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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF ASPERGILLUS NIGER (GEP 44) IN WISTAR RATS

CRO report number 3716/03

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Experimental work:

Keywords:
90-day
Toxicology
GEP-44
Aspergillus niger
Sub-chronic
GLP
Endoprotease
Oral

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Signature author: Date Manuscript March 18, 2004 Rallis Research Centre, Bangalore, India	Signature responsible manager:

RALLIS RESEARCH CENTRE
Peenya, Bangalore - 560 058.

FINAL REPORT

(COPY No. 2/4)

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

STUDY No.: 3716/03

STUDY DIRECTOR AND AUTHOR: Dr.H.KRISHNAPPA

SPONSORED BY

DSM FOOD SPECIALTIES
A. FLEMINGLAAN 1
POBOX 1, 2600MA DELFT
THE NETHERLANDS

TEST FACILITY

TOXICOLOGY DEPARTMENT
RALLIS RESEARCH CENTRE
RALLIS INDIA LIMITED
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PEENYA II PHASE, BANGALORE - 560 058
INDIA

DATE OF SUBMISSION: MARCH 18, 2004

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QUALITY ASSURANCE STATEMENT

The Study No.: 3716/03, entitled "Repeated dose 90-day Oral Toxicity Study by gavage with enzyme preparation of *Aspergillus niger* (GEP44) in Wistar rats" has been inspected in accordance with the OECD Principles of Good Laboratory Practice (GLP) for the testing of chemicals [{OECD, C(97) 186/Final}] and [(US) EPA, FIFRA (40 CFR part 160)].

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

INSPECTIONS DATE	PHASE	REPORTING DATE
	INITIATION PHASE	
18.08.2003	Study plan review	18.08.2003
	IN LIFE PHASE	
29.08.2003	Acclimatization	01.09.2003
01.09.2003	Test item preparation, veterinary examination, initial body weights, cage change and test item administration as gavage	08.09.2003
22.10.2003	Daily observations	27.10.2003
21.11.2003	Measurement of grip strength, motor activity and functional observation battery	24.11.2003

contd.

QUALITY ASSURANCE STATEMENT contd.

INSPECTIONS DATE	PHASE	REPORTING DATE
	IN LIFE PHASE contd.	
29.11.2003	Preparation of blood smears	01.12.2003
01.12.2003	Terminal sacrifice, analysis for haematology and clinical chemistry – males	08.12.2003
	REPORTING PHASE	
01.03.2004 to 12.03.2004	Draft report review	12.03.2004
17.03.2004	Final report review	17.03.2004

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: 18/03/2004

Satish Murthy. V

(Mr.SATISH MURTHY. V)
Head, Quality Assurance Unit
Rallis Research Centre, Bangalore

RALLIS RESEARCH CENTRE
Peenya, Bangalore - 560 058.

STATEMENT OF CONFIDENTIALITY

The report contains **confidential** and **proprietary** information of DSM Food Specialties, A. Fleminglaan 1, Pobox 1, 2600MA Delft, THE NETHERLANDS which will not be disclosed to anyone except the employees of this company or to persons authorised by law or judicial judgement without the expressed or a written approval of DSM Food Specialties, A. Fleminglaan 1, Pobox 1, 2600MA Delft, THE NETHERLANDS.

GLP COMPLIANCE STATEMENT

The study was performed in compliance with the OECD Principles of Good Laboratory Practice (GLP) for the testing of chemicals as specified by EU legislation (enacted in the German Chemical Law, dated July 25, 1994 Appendix 1 to § 19a, Bundesgesetzblatt, Part I of July 29, 1994) and the Good Laboratory Practice Standards of [(US) EPA, FIFRA (40 CFR part 160)] and International [{OECD, C(97) 186/Final} [ENV/MC/CHEM(98)/17] adopted on 26th November, 1997] Legislation and also in accordance with the Standard Operating Procedures.

The study was performed in compliance with OECD Guideline No. 408 for testing of chemicals, "Repeated Dose 90-day Oral Toxicity Study in Rodents" adopted on September 21, 1998, in compliance with Commission Directive 87/302/EEC of November 18, 1987 Part B:Methods for Determination of Toxicity: Subchronic Oral Toxicity Test : 90 day Repeated Oral Dose using Rodent species (No. L133/8) and United States Environmental Protection Agency, [Prevention, Pesticides and Toxic Substances (7101)] Health Effects Test Guidelines OPPTS 870.3100 "90-day Oral Toxicity in Rodents" [EPA 712-C-98-199] August 1998. This study was also conducted as per the mutually agreed Study Plan signed by Study Director on 20.08.2003 and by Monitoring Scientist on 27.08.2003. This study did not include recovery groups for the control and high dose groups.

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 might have affected the quality or integrity of the data. 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.

Date: 18/3/04

(Dr.H.KRISHNAPPA)
Study Director

STUDY DETAILS

Study Title	:	Repeated dose 90-day Oral Toxicity Study by gavage with enzyme preparation of *Aspergillus niger* (GEP44) in Wistar rats
Study Number	:	3716/03
Sponsor	:	DSM Food Specialties A. Fleminglaan 1 Pobox 1 2600MA Delft THE NETHERLANDS
Monitoring Scientist	:	Dr.Ir Mariëlla Kuilman-Wahls DSM Food Specialties Regulatory Affairs Postpoint 001-0490 P.O. Box 1, 2600MA Delft THE NETHERLANDS
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
Experimental Period		
Acclimatization	:	Start : 27-08-2003 End : 31-08-2003
First day of treatment	:	01-09-2003
Last day of treatment	:	29-11-2003
Date of sacrifice	:	01-12-2003 and 02-12-2003

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STUDY PERSONNEL

The following personnel participated in the conduct of the study.

Name	Signature	Date
Dr.H.KRISHNAPPA M.V.Sc., Study Director and Study Veterinarian Chronic Section		18/3/04
Mr.P.M.SATHISH M.Sc., Technical Co-ordinator Chronic Section		17-03-2004
Mr.M.Y.SUNAGAR M.Sc., Laboratory Investigations Haematology, Clinical chemistry and Metabolism Section		17/03/04
Dr.B.S.MADHUKAR B.V.Sc., Necropsy and Histotechniques Histopathology Section		17/3/04
Mr.VIJAYA KUMAR M.Sc., Histotechniques Histopathology Section		17/3/04

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STUDY PERSONNEL

Name	Signature	Date
Dr.P.ANIL KUMAR M.V.Sc., Study Pathologist Histopathology Section (Resigned on 28.02.2004 - Signed by the Study Director on his behalf)		18/3/04
Dr.K.KAMALA M.V.Sc., Peer Review Pathologist Histopathology Section	K.K	17/3/2004
Mr. H.S.ANAND M.Sc.,(Agri) Analytical Chemist Residue/Analytical Department		17/03/2004
Mr.SANJEEV.V.HULSOOR B.Sc., Data Entry EDP Section		17/3/04
Mr.K.V.ANANTHAPADMANABHA M.Sc., Histopathology Data Entry and Data analyses EDP Section	K.V. Anantha	17.3.2004
Mr.M.VENKATESULU B.Sc., Data Analyses and Report Compilation EDP Section	M. Venkatesulu	17.3.2004

