40	292.54
	Rf5999	141.13	194.21	247.24	289.81	329.91
	Rf6000	133.24	187.45	243.45	291.49	331.57
G4	Rf6007	150.52	210.46	268.52	309.16	351.67
4000	Rf6008	140.09	187.60	231.26	268.52	300.65
	Rf6009	138.74	194.45	247.14	287.59	327.85
	Rf6010	136.16	179.59	222.75	267.23	292.03
	Rf6011	127.01	178.75	229.90	290.04	325.03
	Rf6012	121.65	171.31	221.81	266.75	307.44

$: Initial week before administration of test item

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APPENDIX 6. Individual Cumulative Net Body Weight Gains (g) - Males

Group No. Dose (mg/kg Bwt/day)	Rat No.	Day/Week 8/1	15/2	22/3	29/4
G1	Rf5971	50.30	112.50	166.42	213.58
0	Rf5972	43.49	94.64	132.19	170.41
	Rf5973	54.43	103.62	142.48	183.40
	Rf5974	43.04	91.56	130.03	160.11
	Rf5975	62.38	117.88	162.71	200.30
	Rf5976	53.81	105.71	148.47	176.78
G2	Rf5983	49.26	96.32	130.53	155.60
500	Rf5984	53.15	113.24	153.04	197.74
	Rf5985	50.57	93.72	142.18	175.61
	Rf5986	48.88	103.88	144.48	174.88
	Rf5987	48.29	99.59	132.42	166.38
	Rf5988	57.56	113.74	145.11	178.72
G3	Rf5995	38.03	83.50	119.43	144.63
1500	Rf5996	47.09	96.27	124.41	157.06
	Rf5997	50.67	108.33	147.30	184.21
	Rf5998	47.64	96.52	135.17	169.31
	Rf5999	53.08	106.11	148.68	188.78
	Rf6000	54.21	110.21	158.25	198.33
G4	Rf6007	59.94	118.00	158.64	201.15
4000	Rf6008	47.51	91.17	128.43	160.56
	Rf6009	55.71	108.40	148.85	189.11
	Rf6010	43.43	86.59	131.07	155.87
	Rf6011	51.74	102.89	163.03	198.02
	Rf6012	49.66	100.16	145.10	185.79

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 7. Individual Body Weights (g) - Females

Group No. Dose (mg/kg Bwt/day)	Rat No.	Day/Week 1/$	8/1	15/2	22/3	29/4
G1	Rf5977	105.36	113.10	131.33	138.14	147.37
0	Rf5978	100.62	123.35	152.67	172.71	187.08
	Rf5979	114.58	134.34	153.89	164.75	176.93
	Rf5980	102.51	121.76	146.72	169.27	181.72
	Rf5981	119.51	134.24	154.66	171.21	184.64
	Rf5982	109.24	133.10	149.89	161.26	177.47
G2	Rf5989	105.60	126.10	148.09	163.64	178.44
500	Rf5990	115.36	143.24	164.58	184.70	199.45
	Rf5991	124.36	146.50	169.94	186.02	199.72
	Rf5992	103.23	128.21	146.91	166.01	181.02
	Rf5993	103.57	125.10	159.76	181.95	201.57
	Rf5994	101.74	129.25	150.18	161.05	173.08
G3	Rf6001	95.28	120.44	143.90	160.10	171.59
1500	Rf6002	104.60	121.93	142.17	163.09	170.11
	Rf6003	107.91	140.46	159.55	184.31	201.47
	Rf6004	107.69	133.01	156.47	178.96	203.97
	Rf6005	112.20	135.41	153.77	166.32	177.95
	Rf6006	115.82	143.80	167.55	180.41	185.98
G4	Rf6013	106.36	131.65	150.65	174.01	182.93
4000	Rf6014	108.55	130.44	149.26	160.71	170.56
	Rf6015	110.71	133.29	152.16	171.08	181.57
	Rf6016	105.84	134.36	152.91	174.02	185.51
	Rf6017	101.56	134.49	160.57	182.75	190.92
	Rf6018	109.93	128.24	141.47	154.40	164.99

$: Initial week before administration of test item

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APPENDIX 8. Individual Cumulative Net Body Weight Gains (g) - Females

Group No. Dose (mg/kg Bwt/day)	Rat No.	Day/Week 8/1	15/2	22/3	29/4
G1	Rf5977	7.74	25.97	32.78	42.01
0	Rf5978	22.73	52.05	72.09	86.46
	Rf5979	19.76	39.31	50.17	62.35
	Rf5980	19.25	44.21	66.76	79.21
	Rf5981	14.73	35.15	51.70	65.13
	Rf5982	23.86	40.65	52.02	68.23
G2	Rf5989	20.50	42.49	58.04	72.84
500	Rf5990	27.88	49.22	69.34	84.09
	Rf5991	22.14	45.58	61.66	75.36
	Rf5992	24.98	43.68	62.78	77.79
	Rf5993	21.53	56.19	78.38	98.00
	Rf5994	27.51	48.44	59.31	71.34
G3	Rf6001	25.16	48.62	64.82	76.31
1500	Rf6002	17.33	37.57	58.49	65.51
	Rf6003	32.55	51.64	76.40	93.56
	Rf6004	25.32	48.78	71.27	96.28
	Rf6005	23.21	41.57	54.12	65.75
	Rf6006	27.98	51.73	64.59	70.16
G4	Rf6013	25.29	44.29	67.65	76.57
4000	Rf6014	21.89	40.71	52.16	62.01
	Rf6015	22.58	41.45	60.37	70.86
	Rf6016	28.52	47.07	68.18	79.67
	Rf6017	32.93	59.01	81.19	89.36
	Rf6018	18.31	31.54	44.47	55.06

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 9. Individual Cagewise Average Food Intake (g/rat/day)) [To Calculate Dietary Concentration for the next week] - Males

Group No.	Rat Nos.			Weeks			
	From	To	Cage No.	1#	1@	2@	3@
G1	Rf5971	Rf5972	1	17.4	21.2	25.0	27.9
	Rf5973	Rf5974	2	17.5	21.8	23.9	26.1
	Rf5975	Rf5976	3	18.5	23.5	27.1	29.8
G2	Rf5983	Rf5984	7	19.8	22.0	25.6	27.4
	Rf5985	Rf5986	8	18.0	21.2	23.8	26.5
	Rf5987	Rf5988	9	20.4	23.1	25.2	26.1
G3	Rf5995	Rf5996	13	17.5	21.4	23.2	25.4
	Rf5997	Rf5998	14	18.6	21.8	24.2	26.2
	Rf5999	Rf6000	15	19.6	23.8	26.8	28.8
G4	Rf6007	Rf6008	19	19.4	25.1	28.6	28.1
	Rf6009	Rf6010	20	19.0	24.0	26.4	27.4
	Rf6011	Rf6012	21	17.8	22.9	24.8	29.3

#: Day 4 of acclimatization period
@: Day 6 of the respective week

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 72/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 10. Individual Cagewise Average Food Intake (g/rat/day)) [To Calculate Dietary Concentration for the next week] - Females

Group No.	Rat Nos.			Weeks			
	From	To	Cage No.	1#	1@	2@	3@
G1	Rf5977	Rf5978	4	14.6	17.3	19.2	17.9
	Rf5979	Rf5980	5	15.8	17.0	21.0	19.8
	Rf5981	Rf5982	6	14.9	16.8	18.3	17.7
G2	Rf5989	Rf5990	10	14.3	16.0	16.8	17.7
	Rf5991	Rf5992	11	17.1	17.1	18.3	19.3
	Rf5993	Rf5994	12	14.6	16.3	17.4	18.2
G3	Rf6001	Rf6002	16	14.4	14.5	16.3	16.4
	Rf6003	Rf6004	17	15.1	16.5	17.2	18.3
	Rf6005	Rf6006	18	17.9	17.1	17.2	18.3
G4	Rf6013	Rf6014	22	15.5	15.1	17.5	16.9
	Rf6015	Rf6016	23	16.0	17.1	18.2	20.0
	Rf6017	Rf6018	24	15.8	16.5	17.4	18.5

#: Day 4 of acclimatization period
@: Day 6 of the respective week

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 11. Individual Cagewise Average Food Intake (g/rat/day) - Males

Group No. / Dose (mg/kg Bwt/day)	Rat Nos. From	Rat Nos. To	Cage No.	Weeks 1	2	3	4
G1	Rf5971	Rf5972	1	21.5	25.7	28.0	28.8
0	Rf5973	Rf5974	2	21.9	24.1	26.1	26.5
	Rf5975	Rf5976	3	23.6	27.3	29.6	28.9
G2	Rf5983	Rf5984	7	22.2	26.0	27.5	27.0
500	Rf5985	Rf5986	8	21.3	24.1	26.9	27.4
	Rf5987	Rf5988	9	23.0	25.3	26.4	27.4
G3	Rf5995	Rf5996	13	21.5	23.5	25.9	27.1
1500	Rf5997	Rf5998	14	21.9	24.2	26.3	27.3
	Rf5999	Rf6000	15	23.8	26.7	28.9	29.3
G4	Rf6007	Rf6008	19	25.4	28.5	28.7	29.3
4000	Rf6009	Rf6010	20	24.3	26.3	27.7	27.8
	Rf6011	Rf6012	21	23.0	25.0	30.0	29.6

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 12. Individual Cagewise Average Food Intake (g/rat/day) - Females

Group No. Dose (mg/kg Bwt/day)	Rat Nos. From	To	Cage No.	Weeks 1	2	3	4
G1	Rf5977	Rf5978	4	16.4	18.7	18.0	17.1
0	Rf5979	Rf5980	5	16.9	20.4	19.8	19.4
	Rf5981	Rf5982	6	16.6	18.3	17.6	19.3
G2	Rf5989	Rf5990	10	16.0	17.3	17.9	18.3
500	Rf5991	Rf5992	11	17.4	18.7	19.1	19.6
	Rf5993	Rf5994	12	16.3	17.9	18.7	19.7
G3	Rf6001	Rf6002	16	14.6	16.4	16.6	18.0
1500	Rf6003	Rf6004	17	16.6	17.1	18.4	19.3
	Rf6005	Rf6006	18	17.4	18.8	18.6	18.6
G4	Rf6013	Rf6014	22	15.3	17.4	17.4	18.7
4000	Rf6015	Rf6016	23	17.4	18.2	20.0	19.4
	Rf6017	Rf6018	24	16.7	18.0	18.6	17.9

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 13. Individual Haematological Values at Termination - Males

Group No. Dose (mg/kg Bwt/day)	Rat No.	WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV fl	MCH pg	MCHC g/l	Plat G/l	P.T. s	Neut %	Lymp %	Eosi %	Mono %	Baso %
G1	Rf5971	3.5	7.21	142	0.426	59.1	19.7	333	1111	14.7	4	95	1	0	0
0	Rf5972	4.5	6.61	145	0.401	60.7	21.9	362	1073	14.2	7	93	0	0	0
	Rf5973	5.4	7.07	146	0.410	58.0	20.7	356	932	17.7	4	96	0	0	0
	Rf5974	5.8	7.58	151	0.408	53.8	19.9	370	938	19.4	7	93	0	0	0
	Rf5975	5.7	7.22	146	0.438	60.7	20.2	333	985	15.6	6	94	0	0	0
	Rf5976	4.5	6.91	147	0.405	58.6	21.3	363	993	12.2	5	95	0	0	0
G2	Rf5983	4.2	6.92	156	0.427	61.7	22.5	365	1094	14.3	10	88	2	0	0
500	Rf5984	3.8	7.54	161	0.438	58.1	21.4	368	1007	16.2	7	93	0	0	0
	Rf5985	5.3	7.25	153	0.407	56.1	21.1	376	843	15.0	4	96	0	0	0
	Rf5986	6.2	6.61	155	0.409	61.9	23.4	379	993	13.7	5	93	1	1	0
	Rf5987	5.5	7.22	159	0.424	58.7	22.0	375	912	16.6	6	93	1	0	0
	Rf5988	6.0	6.97	155	0.392	56.2	22.2	395	915	17.5	7	93	0	0	0
G3	Rf5995	5.3	6.65	155	0.389	58.5	23.3	398	1046	14.7	4	96	0	0	0
1500	Rf5996	5.5	7.25	169	0.431	59.4	23.3	392	1060	15.8	9	91	0	0	0
	Rf5997	5.3	6.13	158	0.390	63.6	25.8	405	918	15.6	8	91	0	1	0
	Rf5998	4.9	6.61	150	0.370	56.0	22.7	405	1085	15.6	9	89	2	0	0
	Rf5999	3.5	6.63	156	0.384	57.9	23.5	406	1006	17.0	5	95	0	0	0
	Rf6000	3.2	5.98	148	0.358	59.9	24.7	413	944	15.4	8	92	0	0	0
G4	Rf6007	4.5	6.70	151	0.389	58.1	22.5	388	997	17.3	5	95	0	0	0
4000	Rf6008	5.8	7.07	156	0.427	60.4	22.1	365	998	17.5	7	92	0	1	0
	Rf6009	5.3	7.15	157	0.409	57.2	22.0	384	916	20.1	4	96	0	0	0
	Rf6010	3.1	7.13	156	0.432	60.6	21.9	361	1101	16.7	6	94	0	0	0
	Rf6011	4.3	7.33	158	0.420	57.3	21.6	376	1017	13.4	8	91	1	0	0
	Rf6012	4.3	6.83	151	0.400	58.6	22.1	377	988	13.3	7	91	2	0	0

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 76/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 14. Individual Haematological Values at Termination - Females

Group No. / Dose (mg/kg Bwt/day)	Rat No.	WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV fl	MCH pg	MCHC g/l	Plat G/l	P.T. s	Neut %	Lymp %	Eosi %	Mono %	Baso %
G1	Rf5977	4.2	6.77	147	0.397	58.6	21.7	370	934	14.9	5	95	0	0	0
0	Rf5978	3.1	6.94	154	0.404	58.2	22.2	381	1012	17.8	6	93	0	1	0
	Rf5979	3.0	7.36	162	0.419	56.9	22.0	387	916	15.4	8	92	0	0	0
	Rf5980	2.4	7.72	155	0.411	53.2	20.1	377	1100	16.1	5	94	1	0	0
	Rf5981	3.4	6.65	155	0.391	58.8	23.3	396	990	14.8	4	96	0	0	0
	Rf5982	2.4	6.82	145	0.399	58.5	21.3	363	953	15.3	6	90	2	2	0
G2	Rf5989	6.5	6.99	159	0.406	58.1	22.7	392	824	15.1	9	91	0	0	0
500	Rf5990	3.2	6.79	156	0.379	55.8	23.0	412	991	15.3	11	89	0	0	0
	Rf5991	2.6	6.94	156	0.397	57.2	22.5	393	913	13.3	9	90	0	1	0
	Rf5992	3.4	6.32	153	0.372	58.9	24.2	411	1010	15.8	5	94	1	0	0
	Rf5993	3.8	6.02	151	0.370	61.5	25.1	408	1038	13.4	4	96	0	0	0
	Rf5994	3.4	7.01	160	0.392	55.9	22.8	408	837	14.4	6	93	1	0	0
G3	Rf6001	3.0	6.26	155	0.373	59.6	24.8	416	939	15.3	3	97	0	0	0
1500	Rf6002	3.5	7.30	159	0.388	53.2	21.8	410	1075	15.2	4	95	1	0	0
	Rf6003	1.5	6.85	153	0.386	56.4	22.3	396	1052	15.8	6	93	0	1	0
	Rf6004	5.4	6.76	155	0.411	60.8	22.9	377	1017	15.0	5	95	0	0	0
	Rf6005	6.8	7.12	157	0.404	56.7	22.1	389	1032	14.7	8	91	1	0	0
	Rf6006	11.4	7.89	140	0.428	54.2	17.7	327	393	15.3	6	92	2	0	0
G4	Rf6013	4.0	6.72	155	0.402	59.8	23.1	386	938	15.5	6	94	0	0	0
4000	Rf6014	4.0	7.36	158	0.394	53.5	21.5	401	1009	18.8	4	96	0	0	0
	Rf6015	4.9	7.20	150	0.385	53.5	20.8	390	903	17.0	9	91	0	0	0
	Rf6016	5.4	6.65	155	0.396	59.5	23.3	391	1027	17.0	7	90	1	2	0
	Rf6017	3.8	6.51	153	0.385	59.1	23.5	397	1179	18.7	6	94	0	0	0
	Rf6018	2.7	7.20	160	0.416	57.8	22.2	385	996	18.1	11	89	0	0	0

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 15. Individual Clinical Chemistry Values at Termination - Males

Group No. Dose (mg/kg Bwt/day)	Rat No.	Glu mmol/l	BUN mmol/l	Urea mmol/l	Tot.Pro g/l	AST U/l	ALT U/l	Alp U/l	GGT U/l	Creat µmol/l	Alb g/l	Chol mmol/l	Na mEq/l	K mEq/l
G1	Rf5971	7.51	2.08	4.45	64.0	66	36	220	2	38	35.2	2.24	143.5	4.26
0	Rf5972	7.13	2.83	6.06	63.1	64	43	259	5	39	35.3	2.29	142.3	4.82
	Rf5973	7.77	2.02	4.33	61.8	65	33	255	4	35	35.8	1.95	143.8	4.19
	Rf5974	8.08	1.95	4.18	62.1	76	41	286	0	37	35.3	1.67	142.4	3.92
	Rf5975	8.64	1.78	3.81	61.7	70	40	260	7	38	34.1	1.74	144.5	5.78
	Rf5976	7.67	2.42	5.18	66.3	65	39	262	0	39	38.7	1.86	143.3	4.39
G2	Rf5983	7.80	2.48	5.31	64.5	60	27	210	7	39	37.4	2.48	143.8	4.87
500	Rf5984	5.76	2.26	4.84	62.2	84	39	292	4	39	36.3	2.10	142.8	3.52
	Rf5985	7.23	1.92	4.11	63.5	84	51	274	4	38	36.8	2.06	143.5	4.31
	Rf5986	7.54	2.10	4.50	61.7	65	34	243	2	37	34.3	2.30	143.9	3.46
	Rf5987	8.18	2.48	5.31	64.3	65	40	235	7	39	36.9	1.80	144.1	3.73
	Rf5988	8.85	2.08	4.45	61.9	56	35	237	7	36	34.8	1.99	141.7	4.27
G3	Rf5995	8.49	2.54	5.44	65.3	75	40	262	11	40	38.1	2.30	143.6	3.62
1500	Rf5996	9.43	2.74	5.87	66.7	60	34	255	9	40	38.7	2.50	143.9	4.24
	Rf5997	7.52	1.76	3.77	65.0	70	39	219	11	36	36.9	2.63	143.9	4.06
	Rf5998	7.18	2.17	4.65	63.3	61	43	252	7	33	35.7	2.55	142.8	3.95
	Rf5999	7.34	1.73	3.70	63.0	58	29	208	0	34	35.7	2.09	143.8	4.00
	Rf6000	7.28	2.03	4.35	61.1	60	32	255	9	36	34.4	2.42	144.1	3.85
G4	Rf6007	7.58	2.12	4.54	61.5	65	29	232	0	36	35.7	1.66	141.7	3.49
4000	Rf6008	6.77	2.67	5.72	63.2	74	37	252	18	54	35.1	2.11	143.2	4.47
	Rf6009	7.21	2.13	4.56	62.4	56	33	274	9	36	35.6	1.77	144.5	4.27
	Rf6010	7.46	2.12	4.54	65.3	60	37	227	4	41	36.0	2.10	144.9	4.07
	Rf6011	8.31	1.95	4.18	62.8	72	34	235	5	36	37.3	1.78	143.6	4.17
	Rf6012	7.70	1.80	3.85	62.2	65	39	212	7	37	36.2	2.02	144.6	4.07

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 78/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 16. Individual Clinical Chemistry Values at Termination - Females

Group No. Dose (mg/kg Bwt/day)	Rat No.	Glu mmol/l	BUN mmol/l	Urea mmol/l	Tot.Pro g/l	AST U/l	ALT U/l	GGT U/l	GGT U/l	Creat µmol/l	Alb g/l	Chol mmol/l	Na mEq/l	K mEq/l
G1	Rf5977	7.48	2.24	4.80	63.4	67	34	239	7	38	35.8	2.32	143.2	4.29
0	Rf5978	4.95	2.08	4.45	58.8	71	33	174	0	38	34.0	1.69	141.5	3.91
	Rf5979	6.18	2.72	5.82	65.7	67	32	137	2	39	37.7	1.97	142.9	4.53
	Rf5980	5.29	2.28	4.88	63.3	71	31	212	0	40	36.0	1.87	142.3	3.23
	Rf5981	6.57	3.38	7.24	63.7	78	31	183	4	43	37.3	2.07	142.5	3.75
	Rf5982	7.41	3.14	6.72	63.9	73	34	176	7	47	36.9	2.36	144.0	4.76
G2	Rf5989	6.74	3.66	7.84	64.9	67	33	192	7	54	36.6	2.23	142.9	4.27
500	Rf5990	5.71	2.19	4.69	63.9	69	34	186	0	40	37.5	2.17	144.0	4.17
	Rf5991	6.48	2.27	4.86	64.5	69	32	153	4	47	35.3	2.64	141.2	3.79
	Rf5992	5.55	2.77	5.93	62.8	69	32	174	9	40	36.8	1.94	142.6	3.80
	Rf5993	5.56	2.63	5.63	62.8	69	31	158	4	40	35.5	1.99	142.9	3.93
	Rf5994	5.83	2.42	5.18	64.7	70	29	191	7	40	38.4	1.85	143.2	4.33
G3	Rf6001	5.38	2.37	5.07	63.3	84	29	227	5	40	36.4	2.46	142.9	3.65
1500	Rf6002	5.24	2.37	5.07	63.2	68	32	179	2	37	37.6	1.92	144.0	3.99
	Rf6003	6.92	2.57	5.50	63.7	62	29	166	4	43	36.8	1.69	143.4	3.76
	Rf6004	7.16	2.62	5.61	62.5	71	40	182	7	40	35.4	2.44	144.2	4.17
	Rf6005	6.64	2.42	5.18	63.9	84	36	125	2	42	36.2	2.32	140.2	3.49
	Rf6006	6.91	1.86	3.98	65.7	100	38	212	2	43	35.6	2.09	143.0	4.62
G4	Rf6013	5.25	3.48	7.45	64.3	71	29	152	7	46	35.8	1.88	144.6	4.40
4000	Rf6014	4.80	2.23	4.78	61.6	66	26	135	4	42	36.2	2.06	143.6	4.68
	Rf6015	7.61	2.23	4.78	62.5	74	31	180	11	41	36.6	1.98	145.0	4.17
	Rf6016	6.22	3.28	7.02	62.4	58	24	156	0	47	34.0	2.33	142.3	3.73
	Rf6017	7.02	3.23	6.92	62.7	61	34	150	7	37	37.4	1.76	143.7	3.40
	Rf6018	6.78	2.30	4.93	65.7	65	27	136	7	38	37.7	2.57	144.8	4.57

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 79/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 17. Individual Terminal Fasting Body Weights, Organ Weights and Organ Weight Ratios -Males

Group No.	Rat	Fasting	Organ weights(g)										Organ weight ratios(%)							
Dose (mg/kg Bwt/day)	No.	Bwt (g)	Adrenals	Testes	Kidneys	Liver	Heart	Brain	Epididym	Thymus	Spleen	Adrenals	Testes	Kidneys	Liver	Heart	Brain	Epididym	Thymus	Spleen
G1	Rf5971	324.76	0.056	3.547	2.494	11.009	1.178	1.829	0.846	0.839	0.629	0.017	1.092	0.768	3.390	0.362	0.563	0.261	0.258	0.194
0	Rf5972	264.17	0.039	2.706	2.009	8.803	1.011	1.668	0.633	0.663	0.406	0.015	1.024	0.760	3.332	0.383	0.631	0.240	0.251	0.154
	Rf5973	310.48	0.055	3.474	2.411	9.786	1.136	1.895	0.896	0.735	0.573	0.018	1.119	0.777	3.152	0.366	0.610	0.289	0.237	0.185
	Rf5974	253.46	0.062	3.132	1.843	8.253	0.875	1.790	0.838	0.545	0.690	0.024	1.236	0.727	3.256	0.345	0.706	0.331	0.215	0.272
	Rf5975	314.36	0.050	3.289	2.687	10.786	1.217	1.970	0.874	0.482	0.480	0.016	1.046	0.855	3.431	0.387	0.627	0.278	0.153	0.153
	Rf5976	285.30	0.061	3.174	2.134	8.844	1.026	1.943	0.966	0.640	0.531	0.021	1.113	0.748	3.100	0.360	0.681	0.339	0.224	0.186
G2	Rf5983	264.01	0.044	2.946	1.846	8.695	1.033	1.794	0.735	0.654	0.414	0.017	1.116	0.699	3.293	0.391	0.680	0.278	0.248	0.157
500	Rf5984	305.51	0.050	3.327	2.418	9.246	1.069	1.874	0.894	0.631	0.578	0.016	1.089	0.791	3.026	0.350	0.613	0.293	0.207	0.189
	Rf5985	293.17	0.064	3.352	2.208	9.591	1.066	1.961	0.658	0.642	1.035	0.022	1.143	0.753	3.271	0.364	0.669	0.224	0.219	0.353
	Rf5986	268.59	0.048	3.322	1.932	8.304	1.177	1.809	0.827	0.772	0.600	0.018	1.237	0.719	3.092	0.438	0.674	0.308	0.287	0.223
	Rf5987	275.01	0.056	3.562	2.151	8.541	1.010	1.866	0.872	0.612	0.570	0.020	1.295	0.782	3.106	0.367	0.679	0.317	0.223	0.207
	Rf5988	311.08	0.048	3.446	2.420	10.229	1.062	1.870	0.896	0.554	0.516	0.015	1.108	0.778	3.288	0.341	0.601	0.288	0.178	0.166
G3	Rf5995	247.09	0.047	3.525	2.004	7.588	1.028	1.735	0.692	0.901	0.615	0.019	1.427	0.811	3.071	0.416	0.702	0.280	0.365	0.249
1500	Rf5996	268.29	0.053	2.969	1.932	8.720	1.004	1.909	0.806	0.581	0.502	0.020	1.107	0.720	3.250	0.374	0.712	0.300	0.217	0.187
	Rf5997	292.96	0.051	3.498	2.242	9.530	1.273	1.888	0.813	0.688	0.819	0.017	1.194	0.765	3.253	0.435	0.644	0.278	0.235	0.280
	Rf5998	272.87	0.041	3.483	2.148	8.898	0.969	1.692	0.798	0.580	0.572	0.015	1.276	0.787	3.261	0.355	0.620	0.292	0.213	0.210
	Rf5999	306.63	0.052	3.222	2.615	9.785	1.181	1.808	0.763	0.750	0.537	0.017	1.051	0.853	3.191	0.385	0.590	0.249	0.245	0.175
	Rf6000	306.34	0.049	3.147	2.356	10.008	1.065	1.806	0.828	0.561	0.534	0.016	1.027	0.769	3.267	0.348	0.590	0.270	0.183	0.174
G4	Rf6007	322.51	0.061	2.798	2.532	10.431	1.123	1.926	0.799	0.742	0.561	0.019	0.868	0.785	3.234	0.348	0.597	0.248	0.230	0.174
4000	Rf6008	276.31	0.047	2.892	2.165	8.191	1.085	1.776	0.806	0.614	0.456	0.017	1.047	0.784	2.964	0.393	0.643	0.292	0.222	0.165
	Rf6009	302.11	0.058	3.409	2.580	10.199	1.121	1.877	0.820	0.540	0.501	0.019	1.128	0.854	3.376	0.371	0.621	0.271	0.179	0.166
	Rf6010	269.46	0.047	2.705	1.898	8.929	0.998	1.876	0.816	0.707	0.495	0.017	1.004	0.704	3.314	0.370	0.696	0.303	0.262	0.184
	Rf6011	300.25	0.043	3.028	2.240	9.223	1.130	1.827	0.663	0.579	0.507	0.014	1.008	0.746	3.072	0.376	0.608	0.221	0.193	0.169
	Rf6012	278.06	0.052	3.169	2.201	9.082	1.014	1.837	0.786	0.680	0.494	0.019	1.140	0.792	3.266	0.365	0.661	0.283	0.245	0.178

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 80/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 18. Individual Terminal Fasting Body Weights, Organ Weights and Organ Weight Ratios -Females

Group No. / Dose (mg/kg Bwt/day)	Rat No.	Fasting Bwt (g)	Organ weights(g)								Organ weight ratios(%)							
			Adrenals	Ovaries	Kidneys	Liver	Heart	Brain	Thymus	Spleen	Adrenals	Ovaries	Kidneys	Liver	Heart	Brain	Thymus	Spleen
G1	Rf5977	140.89	0.053	0.093	1.143	4.513	0.637	1.672	0.414	0.340	0.038	0.066	0.811	3.203	0.452	1.187	0.294	0.241
0	Rf5978	170.75	0.065	0.124	1.316	5.065	0.658	1.630	0.490	0.358	0.038	0.073	0.771	2.966	0.385	0.955	0.287	0.210
	Rf5979	163.42	0.058	0.099	1.275	4.784	0.686	1.731	0.454	0.363	0.035	0.061	0.780	2.927	0.420	1.059	0.278	0.222
	Rf5980	170.42	0.062	0.096	1.339	5.324	0.640	1.662	0.495	0.345	0.036	0.056	0.786	3.124	0.376	0.975	0.290	0.202
	Rf5981	171.66	0.065	0.118	1.306	5.665	0.651	1.650	0.378	0.394	0.038	0.069	0.761	3.300	0.379	0.961	0.220	0.230
	Rf5982	163.79	0.058	0.099	1.160	5.308	0.743	1.675	0.419	0.299	0.035	0.060	0.708	3.241	0.454	1.023	0.256	0.183
G2	Rf5989	165.60	0.054	0.119	1.222	5.206	0.677	1.591	0.583	0.312	0.033	0.072	0.738	3.144	0.409	0.961	0.352	0.168
500	Rf5990	185.44	0.072	0.133	1.340	5.845	0.686	1.799	0.481	0.438	0.039	0.072	0.723	3.152	0.370	0.970	0.259	0.236
	Rf5991	189.72	0.062	0.124	1.236	5.718	0.745	1.772	0.531	0.417	0.033	0.065	0.651	3.014	0.393	0.934	0.280	0.220
	Rf5992	165.97	0.060	0.104	1.364	5.124	0.677	1.855	0.472	0.411	0.036	0.063	0.822	3.087	0.408	1.118	0.284	0.248
	Rf5993	183.50	0.071	0.120	1.439	6.080	0.816	1.738	0.599	0.539	0.039	0.065	0.784	3.313	0.445	0.947	0.326	0.294
	Rf5994	160.28	0.062	0.123	1.267	5.164	0.672	1.775	0.448	0.353	0.039	0.077	0.790	3.222	0.419	1.107	0.280	0.220
G3	Rf6001	161.87	0.062	0.098	1.247	5.210	0.685	1.767	0.390	0.379	0.038	0.061	0.770	3.219	0.423	1.092	0.241	0.234
1500	Rf6002	161.60	0.065	0.099	1.236	5.088	0.678	1.764	0.439	0.356	0.040	0.061	0.765	3.149	0.420	1.092	0.272	0.220
	Rf6003	180.54	0.064	0.109	1.409	5.982	0.782	1.848	0.535	0.446	0.035	0.060	0.780	3.313	0.433	1.024	0.296	0.247
	Rf6004	185.54	0.053	0.134	1.406	6.407	0.819	1.730	0.658	0.494	0.029	0.072	0.758	3.453	0.441	0.932	0.355	0.266
	Rf6005	168.11	0.056	0.114	1.234	5.388	0.777	1.671	0.552	0.339	0.033	0.068	0.734	3.205	0.462	0.994	0.328	0.202
	Rf6006	179.16	0.074	0.140	1.364	5.789	0.697	1.678	0.529	0.491	0.041	0.078	0.761	3.231	0.389	0.937	0.295	0.274
G4	Rf6013	170.32	0.063	0.114	1.388	5.581	0.799	1.740	0.663	0.450	0.037	0.067	0.815	3.277	0.469	1.022	0.389	0.264
4000	Rf6014	161.57	0.065	0.106	1.271	5.266	0.673	1.762	0.603	0.351	0.040	0.066	0.787	3.259	0.417	1.091	0.373	0.217
	Rf6015	167.14	0.057	0.120	1.226	5.589	0.673	1.734	0.489	0.479	0.034	0.072	0.734	3.344	0.403	1.037	0.293	0.287
	Rf6016	174.24	0.058	0.116	1.282	5.561	0.687	1.759	0.597	0.350	0.033	0.067	0.736	3.192	0.394	1.010	0.343	0.201
	Rf6017	175.59	0.076	0.133	1.371	5.908	0.707	1.854	0.536	0.419	0.043	0.076	0.781	3.365	0.403	1.056	0.305	0.239
	Rf6018	148.96	0.062	0.102	1.183	4.747	0.627	1.589	0.366	0.287	0.042	0.068	0.794	3.187	0.421	1.067	0.246	0.193

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 81/140

21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 19. INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-MALES

Group No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G1	Rf5971	0	NAD	LIVER: Necrobiotic focus(i) 1 STOMACH: Cystic gland(s) 1a THYROIDS: Ultimobranchial cyst
G1	Rf5972	0	KIDNEYS(Bilateral):Pelvis dilated	KIDNEYS: Dilatation of pelvis 4-Bilateral Papillary necrosis 1a Tubulointerstitial nephritis 2a Hyaline droplets-tubular epithelium 2 EPIDIDYMIDES: Lymphocytic infiltration 1a
G1	Rf5973	0	NAD	KIDNEYS: Hyaline droplets-tubular epithelium 3 Basophilic tubules 2a THYROIDS: Ectopic thymus URINARY BLADDER: Epithelial hyperplasia 1a
G1	Rf5974	0	NAD	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Hyaline droplets-tubular epithelium 2
G1	Rf5975	0	NAD	LIVER: Necrobiotic focus(i) 1
G1	Rf5976	0	THYMUS:Discolouration-red (One lobe)	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Proteinaceous material in tubules 1a Hyaline droplets-tubular epithelium 2 THYMUS: Haemorrhage 3a RECTUM: Tissue present no change
G2	Rf5983	500	NAD	
G2	Rf5984	500	NAD	RECTUM: Tissue present no change

contd.

1: Minimal, 2: Mild, 3: Moderate, 4: Severe, a: Focal/Multifocal, d: Diffuse

TOXI-4091/04
052/8-CLSN/28-OR
PAGE No. 82/140

21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 19 contd. INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-MALES

Group No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G2	Rf5985	500	TESTES(Unilateral):Flabby SPLEEN:Enlarged-4.0 cm	RECTUM: Tissue present no change TESTES: Atrophy-seminiferous tubules 4-unilateral SPLEEN: Tissue present no change
G2	Rf5986	500	NAD	RECTUM: Tissue present no change
G2	Rf5987	500	NAD	RECTUM: Tissue present no change
G2	Rf5988	500	NAD	RECTUM: Tissue present no change
G3	Rf5995	1500	KIDNEYS(Bilateral):Pelvis dilated	RECTUM: Tissue present no change KIDNEYS: Dilatation of pelvis 3-bilateral Basophilic tubules 1a
G3	Rf5996	1500	NAD	RECTUM: Tissue present no change
G3	Rf5997	1500	CECUM:Discolouration-red	RECTUM: Tissue present no change CECUM: Congestion 2
G3	Rf5998	1500	KIDNEYS(Unilateral):Pelvis dilated	RECTUM: Parasite(s) KIDNEYS: Basophilic tubules 1a Dilatation of pelvis 4-unilateral Urothelial hyperplasia 1a
G3	Rf5999	1500	NAD	RECTUM: Parasite(s)
G3	Rf6000	1500	NAD	RECTUM: Tissue present no change
G4	Rf6007	4000	NAD	KIDNEYS: Hyaline droplets-tubular epithelium 2 RECTUM: Inflammation-chronic 1a

1: Minimal, 2: Mild, 3: Moderate, 4: Severe, a: Focal/Multifocal, d: Diffuse

contd.