LIST OF COMMONLY USED ABBREVIATIONS AND SYMBOLS

A.I.	Active Ingredient
Alb	Albumin
ALT	Alanine aminotransferase
App	Appendix / Appendices
Approx.	Approximately
AST	Aspartate aminotransferase
Baso	Basophils
BUN	Blood Urea Nitrogen
Bwt	Body weight
Ca	Calcium
Chol	Cholesterol
Cl	Chloride
Creat	Creatinine
Cm	Centimetre
Cm^3	Cubic Centimetre
Eosi	Eosinophil
EDTA	Ethylene Diamine Tetra Acetic Acid
Epididym	Epididymides
F	Female
fl	Femto litre
g	gram
G/l	Giga/litre
G	Group
GGT	Gamma Glutamyl Transpeptidase
GIT	Gastro Intestinal Tract
Glu	Glucose
H	Height
Hb	Haemoglobin
Hct	Haematocrit
K	Potassium
kg	kilogram
L	Length
l	litre
Lymp	Lymphocyte
M	Male
m	meter
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
mEq	milli Equivalent
mg	milligram
min	minute
ml	milli litre
mm	millimetre
mmol	millimole
mn	micron
Mono	Monocytes
NA	Not Applicable
Na	Sodium
NAD	No Abnormality Detected
Neut	Neutrophil
nm	nanometer
No.	Number
pg	picogram
Pi	Inorganic phosphorus
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.Bil	Total Bilirubin
Tot.Pro	Total Plasma Protein
U	Units
UV	Ultra violet
W	Width
WBC	White Blood Corpuscles
%	per cent
µmol	micromole
°F	Degree Fahrenheit
°C	Degree Celsius

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY

Enzyme preparation of *Aspergillus niger* (GEP44) was tested for its toxic potential in a "Repeated dose 90-day Oral Toxicity Study by gavage in Wistar rats". The quantities of test item were measured as volume based on the density (density: 1.0785 g/cm^3). The test item was dissolved in double distilled water and administered by oral gavage at doses of 2000 and 7000 mg/kg Bwt/day to low (G2) and mid (G3) dose groups of rats at an equivolume dose of 20 ml/kg Bwt/day. For high dose (G4) group rats, the undiluted test item was administered at a dose volume of 18.54 ml/kg Bwt/day to achieve a dose of 20000 mg/kg Bwt/day. The concurrent control (G1) group received double distilled water without the test item at an equivolume dose of 20 ml/kg Bwt/day. All the study groups consisted of 10 male and 10 female rats per group. The identity of the test item was provided by the sponsor by a certificate of analysis. The results of the stability of the test item were provided by the sponsor. The gavage solutions on day 1 and at months 2 and 3 of treatment period were analysed for protein content.

Animals from all the groups were observed for clinical signs, eye affections, physical abnormalities, changes in body weights, food consumption and functional observation battery. Laboratory investigations on haematology and clinical chemistry were performed at sacrifice. The rats were subjected to detailed necropsy at terminal sacrifice.

Histopathological evaluation was carried out on all the tissues and organs collected from control and high dose group rats, gross lesions and lungs from low and mid dose groups.

Under the experimental conditions described in the Material and Method section, the following results were obtained:

A. SUMMARY OF RESULTS

1. Clinical Signs and Pre-terminal Deaths:

   There were no treatment-related clinical signs at any of the tested doses and there were no pre-terminal deaths.
   Functional Observation Battery (neurological examination), ophthalmological examination, veterinary and clinical examinations did not reveal any treatment related findings.

2. Body Weights and Food Consumption:

   No treatment related effects on body weights and net body weight gains were observed in males at all the tested doses. Females of the high dose group gained significantly more weight than the control group, resulting in higher body weights. Males of the high dose group consumed significantly less feed compared to the control group. For females no differences in food consumption were observed. Higher body weight gain by high dose females and lower food consumption by high dose males can be attributed to the extra energy intake through the test compound. Thus, results in body weights and food consumption did not show any treatment-related relevant toxicological effect in either sex.

3. Laboratory Investigations:
   a. Haematology:
   No treatment-related changes were observed in all the haematological parameters tested in either sex.

   b. Clinical Chemistry:

   Biochemical investigations did not reveal any treatment-related findings in either sex.

4. Terminal fasting body weights, Organ weights and Organ weight ratios:

   There were no treatment related changes in the terminal fasting body weights, organ weights and organ weight ratios in males and females.

5. Gross and Histopathology:

   There were no treatment related gross and histopathological changes in males and females.

B. NO OBSERVED ADVERSE EFFECT LEVEL (NOAEL)

The results of this study indicate that oral administration of enzyme preparation of *Aspergillus niger* (GEP44) to Wistar rats at concentrations of 2000, 7000 and 20000 mg/kg Bwt/day does not reveal any adverse effect on general health, growth, food consumption, neurological findings, haematological parameters, biochemical parameters, fasting body weights, organ weights and their ratios, gross pathology and histopathology.

In light of the results discussed above, as no changes of toxicological significance were noted among the animals that received a concentration of 20000 mg/kg Bwt/day, this level is considered to be the No Observed Adverse Effect Level (NOAEL) of enzyme preparation of *Aspergillus niger* (GEP44) in Wistar rats, under the test conditions and the doses employed.

Date: 18/3/04

(Dr.H.KRISHNAPPA)
Study Director

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INTRODUCTION

The purpose of this Repeated Dose 90-day Oral Toxicity Study in Rodents was to assess the systemic toxic potential resulting from the repeated exposure to the test item when administered by gavage to rats. A No Observed Adverse Effect Level (NOAEL) was evaluated. The rats were observed during the entire experimental schedule. This study may provide a part of the rational basis for toxicological risk assessment in man.

MATERIAL AND METHOD

1. TEST SPECIES

Animals	:	Hsd Cpb: WU rats conventionally bred (in-house random bred)
Source	:	Toxicology Department, Rallis Research Centre Rallis India Limited Bangalore - 560 058, INDIA
No. of groups	:	Four groups: Vehicle control, low, mid and high dose groups
No. of rats/group	:	Twenty rats (10 males and 10 females)
Age of rats at the start of treatment	:	7 weeks

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

	Males	Females
G1	194 ± 7.8	157 ± 6.3
G2	194 ± 8.6	156 ± 7.1
G3	192 ± 13.3	155 ± 8.9
G4	196 ± 10.8	157 ± 7.7

Identification	:	By rat accession number, cage card and body marking. During acclimatization period, the rats were temporarily marked using 0.5% (w/v) crystal violet solution. During treatment period, 10% solution of turmeric in 70% alcohol was used as permanent body marking.
Acclimatization	:	After veterinary examination, for good health and suitability for the study, the rats were acclimatized for five days before start of the treatment. Females used in the study were nulliparous and non-pregnant.