TOXI-4091/04
052/6-CLSN/28-OR
PAGE No. 83/148

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 19 contd. INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-MALES

Group No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G4	Rf6008	4000	KIDNEYS:Unilateral:Pelvis dilated	KIDNEYS: Dilatation of pelvis 4-unilateral Hyaline droplets-tubular epithelium 2 RECTUM: Inflammation-chronic 1a
G4	Rf6009	4000	NAD	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Hyaline droplets-tubular epithelium 2 THYROIDS: Ectopic thymus
G4	Rf6010	4000	NAD	KIDNEYS: Hyaline droplets-tubular epithelium 2 ILEUM WITH PEYER'S PATCHES(X3): Tissue present no change RECTUM: Inflammation-chronic 1a
G4	Rf6011	4000	NAD	NAD
G4	Rf6012	4000	NAD	LIVER: Necrobiotic focus(i) 1 RECTUM: Inflammation-chronic 1a THYROIDS: Ectopic thymus

1: Minimal, 2: Mild, 3: Moderate, 4: Severe, a: Focal/Multifocal, d: Diffuse
X3: Peyer's patch not present

TOXI-4091/04
852/8-CLSN/28-OR
PAGE No. 84/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 2B. INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-FEMALES

Group No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G1	Rf5977	0	NAD	NAD
G1	Rf5978	0	NAD	LIVER: Necrobiotic focus(i) 1
G1	Rf5979	0	NAD	LIVER: Necrobiotic focus(i) 1
G1	Rf5980	0	NAD	LIVER: Necrobiotic focus(i) 2
G1	Rf5981	0	NAD	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Mineralisation 1a
G1	Rf5982	0	NAD	LIVER: Necrobiotic focus(i) 1
G2	Rf5989	500	NAD	Tissues not examined
G2	Rf5990	500	NAD	Tissues not examined
G2	Rf5991	500	NAD	Tissues not examined
G2	Rf5992	500	NAD	Tissues not examined
G2	Rf5993	500	NAD	Tissues not examined
G2	Rf5994	500	NAD	Tissues not examined
G3	Rf6001	1500	NAD	Tissues not examined
G3	Rf6002	1500	KIDNEYS(Unilateral):Pelvis dilated	KIDNEYS: Dilatation of pelvis 2-unilateral

1: Minimal, 2: Mild, 3: Moderate, 4: Severe, a: Focal/Multifocal, d: Diffuse

contd.

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 2B contd. INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-FEMALES

Group No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G3	Rf6003	1500	NAD	Tissues not examined
G3	Rf6004	1500	UTERUS:Dilatation-Focal KIDNEYS(Bilateral):Pelvis dilated	UTERUS: Dilatation 2 KIDNEYS: Dilatation of pelvis 2-bilateral Basophilic tubules 1a
G3	Rf6005	1500	NAD	Tissues not examined
G3	Rf6006	1500	NAD	Tissues not examined
G4	Rf6013	4000	NAD	LIVER: Necrobiotic focus(i) 1
G4	Rf6014	4000	NAD	NAD
G4	Rf6015	4000	NAD	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Basophilic tubules 1a RECTUM: Inflammation-chronic 1a
G4	Rf6016	4000	NAD	LIVER: Necrobiotic focus(i) 1
G4	Rf6017	4000	UTERUS:Dilatation	LIVER: Lymphocytic infiltration 1a UTERUS: Dilatation 2
G4	Rf6018	4000	KIDNEYS(Unilateral):Pelvis dilated UTERUS:Dilatation	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Dilatation of pelvis 2-unilateral UTERUS: Dilatation 3

1: Minimal, 2: Mild, 3: Moderate, 4: Severe, a: Focal/Multifocal, d: Diffuse

TOXI-4091/04
052/8-CLSW/28-OR
PAGE No. 86/148

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 21. Certificate of Analysis

CERTIFICATE OF ANALYSIS

from

Borregaard LignoTech Research & Development

Ultrazine FG-R

Batch no.	Specification	DP 955
Dry Solids	36 - 40	26.5 %
Molecular weight average, Mw	40,000 Da - 65,000 Da	46,000 Da
Sample within range 1,000 Da - 250,000 Da	> 90 %	94.6 %
K solid	> 11.5	11.6
Colour in 0.5 % solution	< 0.40 AU	0.32 AU
Phenolic OH	1.5 % - 2.5 %	2.1 %
pH in 10 % solution	2.7 - 3.3	2.9
Viscosity at 38 % DS and 35 °C	100 mPas - 600 mPas	210 mPas
Ash	< 14.0 %	7.0 %
Sulphite, SO_3^{2-}	< 0.5 %	0.3 %
Free oxalate	< 0.5 %	Not detected
Reducing Sugars	2.0 % - 5.0 %	4.7 %
Calcium	< 5.0 %	3.4 %
Methoxyl	10 % - 13 %	11.6 %
Degree of sulfonation	0.3 - 0.7	0.4
Total heavy metals	< 10 ppm	< 7 ppm
Heavy metals (reported in ppm)		
Arsenic	< 0.05	< 0.04 ppm
Mercury	< 0.05	< 0.01 ppm
Cadmium	< 1	0.1 ppm
Lead	< 2	< 0.9 ppm
Chromium	< 5	0.3 ppm
Copper	< 5	3.8 ppm
Nickel	< 5	0.5 ppm
Zinc	< 50	18 ppm
Iron	< 150	51 ppm

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 87/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

APPENDIX 22. Deviation from the Approved Study Plan

AS IN STUDY PLAN	DEVIATION
8.4.2 Concentration, Homogeneity and Stability of the Test Item in Food (Page Nos. 10/25 & 11/25) At the end of the treatment period, the deep frozen samples will be shipped on dry ice to the following address: DSM Nutritional Products Ltd R&D, Analytics Sample Registration Desk Attn. Mr. Daniele Avellina Building 205 Room 6 Wurmisweg 576 4303 Kaiseraugst, Switzerland Phone: +41 61 688 56 34 Fax: +41 61 688 0563 E-Mail: sample-registration-vfha.basel@dsm.com	E-Mail: sample-reg-arc.kaiseraugst@dsm.com

The above mentioned deviation from the approved study plan did not affect the outcome of the study or the interpretation of results.

Date: 20.09.2005

(Mr. E. RAMESH)
Study Director

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 88/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

15. ANNEXURES

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 1. Study Plan and Study plan Amendment

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STUDY PLAN
(COPY No. 1/2)

STUDY PLAN No.	: SP-4091/04
TEST ITEM CODE BY TEST FACILITY	: 052/8-CLSN
STUDY CODE	: 28-OR

REPEATED DOSE (28-DAY) ORAL TOXICITY STUDY WITH CALCIUM LIGNOSULFONATE IN WISTAR RATS

TEST ITEM: CALCIUM LIGNOSULFONATE

STUDY No.: 4091/04

SPONSOR

DSM NUTRITIONAL PRODUCTS LTD
WURMISWEG 576
4303 KAISERAUGST, SWITZERLAND

TEST FACILITY

TOXICOLOGY DEPARTMENT
RALLIS RESEARCH CENTRE
RALLIS INDIA LIMITED
POST BOX No. 5813, PLOT Nos. 21 & 22
PEENYA II PHASE, BANGALORE - 560 058
INDIA

SP-4091/04
052/8-CLSN/28-OR
PAGE No.1/25

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 90/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 1 contd.

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TABLE OF CONTENTS

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 1 contd.

RALLIS RESEARCH CENTRE
Peenya, Bangalore - 560 058.

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 1 contd.

RALLIS RESEARCH CENTRE
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1. **STUDY DETAILS**

Study Title	:	Repeated dose (28-day) oral toxicity study with Calcium Lignosulfonate in Wistar rats
Test Item	:	Calcium Lignosulfonate
Study Number	:	4091/04
Test Facility	:	Toxicology Department Rallis Research Centre Rallis India Limited Post Box No. 5813, Plot Nos. 21 & 22 Peenya II Phase Bangalore – 560 058 INDIA
Sponsor	:	DSM Nutritional Products Ltd Wurmisweg 576 4303 Kaiseraugst, Switzerland
Monitoring Scientist	:	Dr. Edgar Weber DSM Nutritional Products Ltd Bldg 205 / Room 315 P.O. Box 3255 CH-4002 Basel Switzerland
Study Personnel		
Study Director	:	Mr.E.Ramesh
Technical Co-ordinator	:	Mr.B.N.Vishwanath
Study schedule		
Acclimatisation	:	Start: 14.01.2005 End: 18.01.2005
Treatment	:	Start: 19.01.2005 End: 16.02.2005
Sacrifice	:	17.02.2005
Proposed submission of the draft report	:	Latest by April 2005

SP-4091/04
052/8-CLSN/28-OR
PAGE No.4/25

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 93/140

CONFIDENTIAL

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 1 contd.

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2. **QUALITY ASSURANCE**

The Quality Assurance Unit of Rallis Research Centre, Bangalore - 560 058 will inspect the study, the raw data, the draft and final reports. Findings of all inspections will be reported to the Management and to the Study Director. Inspection dates and reporting dates will be entered in the study report. The Quality Assurance Unit has reviewed the final study plan and will receive a copy thereof.

3. **STUDY COMPLIANCE**

The study will be performed in accordance with the following:

- OECD Principles of Good Laboratory Practice (as revised in 1997), Environmental Directorate, Organisation for Economic Co-operation and Development, Paris 1998.
- This study will also be conducted as per the mutually agreed study plan and the Standard Operating Procedures.

4. **STUDY GUIDELINE**

- OECD 407 adopted July 27 1995 (OECD, 1995) [As per the request of sponsor this study will not include recovery groups and neurological examination at the end of treatment will not be carried out].

5. **AMENDMENT PROCEDURES**

This study plan may be amended or be subjected to alterations. In each case any amendment to the approved study plan and the reasons for such amendments will be put in writing and realized only after written consent from the study sponsor. If immediate action is necessary, verbal agreement from the sponsor will be confirmed as soon as possible by study plan amendment. Minor changes of the study plan which do not influence the procedures of the outcome of the study may be subject to the discretion of the Study Director, but will be mentioned in the report.

ADVINUS

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ANNEXURE 1 contd.

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6. **SAFETY PRECAUTIONS**

Gloves, cap, face mask and goggles (if required) will be used in addition to protective body garments and shoes to ensure adequate personal health and safety and to avoid inhalation and skin contact with the test item. In case of eye contact, the eye will be washed thoroughly with water and medical treatment will be sought. In case of skin contact, it will be washed with soap and water with subsequent medical aid.

7. **OBJECTIVE**

The purpose of this Repeated Dose 28 day Oral Toxicity in Rodents study will be to assess the toxicological profile of the test item when administered to rats. The animals will be observed during the entire treatment period. This study may provide information on major toxic effects, target organs and an estimate of a No Observed Effect Level (NOEL) / No Observed Adverse Effect Level (NOAEL).

8. **MATERIALS AND METHODS**

8.1 **TEST SYSTEM**

Animals	:	HsdCpb: WU rats-conventionally bred (in-house random bred) Strain: Wistar Substrain: Hsdola (Parent stock obtained from Harlan, UK Limited).
Justification for selection of species	:	Rat is one of the test systems referred by the guideline.
Source	:	Toxicology Department Rallis Research Centre Bangalore 560 058, INDIA
No. of Groups	:	4 groups: Control, low, mid and high dose
No. of rats / group	:	12 rats (6 males + 6 females)
Age at treatment	:	5 - 8 weeks (exact age will be provided in the report)

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 1 contd.

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Body weight range	:	At the commencement of the treatment, the weight variation of animals used should be minimal not exceed ± 20% of the mean body weight in each sex and group.
Identification	:	By rat accession number, cage card and turmeric colour body marking. The temporary body marking during acclimatization period will be done with crystal violet.
Acclimatization	:	After veterinary examination, for good health and the suitability for the study, the rats will be acclimatized for five days before start of the treatment. Only nulliparous and non-pregnant females will be used in the study.

8.2 **TEST ITEM INFORMATION**

(as furnished by study sponsor)

Name	:	Ultrazine FG-R®
Common Name (active ingredient)	:	Calcium Lignosulfonate
Name to be used in the report	:	Lignosulfonate
Chemical name (IUPAC)	:	Not applicable
Code by test facility	:	052/8-CLSN
CAS No.	:	8061-52-7
Batch No.	:	004 (DP955)
Manufactured by	:	Borregaard Industries Ltd Post Box 162 N-1701 SARPSBORG, Norway
Supplied by		DSM Nutritional Products Ltd Wurmisweg 576 CH-4303 Kaiseraugst, SWITZERLAND

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 1 contd.

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Date of manufacture	:	January 2004
Date of expiry	:	January 2006
Date of receipt at test facility	:	23.12.2004
Purity to be stated in the report	:	About 85%
Physical appearance	:	Brownish free-flowing powder
Storage conditions	:	Ambient (+18 to +36° C), dry
Hazards and precautions	:	Hazards: no specific known Precautions: Standard hygienic procedures (gloves, goggles, face mask)

8.3 **PERFOMANCE OF TEST**

8.3.1 **Husbandry**

Conditions

Animals will be housed under standard laboratory conditions, air conditioned with adequate fresh air supply (12 - 15 air changes/hour). Environment: temperature 22 (±3)°C, relative humidity 30 - 70%, with 12 hours light and 12 hours dark cycle.

The maximum and minimum temperature and relative humidity in the experimental room will be recorded once daily. The relative humidity in the experimental room will be calculated daily from dry and wet bulb temperature recordings.

Housing

Two rats per sex per cage in sterilized standard polypropylene mesh bottom cages (size: L 410 x W 282 x H 150 mm) with stainless steel top grill having facilities for holding powder food in hopper and for drinking water in glass bottle with a stainless steel sipper tube.

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 1 contd.

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Peenya, Bangalore - 560 058

Diet : *ad libitum*

Ssniff rats/mice powder food-maintenance meal - low in germs manufactured by Ssniff Spezialdiäten GmbH., Ferdinand-Gabriel-Weg 16, D-59494 Söest, GERMANY.

Water: *ad libitum*

Deep bore-well water passed through activated charcoal filter and exposed to UV rays in Aquaguard on-line water filter-cum-purifier manufactured by Eureka Forbes Ltd., Mumbai - 400 001, INDIA will be provided to animals in glass bottles with stainless steel sipper tubes.

Analysis: contaminant analysis reports of food and water (close to the study period) will be included in the report.

8.3.2 **Dose Selection**

Three dose levels of 500, 1500 and 4000 mg/kg/day were selected as suggested by the sponsor.

8.3.3 **Grouping**

Grouping is by in-house method of body weight stratification and distribution which is as follows: the rats procured for the study will be weighed and grouped into body weight ranges (Example: 91 - 100, 101 - 110, 111 - 120 g etc.). These body weight stratified rats will be distributed to all the study groups in equal numbers. The rats with extreme body weights will be discarded. The grouping will be done on day 1 of acclimatization.

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ANNEXURE 1 contd.

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8.3.4 **Group Allocation and Number of Animals**

The selected male and female rats will be assigned to control and different treatment groups as shown below:

Group No	Group	Colour of cage card	Dose (mg/kg Bwt/day)	No. of rats	Sex	Rat Numbers From	To
G1	Control	White	0	6	M	Rf5971	Rf5976
				6	F	Rf5977	Rf5982
G2	Low dose	Yellow	500	6	M	Rf5983	Rf5988
				6	F	Rf5989	Rf5994
G3	Mid dose	Green	1500	6	M	Rf5995	Rf6000
				6	F	Rf6001	Rf6006
G4	High dose	Pink	4000	6	M	Rf6007	Rf6012
				6	F	Rf6013	Rf6018

8.3.5 **Route of Administration**

Oral through food, doses expressed as mg test item per kg body weight and day.

8.4 **ANALYSES OF TEST ITEM**

8.4.1 **Identity of the Test Item**

The identity of the test item will be provided by the study sponsor by a certificate of analysis. The responsibility for the correct identity of the test item rests with the sponsor.

8.4.2 **Concentration, Homogeneity and Stability of the Test Item in Food**

All analyses will be performed in duplicate by the Principal Scientist Analytics using the method LS-101/01 in a GLP approved laboratory. Each of the following food admix samples should be of a minimum of 100 gram.

For the assessment of the concentration of the test item in food, samples from all preparations (Groups G1-G4, males and females, weeks 1-4 of treatment) will be taken and kept stored deep frozen (≤ - 20°C).

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ANNEXURE 1 contd.

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To assess the homogeneity of the prepared feed batches, five individual sub samples from different locations of the blender (top, top/mid, mid, mid/bottom, bottom) from the first batch of feed prepared (Groups G1-G4, males and females, week 1) will be collected and kept stored deep frozen (≤ - 20°C).

To investigate the stability of the test item, aliquots (stability samples) of the high and mid dose groups of the first feed batches (Groups G3 and G4, males and females, week 1) will be stored at ambient temperature for 10 days at the test site and subsequently kept stored deep frozen (≤ - 20°C).

At the end of the treatment period, the deep frozen samples will be shipped on dry ice to the following address:

DSM Nutritional Products Ltd
R&D, Analytics
Sample Registration Desk
Attn. Mr. Daniele Avellina
Building 205 Room 6
Wurmisweg 576
4303 Kaiseraugst, Switzerland
Phone: +41 61 688 56 34
Fax: +41 61 688 0563
E-Mail: sample-registration-vfha.basel@dsm.com

The sponsor (sample registration desk and monitoring scientist) will be informed about the shipment including expected day of arrival. Results furnished by the sponsor (including GLP and Quality Assurance Statements) will be included in the report.

8.4.3 **Preparation of Experimental Food with Test Item**

Dietary concentrations will be adjusted to administer specified test item dose levels of 500,1500 and 4000 mg/kg/day. Each time when the diet is prepared, adjustments will be made based on body weights and food

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ANNEXURE 1 contd.

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consumption data from preceding interval and the new concentration will be calculated.

The experimental food will be prepared once in 7 days separately for male and female sexes. The concentration of each batch of the feed mixtures will be calculated based on the mean food consumption and mean body weight per sex and group. Based on the required concentration, the test item will be weighed and mixed in a mixer grinder with approximately 0.5 kg of Ssniff powdered food for approximately 2 minutes to prepare the premix. This premix will be mixed in stainless steel drum with approximately 0.5 kg of Ssniff powdered food for approximately 2 minutes and then added in portions to the remaining bulk food and mixed in ribbon mixer for 20 minutes.

For control group, the required amount of Ssniff powder food will be mixed in a ribbon mixer for 20 minutes. Food for the control group will not be prepared separately for males and females.

No solvent/vehicle will be used in the preparation of the experimental food.

The quantity of experimental food prepared, the amount of test item weighed based on the required concentration will be recorded in the raw data.

8.5 **STORAGE OF THE TEST ITEM INCORPORATED FOOD**

The experimental food will be stored in polyethylene bags within labelled stainless steel drums in the experimental room.

8.6 **TREATMENT**

Each test group will receive food specifically prepared for that group/sex. The treatment will be 7 days a week for 4 weeks.

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8.7 **OBSERVATIONS**

8.7.1 **Veterinary, Clinical and Ophthalmological Examinations, General Clinical Signs and Pre-Terminal Deaths**

a. Veterinary examination

Veterinary examination will be done prior to initiation of treatment and weekly thereafter (± 1 day) during treatment period.

b. Clinical examination

Clinical examination will be done prior to initiation of treatment and once weekly (± 1 day) during treatment period.

c. Ophthalmological examination

Ophthalmological examination will be done with an ophthalmoscope during the acclimatization period for all animals and at the end of treatment. Mydriasis will be induced before examination by using 1% Tropicamide.

d. General Clinical signs and pre-terminal deaths

The animals will be observed for clinical signs (clinical signs of toxicity) once a day. All animals will be observed for morbidity and pre-terminal deaths twice a day. Dead animals will be necropsied immediately or refrigerated for necropsy. Moribund animals will be isolated for necropsy.

8.7.2 **Body Weights**

Individual body weights will be recorded before the administration of test item i.e., day 1 and weekly thereafter.
In addition, to arrive at the nominal dietary level of the test item for the corresponding week the body weights will be recorded on day 4 of acclimatization and day 7 of each week thereafter during the treatment period.

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ANNEXURE 1 contd.

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8.7.3 **Food Intake**

The following method will be adopted for measurement of weekly food consumption.

Day 1[a]: Food input 1500 g (inclusive of mesh, hopper and cage card weight)	Food output on day 8 (inclusive of mesh, hopper and cage card weight)

The cagewise food consumption will be calculated by adding the food consumed in 7 days and by dividing the total by the number of animals per cage to determine the food intake/rat/week. The visual estimation of food spillage will be recorded at each food output recording session and during litter paper change and will be taken into consideration (i.e., the food spillage data/cage/week will be substracted from the food consumed or added to food output data) for the calculation of weekly food consumption. The weekly consumption/rat will be divided by the number of days (7) to obtain food consumption (g)/rat/day. This will be repeated throughout the treatment period.

In addition, to arrive at the nominal dietary level of the test item for the corresponding week the following method will be adopted to measure the food consumption.

Acclimatization period:

Day 1[a]: Food input 1500 g (inclusive of mesh, hopper and cage card weight)	Food output on day 4 (inclusive of mesh, hopper and cage card weight)

Treatment period:

Day 1[a]: Food input 1500 g (inclusive of mesh, hopper and cage card weight)	Food output on day 7 (inclusive of mesh, hopper and cage card weight)

a: Day '1' denotes food input at the start of each week.

The cagewise food consumption will be calculated by adding the food consumed in 4 or 6 days and by dividing the total by the number of animals per cage to determine the food intake/rat/week. The visual

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ANNEXURE 1 contd.

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estimation of food spillage will be recorded at each food output recording session and during litter paper change and will be taken into consideration (i.e., the food spillage data/cage/week will be substracted from the food consumed or added to food output data) for the calculation of weekly food consumption. The weekly food consumption/rat will be divided by the number of days (4 or 6) to obtain food consumption (g)/rat/day. This will be repeated throughout.

Note: Refer Appendix 3 for the calculation of the test item concentrations in food.

8.7.4 **Clinical Laboratory Investigations**

a. Blood smear:

Blood smears will be made by the tail clipping method within three days before sacrifice. The blood smears will be stained by Wright's stain (solution) and the differential leucocyte count will be done by the conventional microscopy.

b. Blood collection:

At the end of the treatment period, all surviving animals will be fasted overnight (water allowed) and blood will be collected from the abdominal aorta under ether anaesthesia. An aliquot of blood will be collected in tubes containing 3.8% sodium citrate solution for determination of prothrombin time and the remaining blood will be collected into EDTA and heparinized tubes for haematology and clinical chemistry respectively.

An aliquot of plasma (from the preparation for clinical chemistry) will be deep frozen and shipped on dry ice to the sponsor (address: see section 8.4.2) for optional biochemical investigations.

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ANNEXURE 1 contd.

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c. Haematology:

The following haematological parameters will be determined using Sysmex TM K-800 Automated Haematology Analyzer (TOA Medical Electronics Co., Kobe, JAPAN).

1. Haemoglobin
2. Red Blood Corpuscles
3. White Blood Corpuscles
4. Haematocrit
5. Platelets

The following calculated RBC associated indices will be recorded from the haematology analyser:

1. Mean Corpuscular Volume
2. Mean Corpuscular Haemoglobin
3. Mean Corpuscular Haemoglobin Concentration

Prothrombin time analysis will be carried out using ST-art-4 coagulation analyser (Diagnostica stago).

d. Clinical chemistry:

Plasma will be separated in a refrigerated centrifuge at 5000 rpm for 15 minutes and analysed using BM-HITACHI 704, (Boehringer Mannheim, Mannheim, GERMANY) Automatic Analyser for the following parameters.

1. Fasting glucose
2. Total cholesterol
3. Creatinine
4. Total plasma protein
5. Albumin
6. Blood Urea Nitrogen (BUN)
7. Alanine amino transferase
8. Aspartate amino transferase
9. Gamma glutamyl transpeptidase
10. Alkaline Phosphatase
11. Urea(calculated by using BUN values)

Na and K will be assayed by Easylyte sodium potassium analyser (Medica corporation, USA).

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ANNEXURE 1 contd.

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8.7.5 **Pathology**

a. Gross necropsy

All rats in the study will be subjected to gross necropsy and the findings will be recorded. Moribund rats will be killed by exsanguination under ether anaesthesia. The animals to be sacrificed at term will be fasted overnight (water allowed), anaesthetised as per the random number list generated for the study, weighed and exsanguinated and then the animal will be subjected to detailed necropsy by a pathologist.

b. Tissue collection

The following organs and tissues will be collected from all rats and preserved in 10% buffered neutral formalin:

1. All gross lesions
2. Brain (Cerebrum, Cerebellum and medulla/pons)
3. Spinal cord - 3 levels (cervical, mid thoracic and lumbar)
4. Stomach
5. Duodenum
6. Jejunum
7. Ileum (with Peyer's patches)
8. Cecum
9. Colon
10. Rectum
11. Liver
12. Kidneys
13. Adrenals
14. Spleen
15. Heart
16. Thymus
17. Thyroid
18. Trachea
19. Lungs (to be inflated with fixative and then immersed in formalin)
20. Testes
21. Epididymides
22. Ovaries
23. Uterus
24. Seminal vesicles
25. Coagulating glands
26. Prostate
27. Urinary bladder
28. Axillary lymph nodes
29. Mesenteric lymph nodes
30. Sciatic nerve
31. Bone marrow smear from femur

c. Organ weights

The following organs will be weighed from all rats of all groups (apart from those found moribund and/ or dead animals): liver, adrenals, kidneys, gonads, brain, epididymides, thymus, heart and spleen. The organ weights as percentage of body weights will also be determined and presented in the report.

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ANNEXURE 1 contd.

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d. Histopathology

Histopathological examination will be carried out on the preserved organs and tissues (including gross lesions) of the high dose group and the control group and of all dead and moribund sacrificed animals. Target organs i.e., those showing gross lesions or changes in size and all gross lesions in low and mid dose groups will also be examined. Further, those tissues suspected of showing test item related histopathological changes in the high dose group will be examined in the lower dose groups.

The tissues will be processed for routine paraffin embedding and 5 micron sections will be stained with Mayer's Haematoxylin-Eosin stain. Unused tissues will be archived.

9. STATISTICAL ANALYSES

Using specific computer programmes, body weights, food consumption and laboratory investigations (haematology and clinical chemistry) data will be compared by Bartlett's test for homogeneity of intragroup variances. When the variances prove to be heterogeneous, the data will be transformed using appropriate transformation. The data with homogeneous intragroup variances will be subjected to one-way analyses of variance (ANOVA - Snedecor and Cochran, 1987). Following ANOVA, if 'F' is found significant, Dunnett's pairwise comparison (Scheffe, 1953) of means of treated groups with control group mean will be done individually. Following a significant difference of the test group from the control group, the Dose response correlation will be estimated and tested by 't' test.

All analyses and comparisons will be evaluated at the 5% ($P \leq 0.05$) level.

Organ weight and organ weight ratio data will be analysed by Student 't' test.

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ANNEXURE 1 contd.

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If a significant difference in values over the control group is observed in a minimum of two treatment groups with linear increase or decrease, the dose correlation co-efficient will be estimated and subjected to 't' test.

Statistically significant differences ($P \leq 0.05$), indicated by the aforementioned tests are designated by the superscripts throughout the report as stated below:

+/- Significantly higher (+)/lower (-) than the control group
d: Significant dose correlation

Pathology data may be statistically analysed at the discretion of the pathologist and the same will be mentioned in the report if done.

Data if required will also be subjected to other statistical tests and will be mentioned in the report.

10. RESULTS

10.1 DATA COMPILATION

All individual animal data will be summarized and presented as tables along with results of statistical analyses. All findings will be presented in the report as per the standard reporting format.

11. REPORTING

- The test report must include the following information, as appropriate:
- The name and address of the sponsors, the test facility along with the study schedule.
- The names and signatures of all personnel involved in the study, including the Study Director and other scientists.
- All study plan deviations, if any
- Vehicle:
  - Justification for the choice of vehicle

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ANNEXURE 1 contd.

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- Test animals:
  - species/strain used;
  - number, age and sex of animals;
  - source, housing conditions, diet etc.;
- Test conditions:
  - details of test item information and certificate of analysis;
  - details of the administration of the test item including dosing volumes and time of dosing;
  - details of food and water quality (including diet type/source, water source);
- Results:
  - tabulation of response data by sex and dose level for each animal (i.e., animals showing signs of toxicity including mortality, nature, severity and duration of effects);
  - tabulation of body weight and body weight changes;
  - individual weights of animals on the day of dosing and at different intervals of the treatment period and at the time of death or sacrifice;
  - time course of onset of signs of toxicity, and whether these were reversible for each animal;
  - gross necropsy and histopathological findings for each animal.
- Discussion and interpretation of results.
- Conclusion.
- A description of all circumstances if any, that may have affected the quality or integrity of the study.
- The Quality Assurance Statement, signed by the Head, Quality Assurance Unit.
- The GLP Compliance Statement, signed by the Study Director.
- The storage locations of all raw data, the report, a sample of the test item and the archiving period.
- GLP certificates.

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ANNEXURE 1 contd.

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Peenya, Bangalore - 560 058.

12. ARCHIVING

Rallis will archive at the archives of the test facility the following for 15 years after completion of the study: study plan, raw data, draft report and final reports. A sample of the test item has been sent from the test item stores to the archives after the receipt of test item. This sample shall be stored for a period of 2 years from the date of this final report or till next GLP inspection, whichever is later, however not beyond 30 years. All tissue specimens will be archived for 5 years, blocks and slides will be archived for 12 years after which these will be handed over to the sponsor or preserved longer at the cost of the sponsor.

13. REPORT DISTRIBUTION

Sponsor : Two signed final reports in original (Copy Nos. 1/3 to 2/3).
Archives : One signed final report in original (Copy No. 3/3).

14. REFERENCES

OECD Principles of Good Laboratory Practice (as revised in 1997), Environmental Directorate, Organisation for Economic Co-operation and Development, Paris 1998.

OECD Guideline No. 407, Repeated Dose 28-day Oral Toxicity study in Rodents, adopted on 27 July 1995.

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 1 contd.

RALLIS RESEARCH CENTRE
Peenya, Bangalore - 560 058.

15. AGREEMENT

This study plan for Study No.: 4091/04, [Repeated dose (28-day) oral toxicity study with Calcium Lignosulfonate in Wistar rats] has been mutually agreed and signed.

for **TEST FACILITY**

1 Mr. E. RAMESH
STUDY DIRECTOR
Date 06 01 2005

2 HEAD, QUALITY ASSURANCE UNIT
Date

3 MANAGEMENT
Date 06/01/2005

for **STUDY SPONSOR**

1 Dr. EDGAR WEBER
MONITORING SCIENTIST
Date: 17-Jan-2005

SP-4091/04
052/8-CLSN/28-OR
PAGE No.22/25

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 111/140

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ANNEXURE 1 contd.

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APPENDIX 1. Daily Work Check List

Month and Year

Room No

Study No

Person's Incharge

Sl No	Work	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1	Temperature@ Max°C																															
	Min°C																															
	Dry°C																															
	Wet°C																															
	RH %																															
2	Observation (morning)																															
3	Cage change																															
4	Feeding																															
5	Litter tray paper change																															
6	Body marking#																															
7	Mesh change																															
8	Bottle change																															
9	Air changes (cycles/hour)*																															
10	Air sampling																															
11	Floor washing																															
12	Room washing																															
13	Fumigation																															
14	Water sampling																															
15	Litter tray change																															
16	Cage Battery change																															
17	Blood smear																															
18	Fasting																															
19	Electrical/Sanitary fittings																															
20	Exhaust side filter and air inlet duct cleaning																															
21	Watering																															
	Observer's Sign																															
	Date																															
	Afternoon observation																															
	Observer's Sign																															
	Date																															

* Transcribed data

Body marking

@ Temperature recording coincides with the morning observation

SP-4091/04
052/8-CLSN/28-OR
PAGE No.23/25

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 112/140

CONFIDENTIAL

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 1 contd.

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APPENDIX 2. Experimental Food Preparation Data

Study No. Study Code

Batch No. Date of Receipt Date of Expiry

Test Item Details			Test Item Code				Premix in Mixer Grinder			Mixing Details		Premix in Stainless Steel Container			Main Mixing in Blender		
Persons Name, Date of Food Mixing (Signature with date	Food Batch No. & Date of Receipt	Group & Sex	Dose (ppm)	Total food (kg)	Chemical (mg/g)	Amount (kg)	Start time	End time	Total time (min)	Premix in Stainless Steel Container Amount (kg)	Start time	End time	Total time (min)	Remaining food (kg)	Start time	End time	Total time (min)

AM : Ante meridian PM : Post meridian

Sampling Details: Batch No; Sampled by

Remarks if any :

~ : Approximately

SP-4091/04
052/8-CLSN/28-OR
PAGE No.24/25

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 113/140

CONFIDENTIAL

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 1 contd.

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APPENDIX 3. Calculation of the Test Item Concentrations in Food

Following method is adapted to arrive at the nominal dietary level of the test item for the next week from the previous week data.

An example to arrive at the test item requirement to achieve the dietary intake of 500 mg/kg Bwt/day for week 2 is as given below:

Assuming average body weight for week 1 = 225.23 g
Assuming average food consumption for week 1 = 25.0 g

$$\text{Food consumption ratio (FCR)} = \frac{\text{Average food consumption of previous week}}{\text{Average body weight of previous week}} \times 1000$$

$$\text{FCR} = \frac{25.0}{225.23} \times 1000$$

$$\text{FCR} = 111.0 \text{ g/kg}$$

$$\text{Concentration of food to be prepared (ppm)} = \frac{\text{Dose}}{\text{FCR}} \times 1000$$

$$\text{Concentration of food to be prepared (ppm)} = \frac{500}{111.0} \times 1000$$

$$\text{Concentration of food to be prepared (ppm)} = 4505$$

i.e., 4505 mg of test item is mixed with 1 kg of food to achieve the intake of 500 mg/kg Bwt/day

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ANNEXURE 1 contd.

RALLIS RESEARCH CENTRE

AMENDMENT TO THE STUDY PLAN No. SP-4091/04 FOR MUTUAL AGREEMENT
(COPY No. 2/2)

Study No	4091/04
Study Title	Repeated dose (28-day) oral toxicity study with Calcium Lignosulfonate in Wistar rats
Test Item Code	052/8-CLSN
Sponsor	DSM Nutritional Products Ltd Wurmisweg 576 4303 Kaiseraugst Switzerland

AMENDMENT No. 1

AS IN STUDY PLAN	AMENDED TO
Concentration, Homogeneity and Stability of the Test Item in Feed (PAGE No. 19/33)	
All analyses will be performed in duplicate by the Principal Scientist Analytics using the method LS-101/01 in a GLP approved laboratory	All analyses will be performed in duplicate using the method LS-101/01 under non-GLP conditions.
Results furnished by the sponsor (including GLP and Quality Assurance Statements) will be included in the report.	The Analytical report signed by the analyst will be included in the report as a separate Annexure.

Date: 28.01.2005

Justification : Since the analysis of feed samples are carried out under non-GLP conditions, as indicated by the sponsor.

AMENDMENT IS MUTUALLY AGREED UPON:

for TEST FACILITY

1. Mr E RAMESH
STUDY DIRECTOR
Date 28.01.2005

2. HEAD, QUALITY ASSURANCE UNIT
Date 28/1/2005

3. MANAGEMENT
Date 28/1/05

for STUDY SPONSOR

1. Dr. EDGAR WEBER
MONITORING SCIENTIST
Date: 04-Feb-2005

Amendment No. 1 to Study plan No. SP-4091/04
052/8-CLSN/28-OR
Page No. 1/1

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

AMENDMENT TO THE STUDY PLAN No. SP-4091/04 FOR MUTUAL AGREEMENT
(COPY No. 2/2)

Study No	4091/04
Study Title	Repeated dose (28-day) oral toxicity study with Calcium Lignosulfonate in Wistar rats
Test Item Code	052/8-CLSN
Sponsor	DSM Nutritional Products Ltd Wurmisweg 576 4303 Kaiseraugst, Switzerland

AMENDMENT No. 2

AS IN STUDY PLAN	AMENDED TO
1. TEST FACILITY (Page No. 1/25) and STUDY DETAILS (Page No. 4/25) RALLIS RESEARCH CENTRE RALLIS INDIA LIMITED	ADVINUS THERAPEUTICS PRIVATE LIMITED
2. Quality Assurance (Page No. 5/25) The Quality Assurance Unit of Rallis Research Centre, Bangalore - 560 058 will inspect the study, the raw data, the draft and final reports.	The Quality Assurance Unit of Advinus Therapeutics Private Limited, Bangalore - 560 058 will inspect the study, the raw data, the draft and final reports.
3. Archiving (Page No. 21/25) Rallis will archive at the archives of the test facility the following for 15 years after completion of the study: study plan, raw data, draft report and final reports.	Advinus will archive at the archives of the test facility the following for 15 years after completion of the study: study plan, raw data, draft report and final reports.