2. HUSBANDRY

Room number: Subchronic laboratory room No. SC – 27.

a. Conditions:

Rats were housed under standard laboratory conditions; the room was air conditioned with 12 - 15 filtered fresh air changes per hour. The maximum and minimum temperature in the experimental room was recorded once daily in the morning hours and it ranged from 19 - 23°C. The relative humidity in the experimental room was calculated once daily from dry and wet bulb temperature recordings and it ranged between 30 - 70%. Further, the experimental room had 12 hour fluorescent light and 12 hour dark cycle.

b. Housing:

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

c. Food:

Ssniff rats/mice pellet food - maintenance meal - low in germs manufactured by Ssniff Spezialdiäten GmbH., Ferdinand-Gabriel-Weg 16, D-59494 Söest, GERMANY was provided ad libitum. Animal diet sample analysis report and feed contaminant analysis report for Ssniff rats/mice diet (maintenance meal) are given in Annexures 1 and 2, respectively.

d. Water:

Protected water: 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 in collaboration with Electrolux, SWEDEN) was provided in glass bottles with stainless steel sipper tube ad libitum. The analysis report and the contaminant analysis report for water samples are given in Annexures 3 and 4, respectively.

3. GROUPING

Grouping was done on the last day of the acclimatization period. Grouping was by in-house method of body weight stratification and distribution as follows. The rats procured for the study were weighed and grouped in the following body weight ranges: 161 – 170, 171 – 180, 181 – 190, 191 – 200 g etc., in case of males and 131 – 140, 141 – 150, 151 – 160 g etc., in case of females (The selected ranges were 181 – 210 g for males and 141 – 170 g for females). These body weight stratified rats were distributed to all the study groups in equal numbers. The rats with extreme body weights/not used for the study were disposed as per the standard operating procedure.

4. DOSE LEVELS AND DOSE JUSTIFICATION

Three dose levels, 2000, 7000 and 20000 mg/kg Bwt/day were selected for the study in consultation with the sponsor. In addition to test doses, a concurrent control group was also included. The dose selection was based on the Repeated dose (14-day) oral toxicity study by gavage in Wistar rats (Study No. 3715/03), in which 2000, 7000 and 20000 mg/kg Bwt/day were used. The results of 14-day study were as follows:

There were no treatment related changes observed in clinical signs, body weights, food consumption, organ weights and their ratios to body weights and also no gross pathological changes at all the doses tested.

Animals in the control group were handled in a manner similar to the treatment groups however, no test item was administered and only vehicle, double distilled water was administered.

5. 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	To
G1	Vehicle control	White	0	10	M	Rf2311	Rf2320
				10	F	Rf2351	Rf2360
G2	Low dose	Yellow	2000	10	M	Rf2321	Rf2330
				10	F	Rf2361	Rf2370
G3	Mid dose	Green	7000	10	M	Rf2331	Rf2340
				10	F	Rf2371	Rf2380
G4	High dose	Pink	20000	10	M	Rf2341	Rf2350
				10	F	Rf2381	Rf2390

6. ROUTE OF ADMINISTRATION

Oral through gavage, dose is expressed as mg/kg Bwt/day.

TEST ITEM INFORMATION: (as furnished by study sponsor)

Common name (active ingredient)	:	Prolyl-oligo peptidase
Chemical name (IUPAC)	:	Enzyme protein
Name to be used in report	:	Enzyme preparation of *Aspergillus niger* (GEP44)
Code by test facility	:	052/7-GEP44
Batch No.	:	JLL03006IDF
Manufactured by	:	DSM Food Specialties 15, Rue des Comtesses Pobox 239 59472 Seclin Cedex FRANCE
Supplied by	:	DSM Food Specialties. A. Fleminglaan 1 Pobox 1 2600MA Delft THE NETHERLANDS
Date of manufacture	:	March 2003
Date of expiry	:	1 Year after production (March 2004)
Date of receipt at test facility	:	14-06-2003
Storage conditions	:	Deep freezer (-68°C to -76°C)
Physical appearance	:	Dark brown liquid
Hazards and precautions	:	Material may be sensitizing by inhalation, so avoid skin and inhalatory contact

ANALYSES OF THE TEST ITEM

1. IDENTITY OF THE TEST ITEM

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

2. STABILITY OF THE TEST ITEM

As per the certificate of analysis provided by the sponsor, the undiluted test item and the test item in water at concentrations of 100 mg/ml and 350 mg/ml is stable at 4°C for 7 days and also at room temperature (21°C) for 48 hours.

3. GAVAGE SAMPLE ANALYSIS

Gavage solutions on day 1 and at months 2 and 3 of the treatment period were analysed for protein content by Micro-Kjeldahl method. In brief, the determination of protein content in enzyme samples was as follows: The total nitrogen content in the sample was determined by digesting the sample with sulphuric acid and digestion mixture. A known volume of digested sample was distilled by using Micro-Kjeldahl distillation unit and the nitrogen content was calculated. The protein content was calculated from the total nitrogen content in the sample by multiplying the total nitrogen content with a factor of 6.25.

4. TEST ITEM PREPARATION AND ADMINISTRATION

The test item solutions were prepared on first day of the treatment and at 3 – 4 day intervals thereafter (within the stability period). The volume of test item was measured based on density (density: 1.0785 g/cm^3). To prepare the test item solution, approximate quantities of 40 g (G2: 37.1 ml) and 140 g (G3: 129.8 ml) of test item was separately measured and volume of G2 and G3 was made upto 400 ml with double distilled water to get the test item concentration of 100 mg (G2) and 350 mg (G3)/ml, respectively.

For Group G4 the undiluted test item was administered at a dose volume of 18.54 ml/kg/day. The dose volume was calculated for individual animals on the first day of the treatment and was adjusted according to the body weights recorded weekly thereafter during the treatment period.

The prepared test item solutions for groups G2 and G3 were made into required number of aliquots depending on daily requirement. The remaining aliquots were stored at 4°C or below 4°C and these were used daily. The required volume of test item for G4 was made into different aliquots depending on daily requirement. The prepared aliquots for G4 were stored at 4°C or below 4°C and these were used daily. The prepared test item solutions and the undiluted test item was stored in a refrigerator in the chronic toxicity facility. Control animals were administered double distilled water at an equivolume dose of 20.0 ml/kg Bwt/day. The test item volume, volume of the test item preparation and administration were varied depending on the body weights of the rats recorded during different intervals of treatment period. The difference between the nominal and actual concentrations did not exceed ± 5%. Test item was administered at an equivolume dose of 20.0 ml/kg Bwt/day except for G4 which was administered at a dose volume of 18.54 ml/kg Bwt/day.

TREATMENT

The test item solutions were administered by gavage to rats of the specific group once daily at approximately the same time (± 2 hours) each day for 90 consecutive days. Similarly the double distilled water (vehicle) was administered by gavage to vehicle control rats for 90 consecutive days at an equivolume dose (20.0 ml/kg Bwt/day). When the total dose volume exceeded the capacity of the syringe (3 ml), then the volume was administered in two portions using 5 ml or 10 ml syringe.

OBSERVATIONS

1. VETERINARY/CLINICAL EXAMINATIONS AND OPHTHALMOLOGICAL EXAMINATIONS, GENERAL CLINICAL SIGNS AND PRE-TERMINAL DEATHS AND NEUROLOGICAL EXAMINATION:

a. Veterinary/Clinical examinations, General clinical signs and Pre-terminal deaths:

Veterinary/clinical examinations were carried out prior to initiation of treatment and at weekly intervals thereafter except for week 13 wherein the veterinary/clinical examinations were carried out on day 6 of that week.

All rats were observed for general clinical signs once a day and for morbidity and pre-terminal deaths twice a day.

b. Ophthalmological examination:

Ophthalmological examination was carried out one day before start of the treatment and at the end of the treatment period prior to sacrifice for all animals. Mydriasis was induced before examination using 1% Tropicamide solution.

c. Neurological examination:

The following neurological examinations were conducted at the end of the treatment period (12^{th}/13^{th} week of the treatment period).

i. Home cage observations:

Observations on rats were made in their home cages and while opening the cages. The rats were observed for

a. Presence or Absence of convulsions
b. Presence or Absence of tremors
c. Palpebral (eyelid) closure was observed for whether the eyelids were

1 = wide open
2 = slightly drooping
3 = drooping eyelids (half closed)
4 = completely shut

ii. Handling observations:

Rats were removed from the cage and then observed for the following reactions.

a. Ease of removal from the cage
   1= Very easy: animals sits quietly, allows investigator to pick it up
   2= Easy; with or without vocalization, without resistance or slight resistance to being picked up.
   3= moderately difficult: animal rears, often following investigator's hand.
   4= Difficult: runs around cage, is hard to grab, with or without vocalization.
   5= Very difficult: tail and throat rattles with or without vocalization, may attack hand.

b. Ease of handling animal in hand: the following observations were made, while handling the animal.
   1= No resistance, animal is easy to handle
   2= Slight resistance: slight resistance to being handled, with or without vocalization.
   3= Moderate resistance: rat may be tense or be rigid in hand, with or without vocalization.
   4= High resistance: squirming/twisting the body, attempting to bite, with or without vocalization.

c. Lacrimation: Rats were observed for whether lacrimation was there or not. If lacrimation was present then its severity i.e., whether it is slight or severe was observed.

d. Chromodacryorrhea (red tears): Rats were observed for presence or absence of red tears.

e. Salivation: Rats were observed for whether salivation was there or not. If salivation was present, then its severity i.e., whether it is slight or severe (active salivation drooling) was observed.

f. Piloerection: Hair coat was observed for piloerection. If piloerection was present, then its severity i.e., whether it is slight or severe was observed.

g. Palpebral (eyelid) closure was observed for i.e., whether the eyelids were:
   1 = wide open
   2 = slightly drooping
   3 = drooping eyelids (half closed)
   4 = completely shut

h. Respiratory character: Rats were observed for the following changes in respiratory character
   1= Normal respiratory character
   2= Rales: abnormal sound accompanying breathing
   3= Retching: repeated unavailing attempts to vomit
   4= Dyspnoeic: labored or difficult breathing
   5= Gasping: short of breath with an open mouth

i. Eye prominence: Rats were observed for
   1= Normal
   2= Exophthalmus: protrusion of eye ball
   3= Enophthalmus: retraction of eye ball in the orbital cavity

j. Muscle tone: Musculature of the limbs was palpated between the thumb and forefinger to confirm whether the muscle was
   1= Firm but not hard (normal)
   2= Soft and flabby
   3= Tense and hard

iii. Open field observations:

To carry out open field observations, the animal was placed in open field arena (Dimension 850 x 587 x 200 mm) and evaluated during a 2 minutes observation period for:

a. Mobility: Scoring was done within 30 seconds of placing the animal in open field arena. The animal was observed to see whether the mobility of the animal was
   1= Normal
   2= Moderately impaired
   3= Totally impaired, locomotion impossible.

b. Backing: Recording was done for the number of times animal takes backward steps during the 2 minute observation period in the open field arena.

c. Grooming: Recording was done for the number of times the animal grooms itself during the 2 minute observation period in the open field arena. Grooming included wiping/rubbing face and head with forepaws, scratching head or body with hind paws and biting the fur.

d. Gait: Gait of the animal was observed for following:
   1= Normal, head horizontal, abdomen just above surface, slight up and down movement with each step.
   2= Walks on tiptoes.
   3= Body drags, abdomen makes contact with surface, body sways.
   4= Hindlimbs splayed or dragging, unable to support weight.
   5= Hunched body, bottom up, nose held down, arched back.
   6= Ataxia, excessive sway or lurches as animal proceeds forward.

e. Convulsions: Rats were observed for presence or absence of convulsions.

f. Tremors: Rats were observed for presence or absence of tremors.

g. Arousal: The animals were observed for whether the arousal was
   1= Very low: stupor, coma, little or no responsiveness
   2= Low: somewhat stuporous
   3= Normal: alert, exploratory movements
   4= Moderately high: slight excitement, tense, excited sudden darting or freezing
   5=Very high. hyperalert, excited, sudden bouts of running or body movements

iv. Sensory observations:

The following sensory observation tests were performed in the open field arena.

a. Startle response (Auditory response): A finger click sound was produced directly above the rat's head and the response was observed for
   1= No reaction
   2= Normal reaction (rat flinches or flicks ear)
   3= Exaggerated reaction (rat jumps, flips)

b. Touch response (Tactile response): The rump was touched with a pencil tip and reaction by the rat was observed for
   1= No reaction
   2= Animal slowly turned, walked away
   3= More energetic response than (2), may include vocalization
   4= Freezes, actual muscle contraction
   5= Bizarre reaction: Jumps, bites or attacks

c. Pupil response (visual response): Using a pen torch, light was shone into the one eye of the rat and the other eye was shielded from the light. The response of the pupil i.e., constriction of the pupil present or absent was recorded. The same procedure was followed for the other eye also.

d. Response to nociceptive stimuli: The tail was gently pressed with a forceps and response from the rat was recorded for
   1= No reaction
   2= Animal turned or walked away
   3= More energetic than (2), may include vocalization
   4= Freezes, actual muscle contraction
   5= Bizarre reaction: jumps, attacks or bites

e. Righting reflex
   1. Righting reflex was checked by placing the animal on its back and observing whether it turns over immediately or not

   2. The animal was dropped upside down from a height of 40 cm above the examination table and its landing (whether it lands right side up) was checked.

v. Neuromuscular observations:

The following neuromuscular observation tests were performed:

a. Grip strength:

The grip strength of fore limbs and hind limbs was determined using Digital force Measurement Instrument (Chatillon grip strength apparatus). Each animal was allowed to grip the T-shaped bar with the paws of the fore limbs and hind limbs and was then pulled backwards gently until the grip was broken and the displayed readings were recorded. Three readings each for fore limbs and hind limbs were recorded.

b. Motor activity:

Motor activity was recorded using photoactometer. Each animal was placed inside the activity cage of the instrument (photoactometer chamber) for 15 minutes and at the end of 15 minutes session, the displayed score was recorded.

c. Hind limbs foot splay:

The heel pads of the hind feet of each rat were painted with ink and the rat was dropped down onto a sheet of white blotting paper from a height of approximately 30-35 cms above the table. The distance in centimetres between the centres of the backs of the heel prints was measured. Three readings were recorded for each rat.

vi. Physiological observations:

a. Body temperature

Thermometer was inserted into the rectum and the displayed temperature in degree Fahrenheit (°F) was recorded after the beep sound indicating completion of equilibration. In the report the body temperature was presented as degree Celsius (°C). The following formula was used to convert Fahrenheit values to Centigrade values.

$$C = \frac{(F-32) \times 5}{9}$$ Where C = Degree Celsius
F = Degree Fahrenheit

2. BODY WEIGHTS:

Individual body weights were recorded on the first day of treatment before the test item administration and at weekly intervals thereafter except for week 13 wherein the body weights were recorded on day 6.