Date: 27-08-2005

Justification : Due to the change in the name of the test facility from Rallis Research Centre to Advinus Therapeutics Private Limited, the security sheet with logo is changed accordingly.

AMENDMENT IS MUTUALLY AGREED UPON:

for TEST FACILITY

1. Mr. E. RAMESH
STUDY DIRECTOR
Date: 27.08.2005

2. HEAD, QUALITY ASSURANCE UNIT
Date: 27/08/2005

3. MANAGEMENT
Date: 27/8/05

for STUDY SPONSOR

1. Dr. EDGAR WEBER
MONITORING SCIENTIST
Date: 29.08.2005

Amendment No. 2 to Study plan No. SP-4091/04
052/8-CLSN/28-OR
Page No. 1/1

CONFIDENTIAL

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 115/140

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ANNEXURE 2. Concentration, Homogeneity and Stability Results

R&D Analytical Research Center (ARC) NON-GLP Analytical Report
Calcium Lignosulfonate
Rallis Research Centre Study No. 4091/04

Analytical Final Report on

The Analyses of the Test Item in Feed

Repeated Dose (28-Day) Oral Toxicity Study with Calcium Lignosulfonate in Wistar Rats

Test facility for Feed Analyses:	DSM Nutritional Products, R&D, Analytical Research Center (ARC), Wurmisweg 576, Bldg. 205 CH-4303 Kaiseraugst, Switzerland
Principal Investigator:	Dr. P. Hofmann, DSM Nutritional Products, R&D, Analytical Research Center (ARC) P.O. Box 3255 CH-4002 Basel, Switzerland
Analyst	Fr. B. Rossi, DSM Nutritional Products, R&D, Analytical Research Center (ARC) P.O. Box 3255 CH-4002 Basel, Switzerland
Rallis Study No:	4091/04
Study sponsor:	DSM Nutritional Products (monitoring scientist Dr. E. Weber), R&D Human Nutrition & Health, Wurmisweg 576 CH-4303 Kaiseraugst, Switzerland
No of Pages:	6
Signature/Date:	(Principal Investigator) 2.8.05

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 116/140

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ANNEXURE 2 contd.

R&D: Analytical Research Center (ARC) **NON-GLP** Analytical Report
Calcium Lignosulfonate
Rallis Research Centre Study No. 4091/04

Study Schedule	Study initiation date:	January 17, 2005
	Sample reception date at VFHA:	February 24, 2005
	Experimental starting date:	March 14, 2005
	Experimental completion date:	April 07, 2005
	End of calculations:	April 07, 2005
	Study completion date:	see date of principal investigator's signature of the report
Test item:	Calcium Lignosulfonate (Ultrazine FG-R®) (=Lignosulfonate)	
	Date of manufacture:	January 2004
	Date of expiry:	January 2006
	Purity:	approx. 85%
Sample material:	Feeds	
Storage conditions:	approx. -20°C at test facility, prior to the analyses 2 to 8°C.	
Theme No.:	6309	
Archive:	The study plan, copies of final report and all raw data of the analytical part of the study will be archived at DSM Nutritional Products, R&D, VFH.	
Analysis required:	Lignosulfonate Content, homogeneity and stability are monitored.	
Analytical Method:	**LIS-103** – a colorimetric method Lignosulfonate is extracted using water. Sodium nitrite solution is added to an acidified aliquot. Prior to the measurement of the extinction at 440 nm diluted ammonia solution is added.	

Approval of Results:

Dr. P. Hofmann
(Principal Investigator)

Date: 2.8.05

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ANNEXURE 2 contd.

Results

The results of the analyses are summarised in the following tables.

Table 1: **Monitoring of the Homogeneity**

Sample Identification	Sample name		Concentration found	Concentration declared	Recovery
ST_001049_000001	1_G1-M&F_top		used as blank		
ST_001049_000002	1_G1-M&F_top/mid		used as blank		
ST_001049_000003	1_G1-M&F_mid		used as blank		
ST_001049_000004	1_G1-M&F_mid/bottom		used as blank		
ST_001049_000005	1_G1-M&F_bottom		used as blank		
ST_001049_000006	1_G2-M_top		3.576		
ST_001049_000007	1_G2-M_top/mid		3.344		
ST_001049_000008	1_G2-M_mid		3.550		
ST_001049_000009	1_G2-M_mid/bottom		3.704		
ST_001049_000010	1_G2-M_bottom		3.601		
		MEAN	**3.55**	**3.259**	**109.1 %**
		StDEV	**0.13**		
		CV [%]	**3.7**		
ST_001049_000011	1_G2-F_top		4.116		
ST_001049_000012	1_G2-F_top/mid		3.447		
ST_001049_000013	1_G2-F_mid		3.781		
ST_001049_000014	1_G2-F_mid/bottom		3.627		
ST_001049_000015	1_G2-F_bottom		3.601		
		MEAN	**3.714**	**3.370**	**110.2 %**
		StDEV	**0.254**		
		CV [%]	**6.8**		
ST_001049_000016	1_G3-M_top		8.531		
ST_001049_000017	1_G3-M_top/mid		8.450		
ST_001049_000018	1_G3-M_mid		8.585		
ST_001049_000019	1_G3-M_mid/bottom		8.585		
ST_001049_000020	1_G3-M_bottom		8.774		
		MEAN	**8.585**	**10.029**	**85.6 %**
		StDEV	**0.1119**		
		CV [%]	**1.4**		
ST_001049_000021	1_G3-F_top		8.396		
ST_001049_000022	1_G3-F_top/mid		8.639		
ST_001049_000023	1_G3-F_mid		8.639		
ST_001049_000024	1_G3-F_mid/bottom		9.205		
ST_001049_000025	1_G3-F_bottom		8.855		
		MEAN	**8.747**	**9.735**	**89.8 %**
		StDEV	**0.303**		
		CV [%]	**3.5**		

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ANNEXURE 2 contd.

R&D Analytical Research Center (ARC) **NON-GLP** Analytical Report
Calcium Lignosulfonate
Rallis Research Centre Study No. 4091/04

Sample Identification	Sample name	Concentration found	Concentration declared	Recovery
ST_001049_000026	1_G4-M_top	24.646		
ST_001049_000027	1_G4-M_top/mid	24.132		
ST_001049_000028	1_G4-M_mid	24.441		
ST_001049_000029	1_G4-M_mid/bottom	24.955		
ST_001049_000030	1_G4-M_bottom	25.315		
	MEAN	**24.698**	**25.960**	**91.6 %**
	StDEV	**0.457**		
	CV [%]	**1.9**		
ST_001049_000031	1_G4-F_top	25.007		
ST_001049_000032	1_G4-F_top/mid	25.187		
ST_001049_000033	1_G4-F_mid	25.212		
ST_001049_000034	1_G4-F_mid/bottom	24.981		
ST_001049_000035	1_G4-F_bottom	24.929		
	MEAN	**25.063**	**25.868**	**96.9 %**
	StDEV	**0.128**		
	CV [%]	**0.5**		

mg/kg
CV = coefficient of variation

Table 2: **Determination of the Concentration**

Sample Identification	Sample name	Concentration found [1])	Concentration declared [1])	Recovery [%]
ST_001049_000040	1_G1-M&F_konz	bLD	0	-
ST_001049_000041	1_G2-M_konz	2.976	3.259	91.3
ST_001049_000048	2_G2-M_konz	3.210	4.065	79.0
ST_001049_000055	3_G2-M_konz	4.410	4.578	96.3
ST_001049_000062	4_G2-M_konz	5.352	5.052	105.9
			Mean Recovery	**93.1 %**
ST_001049_000042	1_G2-F_konz	3.197	3.370	94.9
ST_001049_000049	2_G2-F_konz	3.850	3.951	97.4
ST_001049_000056	3_G2-F_konz	4.083	4.362	93.2
ST_001049_000063	4_G2-F_konz	4.303	4.671	92.1
			Mean Recovery	**94.4 %**
ST_001049_000043	1_G3-M_konz	7.961	10.029	79.4
ST_001049_000050	2_G3-M_konz	9.847	11.729	84.0
ST_001049_000057	3_G3-M_konz	11.526	13.578	84.9
ST_001049_000064	4_G3-M_konz	12.992	14.985	86.7
			Mean Recovery	**83.7 %**

Page 4 of 6

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 119/140

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ANNEXURE 2 contd.

R&D. Analytical Research Center (ARC) **NON-GLP** Analytical Report
Calcium Lignosulfonate
Rallis Research Centre Study No. 4091/04

Sample Identification	Sample name	Concentration found [1)]	Concentration declared [1)]	Recovery [%]
[illegible]_000044	1_G3-F_konz	8.787	9.735	90.3
[illegible]_000051	2_G3-F_konz	10.593	12.084	87.7
[illegible]_000058	3_G3-F_konz	11.446	13.365	85.6
[illegible]_000065	4_G3-F_konz	11.926	14.424	82.7
			Mean Recovery	**86.6 %**
[illegible]_000045	1_G4-M_konz	25.778	26.960	95.6
[illegible]_000052	2_G4-M_konz	28.318	30.267	93.6
[illegible]_000059	3_G4-M_konz	32.370	34.803	93.0
[illegible]_000066	4_G4-M_konz	37.221	38.759	96.0
			Mean Recovery	**94.6 %**
[illegible]_000046	1_G4-F_konz	26.108	25.866	100.9
[illegible]_000053	2_G4-F_konz	28.398	31.662	89.7
[illegible]_000060	3_G4-F_konz	30.637	33.681	91.0
[illegible]_000067	4_G4-F_konz	36.154	36.132	100.1
			Mean Recovery	**95.4 %**

[1)] g/kg
[2)] BLD = below limit of determination

Table 3: **Monitoring of the Stability**

Sample Identification	Sample name	Concentration found [1)]	Initial Concentration [1)]	Recovery [%]
[illegible]_000036	1_G3-M_stab	9.145	7.961	**114.9**
[illegible]_000037	1_G3-F_stab	8.814	8.787	**100.3**
S1_001049_000038	1_G4-M_stab	26.962	25.778	**104.6**
S1_001049_000039	1_G4-F_stab	25.007	26.108	**95.8**

[1)] g/kg

Conclusions

The analytical part of the study consists of monitoring the content, the homogeneity and the stability of lignosulfonate in feed preparations used in the Study No. 4091/04 at Rallis, Bangalore, India.

Content (Table 2)

In the treatment group G1 the absence of added lignosulfonate can be assumed. In relation to the weak but unspecific colour reaction of the blank samples for the feeds of the treatment groups G2 (3 – 5 g/kg) and G4 (25 – 38 g/kg) reasonable recoveries of 94 to 110 % have been found; whereas for treatment group G3 in all analyses recoveries of only around 90 % and lower have been found.

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ANNEXURE 2 contd.

R&D. Analytical Research Center (ARC) **NON-GLP** Analytical Report
Calcium Lignosulfonate
Rallis Research Centre Study No. 4091/04

Homogeneity (Table 1)

The CVs of all homogeneity tests are below 7% with a clear tendency that the CVs decrease with the increase of the concentration of lignosulfonate in the feeds. This is according to the analytical theory that the lower the level the distribution of the analyte is less accurate and homogeneous. And versa the conclusion can be drawn that the analytical procedure is reliable.
The distribution of lignosulfonate in feed therefore can be considered to be homogeneous.

Stability (Table 3)

After 10 days at ambient temperature approx. the same concentrations are found as for the same tests on the concentration and homogeneity part of the analytical part of this study (Tables 1 and 2).
The stability of lignosulfonate in this type of feed can be confirmed.

Distribution list: Archive test facility, DSM Nutritional Products, VFH
Study sponsor, DSM Nutritional Products Ltd., VFH (1 copy)

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ANNEXURE 3. Analysis Report - Animal Diet Sample

RALLIS RESEARCH CENTRE
21 & 22, PEENYA INDUSTRIAL AREA, II PHASE
BANGALORE - 560 058

ANALYSIS REPORT - ANIMAL DIET SAMPLE

From: Residue/Analytical Department
RRC, Bangalore-560 058

To: Toxicology Department
RRC, Bangalore-560 058

Our Ref. No.: SS/TF/1432

Date: 30.11.2004

Sample Details: Name : Ssniff Rats/Mice (Powder) Feed Maintenance

Sampling Date: 05.11.2004

Batch No. : 4764439

Supplier : Ssniff Spezialdiaten GmbH, D-59494 Soest Germany

Manufacturer: Ssniff Spezialdiaten GmbH, D-59494 Soest Germany

ANALYSIS RESULTS
(Analysis on "as is basis")

Sl. No.	Parameter	(%)
1.	Moisture	13.6
2.	Crude protein (N x 6.25)	19.2
3.	Crude fat (Ether extract)	3.0
4.	Crude fibre	4.3
5.	Total ash	5.6
6.	Acid insoluble ash	0.5
7.	Nitrogen free extract	54.3
8.	Calcium (Ca)	0.99
9.	Phosphorus (P)	0.71

30/11/2004

Residue/Analytical Dept.,

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 122/140

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 4. Feed Contaminant Analysis Report for Ssniff Rats/Mice Diet - Maintenance Meal

Landwirtschaftliche Untersuchungs- und Forschungsanstalt
Institut für Tiergesundheit und Lebensmittelqualität GmbH

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D-24116 Kiel
Tel 0431 / 1228-0

eMail: zentrale@lufa-itl.de
Internet: www.lufa-itl.de
Fax. 0431 / 1228-498

LUFA - ITL Gutenbergstr 75-77, 24116 Kiel

RALLIS INDIA LIMITED AGROCHEMI CAL
RESEARCH STATION PLOT NOS
21 & 22, PHASE II
PEENYA INDUSTRIAL AREA
IND 0 BANGALORE-560 058

Date 30.11.2004
Kundennr. 1209576
Seite 1 von 3

PRÜFBERICHT

No. of Analysis 392241

Auftrag	209498	Ref.No.: 1870/04 - work order No. TX-254/04; dated 1-Oct-04, payed by Demand Draft No. 012301 dated 21.10.2004
Probeneingang	12.11.2004	
Probenahme	30.10.2004	
Kunden-Probenbezeichung	ssniff rat/mice diet - maintenance meal batch number: 4764439	
Sample packing	plastic bag	

Analysenparameter	Einheit	Ergebnis	Declaration	Matter	Method
Mycotoxins					
Aflatoxine B1	µg/kg	n.q.<1		OM	HPLC-VOLUFA Bd. III, 16.1.4
Aflatoxine B2	µg/kg	n.q.<1		OM	HPLC-VOLUFA Bd. III, 16.1.4
Aflatoxine G1	µg/kg	n.q.<1		OM	HPLC-VOLUFA Bd. III, 16.1.4
Aflatoxine G2	µg/kg	n.q.<1		OM	HPLC-VOLUFA Bd. III, 16.1.4
Polychlorinated Biphenyles (PCB)					
PCB 28	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
PCB 52	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
PCB 101	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
PCB 118	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
PCB 138	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
PCB 153	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
PCB 180	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
Organochlorous-Pesticides GC-Multiresidueanalysis					
Aldrine	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
Dieldrine	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
Endrine	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
alpha-Chlordane	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
gamma-Chlordane	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
oxy-Chlordane	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
alpha-Endosulfane	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
beta-Endosulfane	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
Endosulfansulfate	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
HCB (Hexachlorobenzene)	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
alpha-HCH	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
beta-HCH	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
delta-HCH	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
epsilon-HCH	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34
gamma-HCH (Lindan)	mg/kg	n.q.<0,005		OM	according to §35 LMBG L00.00-34

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ANNEXURE 4 contd. Feed Contaminant Analysis Report for Ssniff Rats/Mice Diet - Maintenance Meal

Landwirtschaftliche Untersuchungs- und Forschungsanstalt
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Date 30.11.2004
Kundennr. 1209576
Seite 2 von 3

No. of Analysis 392241

Analysenparameter	Einheit	Ergebnis		Declaration	Matter	Method
cis-Heptachlorepoxide	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
Heptachlor	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
trans-Heptachlorepoxide	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
o,p-DDD	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
o,p-DDE	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
o,p-DDT	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
p,p-DDD	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
p,p-DDE	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
p,p-DDT	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
Methoxychlor	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
Quintozene	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
Tecnazene	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
Tetradifon	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
Nitrofen	mg/kg	n.q.<0,005			OM	according to §35 LMBG L00.00-34
Organo-Phosphorous Pesticides GC-Multiresidueanalysis						
Bromophos (-ethyle)	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Bromophos (-methyle)	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Chlorfenvinphos	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Chlorpyriphos (-ethyle)	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Chlorpyriphos (-methyle)	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Chlorthione	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Diazinone	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Dichlorvos	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Dimethoate	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Ethione	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Fenitrothione	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Fenthione	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Malathione	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Mecarbame	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Methidathione	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Parathion (-ethyle)	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Parathion (-methyle)	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Pirimiphos (-ethyle)	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Pirimiphos (-methyle)	mg/kg	0,071			OM	according to §35 LMBG L00.00-34
Profenofos	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34
Sulfotep	mg/kg	n.q.<0,01			OM	according to §35 LMBG L00.00-34

n.b. = nicht bestimmbar / n.n. = nicht nachweisbar
Explanation: OM = original matter, DM = dry matter
LUFA-ITL Dr. Reutter, Tel. 0431/1228230