3. FOOD INTAKE:

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

I. Day 1[a] Food input 450 g Food output on day 8

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

The weekly cagewise food consumption was calculated by dividing the total food consumed by the number of rats per cage to determine the food intake/rat/week. The visual estimation of the food spillage by the rats was determined and the recorded food spillage data was taken in to consideration (i.e., the food spillage data/cage/week was added to the food output data) in 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 except for week 13 of the treatment period wherein the food consumption (g)/rat/day was obtained from food output for 6 days and divided by the number of days (6).

4. CLINICAL LABORATORY INVESTIGATIONS:

Laboratory investigations were carried out at the end of the treatment period.

a. Blood smear:

Blood smears from all the rats were made two to three days (two days prior to sacrifice in males, three days prior to sacrifice in females) prior to sacrifice from all the rats by tail clipping method and stained by modified Wright - Giemsa stain. The Differential Leucocyte Count was determined by conventional microscopy.

b. Blood collection:

At the end of the treatment period, all the animals were fasted overnight (water allowed) and blood was collected from the 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 plasma separation, respectively. Plasma was separated in a refrigerated centrifuge at 5000 rpm for 15 minutes and analysed for clinical chemistry parameters.

c. Haematology:

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

1. Haemoglobin (Hb)
2. Red Blood Corpuscles (RBC)
3. White Blood Corpuscles (WBC)
4. Haematocrit (Hct)
5. Platelets (Plat)

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

1. Mean Corpuscular Volume (MCV)
2. Mean Corpuscular Haemoglobin (MCH)
3. Mean Corpuscular Haemoglobin Concentration (MCHC)

Prothrombin time analysis was carried out immediately after blood collection using STArt-4 Coagulation Analyser (Diagnostica stago).

d. Clinical chemistry:

Plasma was analysed using Automatic clinical chemistry analyser BM-HITACHI 704 (Boehringer Mannheim, Mannheim, GERMANY) and Boehringer Mannheim (GERMANY) diagnostic kits were used for the assay of the following parameters:

1. Fasting Glucose (Glu) mmol/l:

GOD-POD method: Trinder. P., Ann Clin Biochem., 6:24, 1969.

2. Total Bilirubin (Tot. Bil) µmol/l:

Walters MI., Gerade HW: An ultramicro method for the determination of conjugated and total bilirubin in serum or plasma; Microchem J., 15:231, 1970.

3. Creatinine (Creat) µmol/l:

Jaffe's kinetic method: Fabing DI., Ertingshausen G: Automated reaction rate method for determination of serum Creatinine with the "Centrifichem"; Clin Chem., 17:696, 1971.

4. Blood Urea Nitrogen (BUN) mmol/l:

Urease-GLDH method: Tiffany et al., Clin Chem., 18:829, 1972.

5. Alanine Amino transferase (ALT) U/l:

Infinity ALT reagent based on recommendations of IFCC : IFCC Expert panel on enzymes part 3 J Clin Chem Clin Biochem., 24:481-495, 1986.

6. Aspartate Amino transferase (AST) U/l:

Infinity AST reagent based on recommendations of IFCC : IFCC method for AST J Clin Chem Clin Biochem., 24:497-510, 1986.

7. Calcium (Ca) mmol/l:

Arsenazo III method: Michaylova V, Ilkova P; Photometric determination of microamounts of calcium with Arsenazo III; Anal Chem Acta., 53:194, 1971.

8. Albumin (Alb) g/l:

Bromocresol-green method: Doumas B.T., et al.; In standard methods of Clin Chem Vol 7,(175-189), 1972 Academic Press, Chicago, USA

9. Gamma Glutamyl Transpeptidase (GGT) U/l:

Szasz G., Persijn JP., et al.,: New substrates for measuring γ-glutamyl-transpeptidase activity J Clin Chem Clin Biochem., 12:228, 1973.

10. Chloride (Cl) mEq/l:

Hamilton RS., A direct photometric method for chloride in biological fluids employing mercuric thiocyanate and perchloric acid; Clin Chem., 12:1, 1966.

11. Inorganic Phosphorus (Pi) mmol/l:

Molybdate Method: Daly JA, Ertingshausen G; Direct method for determining inorganic phosphorus in serum with the "Centrifichem"; Clin Chem., 18:263, 1972.

12. Total Plasma Protein (Tot.Pro.) g/l:

Biuret method: Doumas et al., Clin Chem., 27:1642, 1981.

13.Total Cholesterol (mmol/l):

CHOD-POD method: Allain CC, PoonLS, Chan CSG, Richmond W and Fu PC; Clin Chem., 20:470-475, 1974; Roeschlau P, Bernt E and Gruber WA., J Clin Chem Clin Biochem., 12:226, 1974.

14. Urea (mmol/l):

The formula used to calculate urea was BUN / 0.467.

Where BUN value was obtained from BM HITACHI-704 printout.

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

5. PATHOLOGY:

a. Gross necropsy:

All rats in the study were subjected to gross necropsy and the findings were recorded. The animals to be sacrificed at term were fasted overnight (water allowed), anaesthetised using ether anaesthesia as per random numbers generated for the study, weighed and exsanguinated and were subjected to detailed necropsy by a pathologist.

b. Tissue collection:

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

1. Liver
2. Kidneys
3. Lungs #
4. Spleen
5. Heart
6. Aorta
7. Thymus
8. Stomach
9. Duodenum
10. Pancreas
11. Jejunum
12. Ileum with peyer's patches
13. Cecum
14. Colon
15. Rectum
16. Mesenteric lymph nodes
17. Trachea
18. Esophagus
19. Thyroids with Parathyroids
20. Pharynx
21. Larynx
22. Nose
23. Adrenals
24. Urinary bladder
25. Ovaries
26. Uterus
27. Testes
28. Epididymides
29. Prostate
30. Seminal vesicles and coagulating glands
31. Female mammary gland
32. Brain including medulla/pons cerebellum and cerebrum
33. Pituitary
34. Spinal cord at 3 levels - cervical, mid thoracic and lumbar.
35. Sciatic nerves
36. Sternum with bone marrow
37. Bone marrow smear from femur
38. Axillary lymph node
39. Eyes * including retina & optic nerve
40. Skin
41. Salivary glands
42. All gross lesions and masses
43. Thigh musculature**
44. Femur with articular surface**
45. Exorbital lacrymal glands**

* : Collected in Davidson's fluid
** : Did not examine histopathologically, as there was no indication of target organ involvement or signs of toxicity.
# : Were inflated with fixative and then immersed in formalin.

Tissue samples were processed by paraffin embedding technique and sections of 5 microns were stained by Harris Haematoxylin-Eosin stain.

c. Organ weights

After detailed gross necropsy examination, the following organs were collected and weighed: liver, adrenals, kidneys, testes/ovaries, epididymides, uterus, thymus, spleen, brain and heart. The organ weight ratio as percentage of body weights were determined and presented in the report.

d. Histopathology:

Histopathological evaluation was performed on the preserved organs and tissues of all animals of the high dose group and the control group. All gross lesions in low and mid dose groups were also examined.