HRB 5796 AG Kiel
Geschäftsführer
Dr. Paul Wimmer

Commerzbank AG Kiel (210 400 10) 720 40 50
IBAN DE45 2104 0010 0720 4050 00
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Steuernummer: 132/118/70677
Finanzamt Landshut
Ust./VAT-IdNr.: DE813356511

Ein Institut der AGROLAB-Laborgruppe

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 124/140

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ANNEXURE 5. Analysis Report - Water Sample

RALLIS RESEARCH CENTRE
21 & 22, PEENYA INDUSTRIAL AREA, II PHASE
BANGALORE 560 058

ANALYSIS REPORT - WATER SAMPLE

From: Residue/Analytical Dept.
RRC, Bangalore-560 058

To: Toxicology Dept.
RRC, Bangalore-560 058

Our Ref. No: SS/TW/177

Date: 10.02.2005

Sample Details : Source of Collection : Outlet of the Aquaguard (At use point)
Room No. A-21

Date of Collection : 31.01.2005

ANALYSIS RESULTS

Sl. No.	Parameter	Content
1.	Colour	Colourless
2.	Odour	Odourless
3.	Turbidity	Clear
4.	pH	7.92
5.	Electrical Conductivity, dSm^{-1}	1.984
6.	Total solids, (ppm)	938
7.	Suspended solids, (ppm)	17
8.	Dissolved solids, (ppm)	921
9.	Dissolved oxygen (ppm)	6.4
10.	Biochemical Oxygen Demand 5 days at 20°C, (ppm)	3.8
11.	Chemical Oxygen Demand (ppm)	10.4

Sl. No.	Parameter	Content (ppm)
12.	Total hardness as $CaCO_3$	465
13.	Calcium as Ca^{2+}	73
14.	Magnesium as Mg^{2+}	69
15.	Chlorides as Cl^-	275
16.	Sulphates as SO_4^{2-}	67
17.	Carbonates as CO_3^{2-}	NIL
18.	Bicarbonates as HCO_3^-	393
19.	Sodium as Na	76
20.	Potassium as K	8

10/02/2005

Residue/Analytical Dept.,

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 125/140

CONFIDENTIAL

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ANNEXURE 6. Contaminant Analysis Report for Water Sample

15702 22.11.2004 Page 2 of 2

UCL

Wasseranalysis
Wasser W-15

Sample-No.: 04-15702-001
Date of receipt: 11.11.2004

Parameters	Unit	Result	Limit of detection	Method
Analysis of Original sample				
Bromoxynil-octylester	µg/l	< 0.08		DIN 38407 F2,UA
PCB				
PCB-028	µg/l	n.n.	0.02	DIN 38407 F2
PCB-052	µg/l	n.n.	0.02	DIN 38407 F2
PCB-101	µg/l	n.n.	0.02	DIN 38407 F2
PCB-138	µg/l	n.n.	0.02	DIN 38407 F2
PCB-153	µg/l	n.n.	0.02	DIN 38407 F2
PCB-180	µg/l	n.n.	0.02	DIN 38407 F2
Summe PCB 028-180	µg/l	n.n.	0.02	DIN 38407 F2
Sum of PCB (6)	µg/l	n.n.	0.1	DIN 38407 F2
Organochlorine Pesticides				
Hexachlorbenzene	µg/l	< 0.002		DIN 38407 F2,UA
Aldrin	µg/l	< 0.002		DIN 38407 F2,UA
o,p-DDD	µg/l	< 0.002		DIN 38407 F2,UA
p,p-DDD	µg/l	< 0.002		DIN 38407 F2,UA
o,p-DDE	µg/l	< 0.002		DIN 38407 F2,UA
p,p-DDE	µg/l	< 0.002		DIN 38407 F2,UA
o,p-DDT	µg/l	< 0.002		DIN 38407 F2,UA
p,p-DDT	µg/l	< 0.002		DIN 38407 F2,UA
Dieldrin	µg/l	< 0.002		DIN 38407 F2,UA
alpha-Endosulfan	µg/l	< 0.002		DIN 38407 F2,UA
beta-Endosulfan	µg/l	< 0.002		DIN 38407 F2,UA
Endrin	µg/l	< 0.002		DIN 38407 F2,UA
alpha-HCH	µg/l	< 0.002		DIN 38407 F2,UA
beta-HCH	µg/l	< 0.002		DIN 38407 F2,UA
gamma-HCH (Lindane)	µg/l	< 0.002		DIN 38407 F2,UA
delta-HCH	µg/l	< 0.002		DIN 38407 F2,UA
Heptachlor	µg/l	< 0.002		DIN 38407 F2,UA
Heptachlorepoxid	µg/l	< 0.002		DIN 38407 F2,UA
cis-Heptachlorepoxid	µg/l	< 0.002		DIN 38407 F2,UA
trans-Heptachlorepoxid	µg/l	< 0.002		DIN 38407 F2,UA
Methoxychlor	µg/l	< 0.002		DIN 38407 F2,UA
Quintozen	µg/l	< 0.002		DIN 38407 F2,UA

n.n. = kleiner Bestimmungsgrenze n.b. = nicht bestimmbar - = nicht bestimmt UA = Unterauftrag vergeben

Mit freundlichen Grüßen

UCL GmbH

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 126/140

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ANNEXURE 7. GLP Certificate – Germany

Bundesinstitut für Risikobewertung /
Federal Institute for Risk Assessment

BfR

GUTE LABORPRAXIS / GOOD LABORATORY PRACTICE

(gemäß / according to § 19b Abs.2 Nr.3 Chemikaliengesetz)

Eine GLP-Inspektion wurde durchgeführt in / A GLP inspection was carried

Prüfeinrichtung / Test facility

Advinus Therapeutics Private Limited
Peenya Industrial Area, Phase II, Plot Nos. 21&22, P.B. No. 5813
Bangalore – 560 058, INDIA

Prüfkategorien / Area of Expertise

- Prüfungen zur Bestimmung der physikalisch-chemischen Eigenschaften und Gehaltsbestimmungen / Physical-chemical testing
- Prüfungen zur Bestimmung der toxikologischen Eigenschaften / Toxicity studies
- Prüfungen zur Bestimmung der erbgutverändernden Eigenschaften (*in vitro, in vivo*) / Mutagenicity studies
- Ökotoxikologische Prüfungen zur Bestimmung der Auswirkungen auf aquatische und terrestrische Organismen / Environmental toxicity studies on aquatic and terrestrial organisms
- Prüfungen zum Verhalten im Boden im Wasser und in der Luft; Bioakkumulation / Studies on behaviour in soil, water and air; bioaccumulation
- Prüfungen zur Bestimmung von Rückständen / Residue studies
- Spezielle Wirksamkeits- sowie Sicherheitsprüfungen von Arzneimitteln / Impfstoffen / Particular potency as well as safety studies with drugs / vaccines

Datum der Inspektion / Date of inspection

February 16-22 , 2005

Auf der Grundlage des Inspektionsberichtes und der Besprechung über zu erfolgende Maßnahmen wird hiermit bestätigt, dass in dieser Prüfeinrichtung die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können. / Based on the inspection report and the discussion of follow up activities it can be confirmed, that the test facility is able to conduct the aforementioned studies in compliance with the Principles of GLP.

Eine Überprüfung dieser GLP-Bestätigung ist spätestens vier Jahre nach der o. g. Inspektion zu beantragen. Ohne diesen Antrag wird nach Ablauf der Frist die Prüfeinrichtung aus dem deutschen GLP-Überwachungsprogramm genommen und diese GLP-Bestätigung verliert ihre Gültigkeit. / Verification of this GLP Certificate has to be applied four years after the above mentioned inspection at the latest. Elapsing this term, the test facility will be taken out of the German GLP Monitoring Programme and this GLP Certificate becomes invalid.

August 18, 2005
Im Auftrag / For the Director

Dr. H.-W. Hembeck
GLP-Bundesstelle / GLP Federal Bureau

Bundesinstitut für Risikobewertung / Federal Institute for Risk Assessment
Thielallee 88-92
14195 Berlin - GERMANY

INSTITUT FÜR RISIKOBEWERTUNG · BUNDESINSTITUT

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 127/140

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ANNEXURE 8. GLP Certificate – The Netherlands

ENDORSEMENT OF COMPLIANCE

WITH THE OECD PRINCIPLES OF
GOOD LABORATORY PRACTICE

Pursuant to the Netherlands GLP Compliance Monitoring Programme and according to Directive 88/320/EEC the conformity with the OECD Principles of GLP was assessed on 24-28 March 2003 at

Rallis Research Centre
Rallis India Limited
Plot 21&22 Phase II Peenya Industrial Area, PO Box 5813
Bangalore - 560 058 INDIA

It is herewith confirmed that the afore-mentioned test facility is currently operating in compliance with the OECD Principles of Good Laboratory Practice in the following areas of expertise: physical-chemical testing, toxicity studies, mutagenicity studies, environmental studies on aquatic and terrestrial animals, and analytical and clinical chemistry.

NEDERLAND

The Hague, 26 May 2003

Dr Th. Helder
GLP Compliance Monitoring Department

Inspectorate for Health Protection and Veterinary Public Health
Ministry of Health, Welfare and Sport

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 128/140

CONFIDENTIAL

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 9. Historical Data - 30

HISTORICAL CONTROL DATA - 30

SUBCHRONIC (28 DAY) ORAL TOXICITY STUDY IN WISTAR RATS

30.5 : HAEMATOLOGICAL VALUES - MALES (CONTROL GROUP - G1)

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV fl	MCH pg	MCHC g/l	Plat g/l	P.T s	Neut %	Lymp %	Eosi %	Mono %	Baso %
3105/00	Mean	8.4	8.16	161	0.416	51.2	19.7	386	891	17.1	19.3	76	2.2	2.5	0
	SD	1.58	0.46	3.15	0.01	2.91	1.18	6.69	102.98	1.18	3.78	3.85	1.33	1.05	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
3266/01	Mean	@													
	SD														
	N														
3281/01	Mean	7.3	7.98	161	0.439	55	20.2	368	1043	13.1	16.8	79.5	2.3	1.3	0
	SD	1.83	0.14	2.99	0.015	1.59	0.49	8.67	106.75	0.7	7.03	7.29	1.03	2.34	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
3286/01	Mean	5.6	8.08	160	0.425	52.6	19.9	378	944	13.7	13.2	83.2	1.7	2	0
	SD	2.29	0.28	5.28	0.02	1.32	0.49	5.82	100.51	1.52	6.31	8.57	1.03	1.79	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
3309/01	Mean	8.8	7.97	158	0.46	51.0	19.8	389	1225	16.6	11.3	88	0.3	0.3	0
	SD	1.61	0.17	4.65	0.012	1.81	0.86	12.35	119.03	1.65	6.35	6.13	0.52	0.82	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
3632/03	Mean	@													
	SD														
	N														
3432/02	Mean	@													
	SD														
	N														
3691/03	Mean	6.3	7.47	157	0.401	53.7	20.9	390	1021	15	11.1	84.5	3	1.4	0
	SD	1.96	0.28	13.66	0.013	1.06	1.36	30.11	83.44	0.89	3.28	4.25	1.83	0.7	0
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4059/04	Mean	8.3	7.82	156	0.416	53.2	20	377	1104	17.3	11.2	85.5	2.2	1.2	0
	SD	2.56	0.4	3.39	0.021	1.56	0.66	11.22	101	1.27	6.79	6.66	1.47	0.98	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		7.3	7.87	159	0.424	52.9	20.2	382	1053	15	14	83	2	1	0
SD		2.00	0.31	7.82	0.015	1.74	0.97	17.42	99.03	1.21	5.55	6.13	1.35	1.34	0.0
1 SD: Range - Low		5.3	7.56	151	0.409	51.2	19.2	365	954	.14	8	77	1	0	0
1 SD: Range - High		9.3	8.18	167	0.439	54.6	21.2	399	1152	16	20	89	3	2	0
2 SD: Range - Low		3.3	7.25	143	0.394	49.4	18.3	347	855	13	3	71	-1	-2	0
2 SD: Range - High		11.3	8.49	175	0.454	56.4	22.1	417	1251	17	25	95	5	4	0
N: No. of rats		Note: The negative value of 1 SD & 2 SD should be considered as "zero"													
		@: Not evaluated													

HD-28-OR(OGR) 30.5/EDITION 3/2005
PAGE No. 1/4

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 129/140

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ANNEXURE 9 contd.

30.5 contd.: HAEMATOLOGICAL VALUES - FEMALES (CONTROL GROUP - G1)

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV fl	MCH pg	MCHC g/l	Plat g/l	P.T s	Neut %	Lymp %	Eosi %	Mono %	Baso %
	Mean	5.5	7.88	160	0.385	48.9	20.3	416	921	18.1	16.8	77.7	1.8	1.7	0
3105/00	SD	0.86	0.18	4.1	0.01	1.65	0.33	13.07	102.38	1.53	2.64	3.44	0.98	0.52	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	@													
3266/01	SD														
	N														
	Mean	7.7	7.56	158	0.403	53.3	21	393	917	12.7	17.5	81.2	0.8	0.5	0
3281/01	SD	1.65	0.38	4.71	0.015	1.2	0.58	8.67	127.44	0.36	13.74	12.7	0.98	1.22	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	5	7.73	156	0.405	52.4	20.2	386	927	13.4	14.5	81.5	1.8	2.2	0
3286/01	SD	2.04	0.26	3.76	0.01	1.84	0.55	14.67	147.74	0.31	4.59	3.94	1.17	0.98	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	8	7.64	156	0.371	48.6	20.4	420	1209	19.1	8.8	88	1.5	1.7	0
3309/01	SD	2.14	0.31	5.16	0.016	0.74	0.51	8.33	109.43	1.26	3.31	4.77	1.38	1.37	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	@													
3632/03	SD														
	N														
	Mean	@													
3432/02	SD														
	N														
	Mean	5.5	7.41	157	0.387	52.2	21.2	406	738	14.1	11.1	86.2	1.8	0.9	0
3691/03	SD	1.59	0.23	3.07	0.012	1.34	0.45	7.12	75.92	0.59	3.87	4.61	1.03	0.99	0
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Mean	3.9	7.01	152	0.372	53.1	21.7	408	1092	16.8	14	81.8	2.5	1.7	0
4059/04	SD	0.81	0.44	7.26	0.023	1.36	0.39	9.26	75	0.82	2.53	3.97	1.38	1.21	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		5.9	7.53	157	0.387	51.5	20.8	405	944	16	14	83	2	1	0
SD		1.60	0.3	4.69	0.015	1.39	0.47	10.2	106.08	0.9	6.2	6.25	1.15	1.07	0.0
1 SD: Range - Low		4.3	7.23	152	0.372	50.1	20.3	395	838	15	8	77	1	0	0
1 SD: Range - High		7.5	7.83	162	0.402	52.9	21.3	415	1050	17	20	89	3	2	0
2 SD: Range - Low		2.7	6.93	148	0.357	48.7	19.9	385	732	14	2	71	0	-1	0
2 SD: Range - High		9.1	8.13	166	0.417	54.3	21.7	425	1156	18	26	96	4	3	0

N: No. of rats

Note: The negative value of 1 SD & 2 SD should be considered as "zero"

@: Not evaluated

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ANNEXURE 9 contd.

30.5 contd.: HAEMATOLOGICAL VALUES - MALES (CONTROL RECOVERY GROUP - G1R)

Study No		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV fl	MCH pg	MCHC g/l	Plat g/l	P.T s	Neut %	Lymp %	Eosi %	Mono %	Baso %
3105/00	Mean	@													
	SD														
	N														
3265/01	Mean	@													
	SD														
	N														
3281/01	Mean	9	8.18	154	0.42	51.4	18.8	367	957	12.5	12.5	84.3	1.7	1.5	0
	SD	1.63	0.3	3.69	0.02	1.52	0.51	6.83	100.15	0.23	8.78	9.83	1.37	1.05	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
3286/01	Mean	6.8	8.71	162	0.439	50.5	18.6	369	993	16.1	11.2	85.7	2.3	0.8	0
	SD	2.48	0.47	4.93	0.01	1.87	0.52	7.66	69.05	0.7	4.96	6.35	1.97	0.41	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
3309/01	Mean	7.1	8.26	157	0.411	49.7	19	381	906	16.1	10.7	85.8	3	0.5	0
	SD	2.16	0.38	4.85	0.014	0.89	0.64	7.92	290.92	1.73	3.01	3.16	2.1	0.84	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
3632/03	Mean	@													
	SD														
	N														
3432/02	Mean	@													
	SD														
	N														
3691/03	Mean	@													
	SD														
	N														
4059/04	Mean	5.6	7.61	149	0.412	52.7	19.1	362	904	16.6	15.5	80.7	1.5	2.3	0
	SD	1.44	0.13	4.26	0.011	1.4	0.69	11.54	95.96	2.57	5.54	5.47	1.05	1.75	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		7.1	8.24	156	0.421	51.1	18.9	370	940	15	12	84	2	1	0
SD		2.10	0.34	4.46	0.014	1.47	0.60	8.68	164.8	1.59	5.95	6.71	1.68	1.12	0.0
1 SD: Range - Low		5.0	7.90	152	0.407	49.6	18.3	361	775	13	6	77	0	0	0
1 SD: Range - High		9.2	8.58	160	0.435	52.6	19.5	379	1105	17	18	91	4	2	0
2 SD: Range - Low		2.9	7.56	147	0.393	48.2	17.7	353	610	12	0	71	-1	-1	0
2 SD: Range - High		11.3	8.92	165	0.449	54.0	20.1	387	1270	18	24	97	5	3	0

N: No. of rats

Note: The negative value of 1 SD & 2 SD should be considered as "zero"

@: Not evaluated

HD-28-OR(OGR) 30.5/EDITION 3/2005
PAGE No. 3/4

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 131/140

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 9 contd.