The lungs of animals in the low and mid dose groups were subjected to histopathological examination for evidence of infection to provide an assessment of the health status of the animals. The unused tissues were preserved in 10% buffered neutral formalin in labelled bottles and archived.

STATISTICAL ANALYSES

Using specific computer programme, functional observation battery (only body temperature, motor activity score and neuromuscular observations), body weights, cumulative net body weight gains, food consumption, laboratory investigations (haematology and clinical chemistry), organ weights and organ weight ratio data were compared by Bartlett's test for homogeneity of intra group variances. When the variances proved to be heterogeneous, the data was transformed using appropriate transformation. The data with homogeneous intra group variances was subjected to one-way analysis of variance (ANOVA - Snedecor and Cochran, 1987). Following ANOVA, when 'F' was found to be significant, Dunnett's pairwise comparison (Scheffe 1953) of means of treated groups with the mean of the control group was done individually.

Following a significant difference of a test group with the control group, the dose response correlation was estimated by including the control and all the treated groups and tested by 't' test.

All analyses and comparisons are evaluated at 5% ($P \leq 0.05$) level. Throughout this report statistically significant differences ($P \leq 0.05$) indicated by the aforementioned tests are designated by the superscripts as stated below:

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

d : Significant dose correlation

The statistical analysis for clinical signs and ophthalmological examination was not carried out as it was not needed.

RESULTS AND DISCUSSION

Details of the experimental layout and treatment schedule are presented in Table 1.

A. ANALYSES

a. Identity: App. 19

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

b. Stability of the test item: App. 19

As per the certificate of analysis provided by the sponsor, the undiluted test item and the test item in water at concentrations of 100 mg/ml and 350 mg/ml is stable at 4°C for 7 days and also at room temperature (21°C) for 48 hours.

c. Analysis results of protein content and test item concentration in the gavage samples: App. 21

The prepared gavage solutions were analysed for test item concentration on day 1 of treatment and months 2 and 3 of the treatment period. The estimation of test item concentration in the gavage solutions was based on the protein value of the test item which was determined by Micro-Kjeldahl method. The results showed mean concentrations of 99.98 ± 0.52 and 350.00 ± 1.33 mg of the test item/ml as against the nominal concentrations of 100 and 350 mg/ml in the G2 and G3 groups, respectively. The results of analysis of undiluted test item which was gavaged for G4 group, showed a mean concentration of 1079.39 ± 1.74 mg of test item/ml. The three batches of samples analysed for protein content showed mean protein value of 13.90 ± 0.07, 48.65 ± 0.19 and 150.03 ± 0.36 mg/ml of test item in the G2, G3 and G4 groups respectively.

B. IN-LIFE DATA

a. Veterinary/Physical examination, Clinical signs, Ophthalmological examinations and Pre-terminal deaths: Table 2, App. 1 and 2

The observation of all the animals during acclimatization period did not reveal any clinical signs.

Veterinary/physical examination carried out during acclimatization period and prior to the initiation of treatment did not reveal any clinical signs.

Veterinary/physical examination carried out at weekly intervals during treatment period did not reveal any treatment related clinical signs.

Incidences of hair thinning with hair regrowth were observed as follows: in males, one each in low, mid and high dose groups and in case of females, eight in control, two in low dose, five in mid dose and three in the high dose groups. These findings are common findings in our colony particularly in females and were randomly distributed among the various groups. Incidence of injury was observed in one female each in the control and low dose groups.

The ophthalmological examination carried out during acclimatization period and at the end of the treatment period did not reveal any eye abnormalities.

There were no pre-terminal deaths in any of the tested groups.

b. Clinical examination: Table 3, App. 1 and 2

Clinical examination carried out for all the animals prior to the test item administration and at weekly intervals thereafter did not reveal any clinical signs.

c. Functional observation battery:

The neurological examination carried out at the end of the treatment period (12^{th}/13^{th} week) revealed the following findings.

Males: Table 4; App. 3
Treatment did not affect the functional observation parameters in any of the tested doses when compared to control group. Incidences of significantly lower hind limb foot splay values were observed at mid and high dose groups. The observed significant findings are considered to be incidental findings as there were no significant effects in related endpoints (grip strength and motor activity). The findings were not dose-related or associated with any functional alterations.

Females: Table 5; App. 4
Treatment did not affect the functional observation parameters in any of the tested doses when compared to control group. Incidences of significantly lower hind limb foot splay values at mid and high dose groups were observed when compared to the control group. The observed significant findings are considered to be incidental findings as there were no significant effects in related endpoints (grip strength and motor activity). The findings were not dose-related or associated with any functional alterations.

d. Body weights, cumulative net body weight gains and food intake:
Males: Tables 6, 7 & 10; App. 5, 6 & 9 and Figures 1 & 3
No significant changes were observed in the mean body weights and mean cumulative net body weight gains at any of the tested doses. Significantly lower food intake was observed on week 1 at mid and high doses and on weeks 8 to 13 (except on week 12) at high dose when compared to control group. However, the decrease in food intake was not associated with decreasing body weights or retardation in the growth of the animals.

Therefore the decrease in food intake is considered not toxicological relevant, but rather an adaptation on the extra calory intake through the test item.

Females: Tables 8, 9 & 11; App. 7, 8 & 19 and Figures 2 & 4

No significant changes were observed in the mean body weights and cumulative net body weight gains at low and mid dose groups when compared to control group. At high dose the mean body weights and the cumulative net body weight gains were higher throughout the treatment period. Statistical significance was achieved on weeks 6 and 8 to 10 for mean body weights and from week 4 to 13 for the cumulative net body weight gains. The food intake was significantly lower on week 1 in the mid and high dose groups. No significant changes regarding food intake were observed in the low dose group when compared to the control group. The observed significant changes in food intake are considered to be incidental as these findings were not repeated during the remaining weeks of the treatment period. Thus, the elevated body weights at high dose were not associated with increased feed intake, but can be attributed to the extra energy intake through the test item. This can be proven as follows: 20000 mg/kg Bwt/day with a Total Organic Solid content of 25.2% (as per certificate of analysis) counts for 5040 mg x 17 kJ/g = 85.7 kJ/kg Bwt/day extra energy intake, assuming the Total Organic Solid consists predominantly of protein and (poly) saccharides which have an available energy of 17 kJ/g. The female rats consumed about 18 g/rat/day which represents 219.6 kJ/rat/day (Refer Annexure 7) or 219.6 kJ/0.236 g = 930 kJ/kg Bwt/day (236 g is the average of the body weights of the control female animals on week 6 and 8-10). The average weight of the female animals of group G4 in the same weeks is 256 g which is 8.5% more than the average weight of the control animals. This increase can be fully explained by the extra energy intake which is 9.2% (85.7/930).