30.5 contd.: HAEMATOLOGICAL VALUES - FEMALES (CONTROL RECOVERY GROUP - G1R)

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV fl	MCH pg	MCHC g/l	Plat g/l	P.T s	Neut %	Lymp %	Eosi %	Mono %	Baso %
	Mean	@													
3105/00	SD														
	N														
	Mean														
3266/01	SD	@													
	N														
	Mean	5.3	7.85	153	0.399	50.8	19.5	384	959	12.8	11.2	86.3	1.3	1.2	0
3281/01	SD	2.12	0.24	5.33	0.02	1.77	0.62	6.28	87.42	0.51	3.43	4.59	1.03	1.17	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	4.8	8.14	158	0.421	51.8	19.4	375	1039	16.4	7	90.8	1.2	1	0
3286/01	SD	1.74	0.3	3.27	0.01	1.54	0.77	8.78	72.96	1.66	2.97	2.93	0.98	0.89	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	6.1	7.75	150	0.386	49.8	19.3	388	886	14.6	7.7	91.5	0.5	0.3	0
3309/01	SD	1.84	0.14	4.07	0.006	0.53	0.58	8.91	43.17	0.53	3.67	3.51	0.84	0.52	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean														
3632/03	SD	@													
	N														
	Mean														
3432/02	SD	@													
	N														
	Mean														
3691/03	SD	@													
	N														
	Mean	3	7.33	154	0.384	52.5	21	400	836	16.3	14.2	81.7	2	2.2	0
4059/04	SD	0.94	0.39	5.79	0.02	1.18	0.68	8.26	73.35	0.1	3.25	2.5	1.1	1.17	0
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean		4.8	7.77	154	0.398	51.2	19.8	387	930	15	10	88	1	1	0
SD		1.72	0.28	4.72	0.015	1.34	0.67	8.13	71.08	0.91	3.34	3.47	0.99	0.97	0.0
1 SD: Range - Low		3.1	7.49	149	0.383	49.9	19.1	379	859	14	7	85	0	0	0
1 SD: Range - High		6.5	8.05	159	0.413	52.5	20.5	395	1001	16	13	91	2	2	0
2 SD: Range - Low		1.4	7.21	145	0.368	48.5	18.5	371	788	13	3	81	-1	-1	0
2 SD: Range - High		8.2	8.33	163	0.428	53.9	21.1	403	1072	17	17	95	3	3	0

N: No. of rats

Note: The negative value of 1 SD & 2 SD should be considered as "zero"

@: Not evaluated

HD-28-OR(OGR) 30.5/EDITION 3/2005
PAGE No. 4/4

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 132/140

CONFIDENTIAL

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HISTORICAL CONTROL DATA - 30

SUBCHRONIC (28 DAY) ORAL TOXICITY STUDY IN WISTAR RATS

ANNEXURE 9 contd.

30.6 : CLINICAL CHEMISTRY VALUES - MALES (CONTROL GROUP - G1)

Study No.		Glu mmol/l	BUN mmol/l	Urea mmol/l	Tot.Pro g/l	AST U/l	ALT U/l	Alp U/l	GGT U/l	Tot.Bil µmol/l	D.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Tri.Gly mmol/l	Na mEq/l	K mEq/l
	Mean	9.26	3.05	6.54	62.1	65	35		12	3.86		48	34.8	2.52		2.03		142.5	4.40
3105/00	SD	1.22	0.43	0.93	2.79	15.14	4.18	@	3.87	0.77	@	6.37	1.80	0.17	@	0.23	@	1.47	0.31
	N	6	6	6	6	6	6		6	6		6	6	6		6		6	6
	Mean																		
3266/01	SD	@																	
	N																		
	Mean	6.98	2.17	4.64	59.2	76	23		0			47	33.93	3.01		1.98		146.5	3.76
3281/01	SD	0.81	0.31	0.67	1.35	14.77	4.27	@	0.00	@	@	1.72	0.98	0.10	@	0.26	@	1.62	0.19
	N	6	6	6	6	6	6		6			6	6	6		6		6	6
	Mean	8.46	2.51	5.38	65.7	60	37	128	3			47	34.53	2.23		2.42		142.0	4.20
3286/01	SD	0.53	0.21	0.46	1.59	9.72	2.88	8.21	1.37	@	@	7.79	1.34	0.27	@	0.34	@	0.95	0.24
	N	6	6	6	6	6	6	6	6			6	6	6		6		6	6
	Mean	8.71	2.90	6.21	62.4	121	38	131	4	5.18		84	31.5	2.39	2.94	2.24	@	137.1	4.25
3309/01	SD	1.40	0.30	0.64	3.15	45.97	23.91	23.74	2.86	2.49	@	2.83	1.91	0.17	0.34	0.32		2.61	0.31
	N	6	6	6	6	6	6	6	6	6		6	6	6	6	6		6	6
	Mean																		
3232/03	SD	@																	
	N																		
	Mean																		
3432/02	SD	@																	
	N																		
	Mean	8.11	2.92	6.25	60.3	75	34	217	0	5.01	2.61	54	31.6			1.93	0.6	143.0	4.07
3691/03	SD	0.67	0.49	1.04	1.89	6.66	3.27	14.64	0.52	0.75	0.26	2.22	1.01	@	@	0.21	0.14	1.10	0.22
	N	10	10	10	10	10	10	10	10	10	10	10	10			10	10	10	10
	Mean	8.37	2.79	5.97	65.6	86	68		1	4.84		47	34.4	2.21		2.11		143.9	4.21
4059/04	SD	0.72	0.27	0.57	3.16	9.09	11.20	@	0.82	0.70	@	3.03	2.38	0.11	@	0.40	@	2.67	0.27
	N	6	6	6	6	6	6	6	6	6		6	6	6		6		6	6
Mean		8.29	2.74	5.87	62.3	80	39	169	3	4.76	2.61	54	33.3	2.47	2.94	2.10	0.6	142.6	4.14
SD		0.92	0.37	0.79	2.38	20.36	10.57	16.36	1.96	1.31	0.26	4.38	1.59	0.17	0.34	0.29	0.14	1.79	0.26
1 SD: Range - Low		7.37	2.37	5.08	59.9	60	28	153	1	3.45	2.35	50	31.7	2.30	2.60	1.81	0.5	140.8	3.88
1 SD: Range - High		9.21	3.11	6.66	64.7	100	50	185	5	6.07	2.87	58	34.9	2.64	3.28	2.39	0.7	144.4	4.40
2 SD: Range - Low		6.45	2.00	4.29	57.5	39	18	136	-1	2.14	2.09	45	30.1	2.13	2.26	1.52	0.3	139.0	3.62
2 SD: Range - High		10.13	3.48	7.45	67.1	121	60	202	7	7.38	3.13	63	36.5	2.81	3.62	2.68	0.9	146.2	4.66
N: No. of rats		Note: The negative value of 1 SD & 2 SD should be considered as "zero".																	

HD-28-OR(OGR) 30.6/EDITION 3/2005
PAGE No. 1/4

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 133/140

ADVINUS

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 9 contd.

30.6 contd.: CLINICAL CHEMISTRY VALUES - FEMALES (CONTROL GROUP - G1)

Study No.		Glu mmol/l	BUN mmol/l	Urea mmol/l	Tot.Pro g/l	AST U/l	ALT U/l	Alp U/l	GGT U/l	Tot.Bil µmol/l	D.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Tri.Gly mmol/l	Na mEq/l	K mEq/l
	Mean	8.48	2.47	5.28	58.4	76	31	8	3.49			50	34.43	2.22		1.86		141.7	3.70
3105/00	SD	0.49	0.47	1.01	1.58	12.31	5.38	@ 1.26	0.51	@	@	5.33	0.84	0.23	@	0.18	@	1.64	0.44
	N	6	6	6	6	6	6	6	6			6	6	6		6		6	6
	Mean																		
3266/01	SD	@																	
	N																		
	Mean	6.29	2.41	5.15	59.5	95	22	0				52	36.08	2.33		2.26		147.3	4.17
3281/01	SD	1.02	0.24	0.51	3.44	18.96	4.63	@ 0.41	@	@	@	3.83	2.06	0.22	@	0.25	@	1.40	0.76
	N	6	6	6	6	6	6	6				6	6	6		6		6	6
	Mean	7.64	2.78	5.96	64.7	69	37	99 2				55	37.42	2.02		1.75		142	3.70
3286/01	SD	0.73	0.41	0.87	1.50	14.29	7.20	7.89 1.86	@	@	@	5.53	1.31	0.20	@	0.31	@	1.23	0.26
	N	6	6	6	6	6	6	6 6				6	6	6		6		6	6
	Mean	6.23	2.67	5.72	62.9	125	27	95 4	4.48			96	34.9	1.92	2.85	2.08		139.5	3.89
3309/01	SD	0.59	0.25	0.53	2.17	29.49	9.10	9.12 2.53	1.36	@	@	7.40	1.70	0.23	0.41	0.30	@	1.06	0.25
	N	6	6	6	6	6	6	6 6	6			6	6	6	6	6		6	6
	Mean																		
3232/03	SD	@																	
	N																		
	Mean																		
3432/02	SD	@																	
	N																		
	Mean	7.86	2.7	5.77	61.3	75	32	170 2	5.54	3.17	55	31.6				1.87	0.76	142.3	3.8
3691/03	SD	0.85	0.34	0.73	1.79	14.98	4.90	15.38 1.03	0.78	0.61	2.06	0.75	@	@	@	0.21	0.19	1.69	0.25
	N	10	10	10	10	10	10	10 10	10	10	10	10				10	10	10	10
	Mean	7.13	3.25	6.96	62.2	74	34	2	4.71			49	34.5	1.93	@	2.09		142.1	3.97
4059/04	SD	1.07	0.38	0.82	1.21	12.42	2.48	@ 1.10	0.89	@	@	5.21	0.77	0.29		0.38	@	2.20	0.74
	N	6	6	6	6	6	6	6 6	6			6	6	6		6		6	6
Mean		7.33	2.71	5.80	61.5	85	31	130 3	4.70	3.17	59	34.5	2.08	2.85		1.97	0.8	142.5	3.86
SD		0.82	0.36	0.76	2.05	17.75	5.87	12.26 1.47	0.91	0.61	4.90	1.28	0.24	0.41		0.27	0.19	1.59	0.48
1 SD: Range - Low		6.51	2.35	5.04	59.5	67	25	118 2	3.79	2.56	54	33.2	1.84	2.44		1.70	0.6	140.8	3.38
1 SD: Range - High		8.15	3.07	6.56	63.6	103	37	142 4	5.61	3.78	64	35.8	2.32	3.26		2.24	1.0	144.1	4.34
2 SD: Range - Low		5.69	1.99	4.28	57.4	50	19	105 0	2.88	1.95	49	31.9	1.60	2.03		1.43	0.4	139.3	2.90
2 SD: Range - High		8.97	3.43	7.32	65.6	121	43	155 6	6.52	4.39	69	37.1	2.56	3.67		2.51	1.2	145.7	4.82
N: No. of rats																			

21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 9 contd.

30.6 contd.: CLINICAL CHEMISTRY VALUES - MALES (CONTROL RECOVERY GROUP - G1R)

Study No.		Glu mmol/l	BUN mmol/l	Urea mmol/l	Tot.Pro g/l	AST U/l	ALT U/l	Alp U/l	GGT U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pl mmol/l	Chol mmol/l	Na mEq/l	K mEq/l
3105/00	Mean	@														
	SD															
	N															
3266/01	Mean	@														
	SD															
	N															
3281/01	Mean	8.25	3.11	6.65	63.7	67	33	@	6		51	34.35	2.41	2.22	144.2	4.03
	SD	0.99	0.41	0.88	0.99	20.40	6.89	@	4.02	@	11.34	1.57	0.16	0.45	0.85	0.31
	N	6	6	6	6	6	6		6		6	6	6	6	6	6
3286/01	Mean	8.8	2.51	5.38	60.6	61	44	108	0	@	47	35.82	2.1	2.18	140	4.00
	SD	0.69	0.37	0.78	1.43	9.58	4.79	10.65	0.00	@	11.27	1.84	0.18	0.25	1.82	0.42
	N	6	6	6	6	6	6	6	6		6	6	6	6	6	6
3309/01	Mean	@														
	SD															
	N															
3232/03	Mean	@														
	SD															
	N															
3432/02	Mean	@														
	SD															
	N															
3691/03	Mean	@														
	SD															
	N															
4059/04	Mean	7.19	2.64	5.64	61.7	59	36	@	0	4.68	50	33.6	1.92	2.23	143.8	4.13
	SD	0.94	0.36	0.77	2.54	4.23	3.88		0.52	1.50	3.31	1.36	0.15	0.49	2.62	0.29
	N	6	6	6	6	6	6		6	6	6	6	6	6	8	6
Mean		8.08	2.75	5.89	62.0	62	38	108	2	4.68	49	34.6	2.14	2.21	142.7	4.05
SD		0.88	0.38	0.81	1.78	13.24	5.34	10.65	2.34	1.5	9.43	1.60	0.16	0.41	1.91	0.34
1 SD: Range - Low		7.20	2.37	5.08	60.2	49	33	97	0	3.18	40	33.0	1.98	1.80	140.8	3.71
1 SD: Range - High		8.96	3.13	6.70	63.8	75	43	119	4	6.18	58	36.2	2.30	2.62	144.6	4.39
2 SD: Range - Low		6.32	1.99	4.27	58.4	36	27	87	-3	1.68	30	31.4	1.82	1.39	138.9	3.37
2 SD: Range - High		9.84	3.51	7.51	65.6	88	49	129	7	7.68	68	37.8	2.46	3.03	146.5	4.73
N: No. of rats																

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 9 contd.

30.6 contd.: CLINICAL CHEMISTRY VALUES - FEMALES (CONTROL RECOVERY GROUP - G1R)

Study No.		Glu mmol/l	BUN mmol/l	Urea mmol/l	Tot.Pro g/l	AST U/l	ALT U/l	Alp U/l	GGT U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l		Pl mmol/l	Chol mmol/l	Na mEq/l	K mEq/l
	Mean																
3105/00	SD	@															
	N																
	Mean																
3266/01	SD	@															
	N																
	Mean	7.81	3.14	6.72	62.9	59	22	@	8	@	76	37.08		1.93	1.98	144.2	4.12
3281/01	SD	0.97	0.81	1.74	1.74	13.66	5.39	@	9.71	@	5.82	1.29		0.18	0.19	1.38	0.23
	N	6	6	6	6	6	6		6		6	6		6	6	6	6
	Mean	8.19	2.77	5.93	61	77	39	79	0	@	45	37.98		1.86	2.08	142	3.90
3286/01	SD	0.74	0.39	0.83	2.49	12.58	9.74	11.43	0.41	@	9.95	1.84		0.07	0.23	1.38	0.42
	N	6	6	6	6	6	6	6	6		6	6		6	6	6	6
	Mean																
3309/01	SD	@															
	N																
	Mean																
3232/03	SD	@															
	N																
	Mean																
3432/02	SD	@															
	N																
	Mean																
3691/03	SD	@															
	N																
	Mean	5	2.83	6.06	61.4	92	29	@	1	6.42	53	33		1.67	1.71	142.9	3.91
4059/04	SD	0.39	0.56	1.19	1.46	49.29	2.50		0.41	1.94	4.12	1.15		0.25	0.18	2.08	0.21
	N	6	6	6	6	6	6		6	6	6	6		6	6	6	6
Mean		7.00	2.91	6.24	61.8	76	30	79	3	6.42	58	36.0		1.82	1.92	143.0	3.98
SD		0.74	0.61	1.31	1.95	30.41	6.59	11.43	5.62	1.94	7.07	1.46		0.18	0.20	1.65	0.30
1 SD: Range - Low		6.26	2.30	4.93	59.9	46	23	68	-3	4.48	51	34.5		1.64	1.72	141.4	3.68
1 SD: Range - High		7.74	3.52	7.55	63.8	106	37	90	9	8.36	65	37.5		2.00	2.12	144.7	4.28
2 SD: Range - Low		5.52	1.69	3.62	57.9	15	17	56	-8	2.54	44	33.1		1.46	1.52	139.7	3.36
2 SD: Range - High		8.48	4.13	8.86	65.7	137	43	102	14	10.30	72	38.9		2.18	2.32	146.3	4.58
N: No. of rats																	

HD-28-OR(OGR) 30.6/EDITION 3/2005
PAGE No. 4/4
TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 136/140

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21 & 22, Peenya, Phase II, Bangalore 560 058, India

ANNEXURE 9 contd.