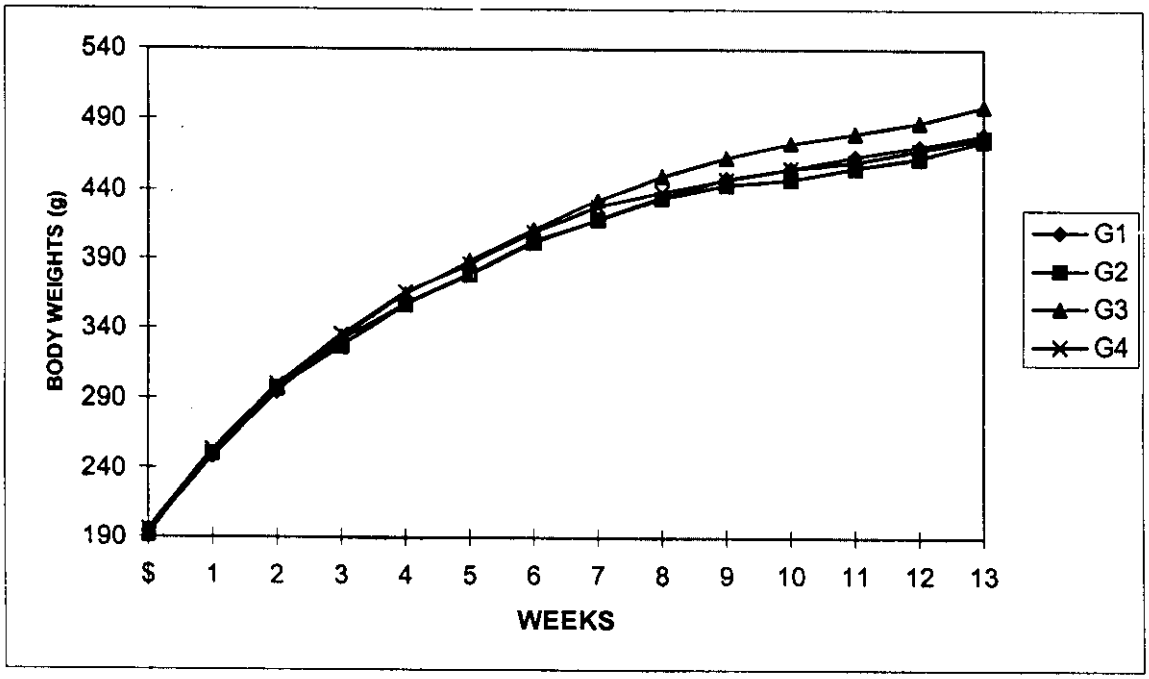

FIGURE 1: BODY WEIGHT AND GROWTH CURVES-MALES

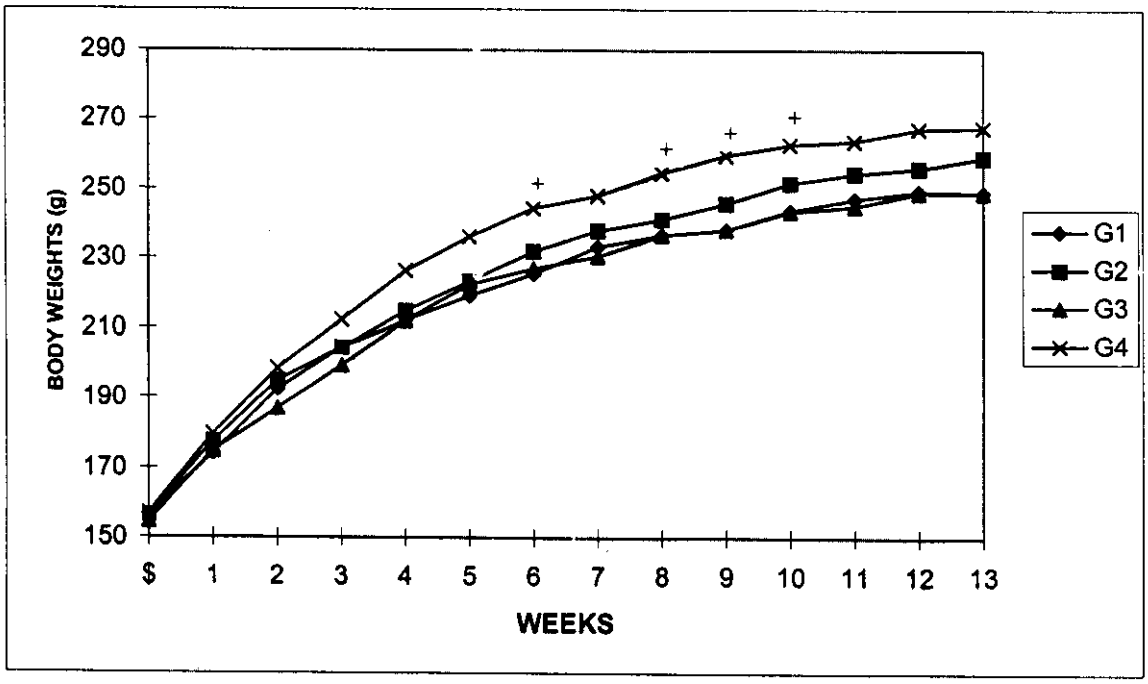

FIGURE 2: BODY WEIGHT AND GROWTH CURVES-FEMALES

Note: +: Significantly higher(+) than the control group

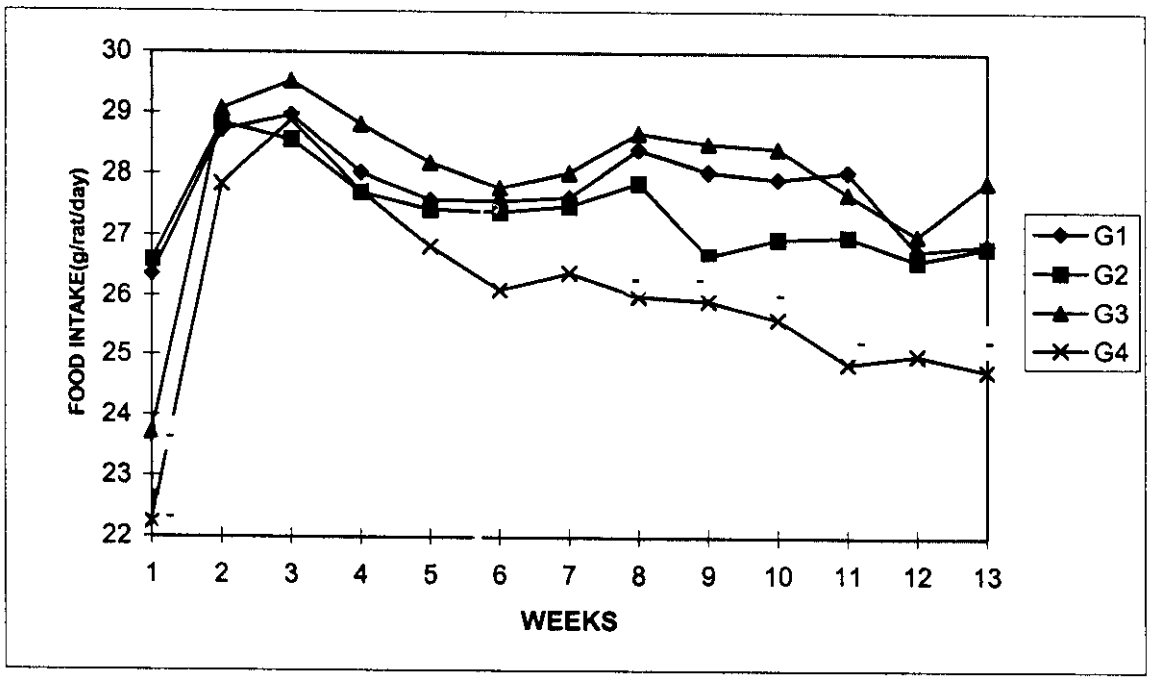

FIGURE 3: FOOD CONSUMPTION CURVES - MALES

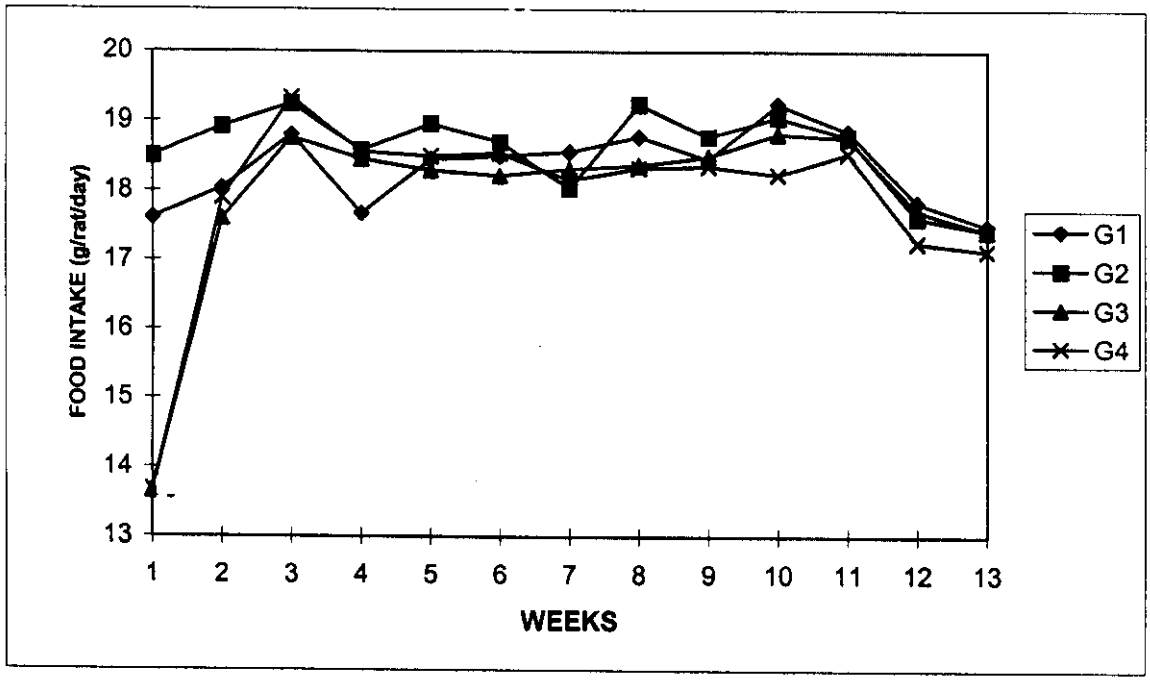

FIGURE 4: FOOD CONSUMPTION CURVES - FEMALES

Note: -: Significantly lower(-) than the control group

C. CLINICAL LABORATORY INVESTIGATIONS

a. Haematology:

Males: Table 12, App. 11

Haematological investigation revealed no adverse changes attributable to the administration of the test item. Incidences of decreased leukocyte counts were observed at low and mid doses. No significant changes were observed at high dose when compared to control group. Observed significant changes are considered to be incidental findings due to the absence of such findings at high dose and as all values are found within the range of historical control data.

Females: Table 13, App. 12

The RBC counts at high dose were significantly lower, while MCH level at mid and high dose groups were significantly higher. The platelet counts at mid and high dose, the prothrombin time at low dose and monocyte percentage at all the treated doses were significantly lower when compared to the control group. The significant changes observed for platelets and monocytes are considered to be not treatment related as there was no dose response relationship and the values are found within the range of historical control data. Moreover, the high percentage of monocytes in the control group can be attributed to only one animal. The significant change observed for prothrombin time at the low dose is considered to be an incidental finding in the absence of a similar change in the higher dose levels. The decrease in RBC counts is considered not related to treatment as no effects on other relevant blood parameters, except MCH, have been observed and the level of bilirubin is not increased. The increase in MCH results from the decreased in RBC. As no other relevant blood parameters are affected and no dose relationship is present, the increase in MCH is considered to be not related to treatment.

b. Clinical chemistry:

Males: Table 14, App. 13

Higher total bilirubin level at high dose and lower creatinine level at low and mid doses were observed when compared to control group. The observed changes for the creatinine level are considered to be not treatment related in the absence of a similar change at the high dose level. The increased total bilirubin level at high dose group is also considered to be not treatment-related as no effects on other blood parameters (e.g. RBC counts) are observed. Moreover, the values are found within the range of the historical control data.

Females: Table 15, App. 14