HISTORICAL CONTROL DATA - 30

SUBCHRONIC (28 DAY) ORAL TOXICITY STUDY IN WISTAR RATS

30.7: FASTING BODY WEIGHTS, ORGAN WEIGHTS AND ORGAN WEIGHT RATIOS - MALES (CONTROL GROUP - G1)

Study No.		Fasting Bwt (g)	Organ weights (g) Adrenals	Testes	Kidneys	Liver	Lungs	Heart	Brain	Epididym	Thymus	Spleen	Organ weight ratios (%) Adrenals	Testes	Kidneys	Liver	Lungs	Heart	Brain	Epididym	Thymus	Spleen
	Mean	355	0.061	3.658	2.580	12.068		1.268	1.958	1.155	0.654	0.682	0.017	1.031	0.727	3.402		0.358	0.553	0.326	0.184	0.193
3105/00	SD	15.26	0.005	0.325	0.244	0.899	@	0.095	0.121	0.106	0.096	0.064	0.002	0.084	0.055	0.219	@	0.032	0.043	0.025	0.026	0.019
	N	6	6	6	6	6		6	6	6	6	6	6	6	6	6		6	6	6	6	6
	Mean	322	0.055	3.354	2.248	10.510		1.177	1.914	1.101	0.609	0.634	0.017	1.044	0.698	3.256		0.366	0.595	0.342	0.188	0.197
3266/01	SD	15.69	0.007	0.203	0.161	1.299	@	0.104	0.082	0.111	0.113	0.047	0.002	0.090	0.041	0.308	@	0.042	0.035	0.038	0.027	0.016
	N	6	6	6	6	6		6	6	6	6	6	6	6	6	6		6	6	6	6	6
	Mean	304	0.061	3.386	2.127	9.590	1.872	1.060	1.924	0.951	0.548	0.608	0.020	1.121	0.700	3.153	0.618	0.348	0.636	0.314	0.182	0.200
3281/01	SD	21.52	0.006	0.382	0.186	0.956	0.122	0.134	0.047	0.105	0.089	0.084	0.002	0.160	0.038	0.143	0.051	0.031	0.046	0.039	0.037	0.026
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	331	0.053	3.398	2.382	11.461	1.942	1.132	1.904	1.136	0.615	0.737	0.016	1.032	0.713	3.456	0.590	0.343	0.577	0.344	0.185	0.224
3286/01	SD	18.10	0.006	0.537	0.233	1.513	0.162	0.082	0.039	0.152	0.157	0.226	0.002	0.161	0.036	0.299	0.068	0.030	0.032	0.048	0.037	0.070
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	328	0.055	3.538	2.341	11.093		1.103	1.868	1.095	0.534	0.621	0.017	1.082	0.715	3.375		0.337	0.572	0.336	0.162	0.191
3309/01	SD	25.87	0.007	0.244	0.191	1.332	@	0.069	0.122	0.055	0.105	0.035	0.002	0.079	0.044	0.201	@	0.009	0.056	0.032	0.024	0.018
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	296	0.046	3.230	2.102	9.820		1.065	1.913	0.905	0.538	0.557	0.016	1.097	0.712	3.322		0.361	0.648	0.307	0.181	0.188
3632/03	SD	15.99	0.004	0.304	0.098	0.555	@	0.047	0.067	0.078	0.090	0.055	0.001	0.134	0.022	0.113	@	0.019	0.023	0.035	0.024	0.013
	N	6	6	6	6	6		6	6	6	6	6	6	6	6	6		6	6	6	6	6
	Mean	261	0.052	2.970	2.151	9.762		1.058	1.098	0.678	0.779	0.615	0.020	1.144	0.823	3.741		0.405	0.734	0.262	0.297	0.235
3432/02	SD	18.62	0.005	0.177	0.235	0.991	@	0.101	0.082	0.061	0.144	0.102	0.002	0.110	0.040	0.190	@	0.012	0.044	0.035	0.041	0.027
	N	6	6	6	6	6		6	6	6	6	6	6	6	6	6		6	6	6	6	6
	Mean	316	0.053	3.265	2.307	9.804		1.119	1.856	1.122	0.574	0.616	0.017	1.042	0.730	3.128		0.356	0.623	0.358	0.182	0.195
3691/03	SD	27.20	0.004	0.402	0.252	1.311	@	0.081	0.051	0.100	0.080	0.079	0.001	0.162	0.025	0.196	@	0.028	0.042	0.043	0.019	0.019
	N	10	10	10	10	10		10	10	10	10	10	10	10	10	10		10	10	10	10	10
	Mean	302	0.053	3.358	2.231	9.604		1.044	1.878	1.078	0.522	0.569	0.018	1.113	0.738	3.178		0.346	0.622	0.358	0.172	0.188
4059/04	SD	12.63	0.007	0.182	0.107	0.542	@	0.057	0.069	0.049	0.121	0.054	0.003	0.076	0.008	0.121	@	0.016	0.028	0.027	0.035	0.016
	N	6	6	6	6	6		6	6	6	6	6	6	6	6	6		6	6	6	6	6
Mean		313	0.054	3.345	2.275	10.388	1.907	1.114	1.933	1.031	0.595	0.626	0.018	1.076	0.729	3.320	0.604	0.356	0.618	0.330	0.192	0.201
SD		20.29	0.010	0.330	0.200	1.110	0.140	0.090	0.080	0.100	0.110	0.100	0.000	0.130	0.040	0.210	0.060	0.030	0.040	0.040	0.030	0.030
1 SD: Range - Low		293	0.044	3.015	2.075	9.278	1.767	1.024	1.753	0.931	0.485	0.526	0.018	0.946	0.689	3.110	0.544	0.328	0.578	0.290	0.162	0.171
1 SD: Range - High		333	0.064	3.675	2.475	11.498	2.047	1.204	1.913	1.131	0.705	0.726	0.018	1.206	0.769	3.530	0.664	0.388	0.658	0.370	0.222	0.231
2 SD: Range - Low		272	0.034	2.685	1.875	8.168	1.627	0.934	1.673	0.831	0.375	0.426	0.018	0.815	0.649	2.900	0.484	0.298	0.538	0.250	0.132	0.141
2 SD: Range - High		354	0.074	4.005	2.675	12.608	2.187	1.294	1.993	1.231	0.815	0.826	0.018	1.336	0.809	3.740	0.724	0.418	0.698	0.410	0.252	0.261

N: No. of rats

@: Not evaluated

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ANNEXURE 9 contd.

30.7 contd.: FASTING BODY WEIGHTS, ORGAN WEIGHTS AND ORGAN WEIGHT RATIOS - FEMALES (CONTROL GROUP - G1)

Study No.		Fasting	Organ weights (g)										Organ weight ratios (%)									
		Bwt (g)	Adrenals	Ovaries	Kidneys	Liver	Lungs	Heart	Brain	Thymus	Spleen	Uterus	Adrenals	Ovaries	Kidneys	Liver	Lungs	Heart	Brain	Thymus	Spleen	Uterus
	Mean	194	0.062		1.420	6.175		0.806	1.820	0.484	0.458		0.032		0.733	3.179		0.415	0.940	0.248	0.235	
3105/00	SD	11.77	0.008	@	0.051	0.534	@	0.062	0.042	0.086	0.059	@	0.005	@	0.036	0.168	@	0.025	0.060	0.037	0.017	@
	N	6	6		6	6		6	6	6	6		6		6	6		6	6	6	6	
	Mean	192	0.064		1.451	5.925		0.791	1.756	0.435	0.456		0.034	0.070	0.758	3.092		0.414	0.920	0.227	0.238	
3256/01	SD	9.67	0.007	@	0.097	0.444	@	0.039	0.069	0.086	0.045	@	0.003	0.012	0.044	0.122	@	0.027	0.066	0.045	0.021	@
	N	6	6		6	6		6	6	6	6		6	6	6	6		6	6	6	6	
	Mean	182	0.065		1.346	5.808	1.356	0.736	1.732	0.488	0.511	0.627	0.036	0.067	0.741	3.192	0.746	0.407	0.959	0.268	0.267	0.347
3281/01	SD	18.04	0.013		0.154	0.844	0.191	0.056	0.089	0.128	0.218	0.215	0.006	0.011	0.045	0.246	0.075	0.033	0.076	0.061	0.144	0.118
	N	6	6		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	193	0.069		1.440	6.081	1.444	0.749	1.794	0.392	0.500	0.595	0.036	0.067	0.746	3.145	0.749	0.388	0.932	0.204	0.257	0.308
3266/01	SD	13.65	0.011		0.084	0.646	0.065	0.048	0.081	0.055	0.129	0.145	0.005	0.009	0.038	0.222	0.048	0.019	0.085	0.035	0.053	0.073
	N	6	6		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	201	0.061		1.434	5.972		0.770	1.837	0.481	0.475		0.030	0.072	0.714	2.974		0.384	0.918	0.239	0.236	
3309/01	SD	12.86	0.005		0.101	0.446	@	0.052	0.056	0.096	0.070	@	0.003	0.010	0.024	0.099	@	0.032	0.057	0.037	0.024	@
	N	6	6		6	6		6	6	6	6		6	6	6	6		6	6	6	6	
	Mean	182	0.057		1.331	6.147		0.757	1.755	0.418	0.428		0.031	0.057	0.730	3.370		0.416	0.964	0.229	0.235	
3632/03	SD	8.29	0.006		0.090	0.622	@	0.039	0.088	0.073	0.050	@	0.002	0.005	0.034	0.267	@	0.016	0.049	0.035	0.030	@
	N	6	6		6	6		6	6	5	6		6	6	6	6		6	6	6	6	
	Mean	166	0.055		1.286	5.918		0.751	1.727	0.508	0.411		0.033	0.063	0.773	3.548		0.453	1.042	0.306	0.248	
3432/02	SD	13.54	0.008		0.146	0.901	@	0.057	0.084	0.067	0.069	@	0.004	0.008	0.053	0.323	@	0.034	0.066	0.032	0.039	@
	N	6	6		6	6		6	6	6	6		6	6	6	6		6	6	6	6	
	Mean	187	0.062		1.356	5.790		0.731	1.777	0.431	0.427		0.033	0.063	0.725	3.099		0.394	0.959	0.230	0.228	
3691/03	SD	22.90	0.008		0.183	0.712	@	0.069	0.061	0.073	0.074	@	0.004	0.007	0.056	0.141	@	0.038	0.060	0.026	0.026	@
	N	10	10		10	10		10	10	10	10		10	10	10	10		10	10	10	10	
	Mean	194	0.068		1.453	5.705		0.767	1.851	0.405	0.438		0.035		0.748	2.934		0.395	0.956	0.210	0.225	
4059/04	SD	13.66	0.009	@	0.147	0.635	@	0.086	0.070	0.066	0.067	@	0.003	@	0.048	0.153	@	0.029	0.035	0.048	0.020	@
	N	6	6		6	6		6	6	6	6		6		6	6		6	6	6	6	
Mean		188	0.063	0.121	1.398	5.936	1.400	0.760	1.783	0.446	0.454	0.611	0.033	0.065	0.740	3.165	0.748	0.406	0.955	0.239	0.242	0.328
SD		15.29	0.010	0.010	0.130	0.660	0.140	0.060	0.080	0.080	0.100	0.180	0.000	0.010	0.040	0.200	0.060	0.030	0.070	0.040	0.050	0.100
1 SD: Range - Low		173	0.053	0.111	1.258	5.276	1.260	0.700	1.703	0.368	0.354	0.431	0.033	0.055	0.700	2.965	0.688	0.376	0.885	0.199	0.192	0.228
1 SD: Range - High		203	0.073	0.131	1.518	6.596	1.540	0.820	1.863	0.528	0.554	0.791	0.033	0.075	0.780	3.365	0.808	0.436	1.025	0.279	0.292	0.428
2 SD: Range - Low		157	0.043	0.101	1.128	4.616	1.120	0.640	1.623	0.288	0.254	0.251	0.033	0.045	0.660	2.765	0.628	0.346	0.815	0.159	0.142	0.128
2 SD: Range - High		219	0.083	0.141	1.648	7.256	1.680	0.880	1.943	0.608	0.654	0.971	0.033	0.085	0.820	3.565	0.868	0.496	1.095	0.319	0.342	0.528

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HD-28-OR(OGR) 30.7/EDITION 3/2005
PAGE No. 2/4

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 138/140

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ANNEXURE 9 contd. 30.7 contd.: FASTING BODY WEIGHTS, ORGAN WEIGHTS AND ORGAN WEIGHT RATIOS - MALES (CONTROL RECOVER GROUP - G1R)

Study No.		Fasting Bwt (g)	Organ weights (g)											Organ weight ratios (%)								
			Adrenals	Testes	Kidneys	Liver	Lungs	Heart	Brain	Epididym	Thymus	Spleen	Adrenals	Testes	Kidneys	Liver	Lungs	Heart	Brain	Epididym	Thymus	Spleen
310500	Mean	@																				
	SD																					
	N																					
	Mean																					
326501	SD	@																				
	N																					
	Mean	361	0.056	3.688	2.439	11.543	2.201	1.165	1.949	1.400	0.538	0.684	0.016	1.025	0.675	3.220	0.610	0.323	0.541	0.387	0.149	0.190
328101	SD	21.02	0.004	0.140	0.282	1.103	0.254	0.061	0.059	0.153	0.076	0.074	0.001	0.078	0.055	0.136	0.067	0.022	0.035	0.026	0.019	0.019
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	371	0.056	3.573	2.423	11.531	2.064	1.233	1.995	1.305	0.568	0.656	0.016	0.971	0.653	3.093	0.557	0.333	0.542	0.357	0.151	0.177
328501	SD	42.85	0.004	0.201	0.268	2.050	0.307	0.138	0.072	0.066	0.158	0.062	0.001	0.099	0.005	0.274	0.065	0.020	0.048	0.051	0.030	0.011
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	368	0.052	3.430	2.372	11.881	@	1.210	1.967	1.291	0.553	0.636	0.014	0.933	0.645	3.221	@	0.329	0.535	0.351	0.151	0.173
330901	SD	18.48	0.007	0.076	0.138	1.329		0.056	0.036	0.078	0.077	0.037	0.002	0.051	0.039	0.263		0.009	0.018	0.026	0.025	0.013
	N	6	6	6	6	6		6	6	6	6	6	6	6	6	6		6	6	6	6	6
	Mean																					
363203	SD	@																				
	N																					
	Mean																					
343202	SD	@																				
	N																					
	Mean																					
369103	SD	@																				
	N																					
	Mean	330	0.046	3.675	2.268	9.871		1.163	1.946	1.343	0.602	0.652	0.014	1.120	0.690	2.987	@	0.353	0.593	0.409	0.182	0.196
405904	SD	23.41	0.004	0.233	0.109	1.032	@	0.071	0.085	0.116	0.078	0.141	0.001	0.126	0.054	0.103		0.013	0.038	0.043	0.019	0.029
	N	6	6	6	6	6		6	6	6	6	6	6	6	6	6		6	6	6	6	6
Mean		358	0.053	3.592	2.376	11.232	2.133	1.193	1.965	1.335	0.565	0.657	0.015	1.012	0.666	3.130	0.584	0.335	0.553	0.376	0.158	0.184
SD		28.14	0.000	0.170	0.210	1.440	0.280	0.090	0.070	0.110	0.100	0.090	0.000	0.090	0.040	0.210	0.070	0.020	0.040	0.040	0.020	0.020
1 SD: Range - Low		330	0.053	3.422	2.166	9.792	1.853	1.103	1.895	1.225	0.465	0.567	0.015	0.922	0.626	2.920	0.514	0.315	0.513	0.336	0.138	0.164
1 SD: Range - High		386	0.053	3.762	2.586	12.672	2.413	1.283	2.035	1.445	0.665	0.747	0.015	1.102	0.706	3.340	0.654	0.355	0.593	0.416	0.178	0.204
2 SD: Range - Low		302	0.053	3.252	1.956	8.352	1.573	1.013	1.825	1.115	0.365	0.477	0.015	0.832	0.586	2.710	0.444	0.295	0.473	0.296	0.118	0.144
2 SD: Range - High		414	0.053	3.932	2.796	14.112	2.693	1.373	2.105	1.555	0.765	0.837	0.015	1.192	0.746	3.550	0.724	0.375	0.633	0.456	0.198	0.224

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HD-28-OR(OGR) 30.7/EDITION 3/2005
PAGE No. 3/4

TOXI-4091/04
052/8-CLSN-28-OR
PAGE No. 139/140

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ANNEXURE 9 contd.

30.7 contd.: FASTING BODY WEIGHTS, ORGAN WEIGHTS AND ORGAN WEIGHT RATIOS - FEMALES (CONTROL RECOVERY GROUP - G1R)

Study No.		Fasting	Organ weights (g)												Organ weight ratios (%)									
		Bwt (g)	Adrenals	Ovaries	Kidneys	Liver	Lungs	Heart	Brain	Thymus	Spleen	Uterus	Adrenals	Ovaries	Kidneys	Liver	Lungs	Heart	Brain	Thymus	Spleen	Uterus
3105/00	Mean	@																				
	SD																					
	N																					
3266/01	Mean																					
	SD	@																				
	N																					
	Mean	194	0.067	0.126	1.416	5.984	1.460	0.769	1.784	0.453	0.428	0.648	0.034	0.065	0.729	3.080	0.752	0.397	0.925	0.234	0.221	0.338
3281/01	SD	13.99	0.014	0.007	0.168	0.733	0.190	0.090	0.037	0.105	0.045	0.100	0.005	0.004	0.051	0.197	0.060	0.030	0.073	0.049	0.018	0.070
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	214	0.062	0.127	1.545	6.142	1.345	0.824	1.812	0.372	0.428	0.565	0.029	0.060	0.723	2.879	0.629	0.387	0.850	0.173	0.200	0.266
3286/01	SD	12.39	0.003	0.020	0.129	0.383	0.132	0.047	0.069	0.074	0.071	0.073	0.002	0.012	0.044	0.180	0.041	0.027	0.063	0.027	0.025	0.043
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	211	0.062	0.126	1.499	5.926	@	0.730	1.787	0.430	0.459	@	0.029	0.060	0.712	2.810	@	0.346	0.847	0.204	0.218	@
3309/01	SD	11.86	0.010	0.013	0.066	0.414	@	0.034	0.065	0.075	0.038	@	0.004	0.005	0.055	0.193	@	0.019	0.032	0.034	0.024	@
	N	6	6	6	6	6	@	6	6	6	6	@	6	6	6	6	@	6	6	6	6	@
	Mean																					
3532/03	SD	@																				
	N																					
	Mean																					
3432/02	SD	@																				
	N																					
	Mean																					
3691/03	SD	@																				
	N																					
	Mean	195	0.061		1.387	5.325		0.815	1.815	0.435	0.425		0.032		0.712	2.737		0.419	0.834	0.224	0.219	
4056/04	SD	10.73	0.007	@	0.060	0.199	@	0.060	0.045	0.020	0.019	@	0.004	@	0.034	0.140	@	0.024	0.064	0.022	0.017	@
	N	6	6		6	6		6	6	6	6		6		6	6		6	6	6	6	
Mean		204	0.063	0.126	1.462	5.844	1.403	0.785	1.800	0.423	0.435	0.607	0.031	0.062	0.719	2.877	0.691	0.387	0.869	0.209	0.215	0.302
SD		12.3	0.010	0.010	0.120	0.470	0.160	0.060	0.060	0.080	0.050	0.090	0.000	0.010	0.050	0.180	0.050	0.030	0.060	0.030	0.020	0.060
1 SD: Range - Low		192	0.053	0.116	1.342	5.374	1.243	0.725	1.740	0.343	0.385	0.517	0.031	0.052	0.669	2.697	0.641	0.357	0.829	0.179	0.195	0.242
1 SD: Range - High		216	0.073	0.136	1.582	6.314	1.563	0.845	1.860	0.503	0.485	0.697	0.031	0.072	0.769	3.057	0.741	0.417	0.949	0.239	0.235	0.362
2 SD: Range - Low		179	0.043	0.106	1.222	4.904	1.083	0.665	1.680	0.263	0.335	0.427	0.031	0.042	0.619	2.517	0.591	0.327	0.769	0.149	0.175	0.182
2 SD: Range - High		229	0.083	0.146	1.702	6.784	1.723	0.905	1.920	0.583	0.535	0.787	0.031	0.082	0.819	3.237	0.791	0.447	1.009	0.269	0.255	0.422
N: No. of rats																						

@: Not evaluated