Blood urea nitrogen and urea levels at low dose were lower, glucose level at mid and high doses and cholesterol at high dose were significantly higher when compared to control group. The decreased BUN and urea levels are considered not treatment related because of their isolated occurrence. The increased cholesterol is considered incidental as no corresponding histopathological findings were observed, it is observed in one sex only and the values are found within the range of historical control data. Increased glucose level at mid and high dose were mainly due to a higher concentration of glucose in a few animals. As no dose relationship is present, no corresponding increase is observed for males and the values are within the range of the historical control data, the increase is considered not related to treatment.

D. TERMINAL FASTING BODY WEIGHTS, ORGAN WEIGHTS AND ORGAN WEIGHT RATIOS: Tables 16 & 17; App. 15 & 16

There were no significant intergroup differences in the terminal fasting body weights in males and females.

Males: Table 16, App. 15

There were no significant intergroup differences in organ weight and organ weight ratios except for a significant increase in relative weight of liver in high dose group when compared to control group. This was considered incidental and not treatment related as the increase was only slight, no corresponding gross and histopathological findings were observed and none of the liver enzymes was affected.

Females: Table 17, App. 16

There were no significant inter group differences in organ weight and organ weight ratios except for a significant increase in the relative weight of the liver in the high dose group when compared to the control group. This was not considered treatment related as there were no corresponding gross and histopathological findings and none of the liver enzymes was affected.

E. GROSS PATHOLOGY: Table 18; App. 17 & 18

Gross examination at necropsy did not reveal any treatment related findings. The changes observed represented common background pathology findings in rats of this strain and age and occurred in one or a few animals only or were randomly distributed among the groups.

F. HISTOPATHOLOGY: Table 19; App. 17 & 18

All microscopic observations were common findings in rats of this strain and age and occurred only incidentally or at similar incidences amongst the control and high dose group. Therefore, they were not considered to be related to treatment. Since there were no treatment related changes in the high dose group animals, tissues from the low and mid dose group animals were not examined, except for gross lesions and lungs.

CONCLUSION

The results of this study indicate that oral administration of enzyme preparation of *Aspergillus niger* (GEP44) to Wistar rats at concentrations of 2000, 7000 and 20000 mg/kg Bwt/day does not reveal any adverse effect on general health, growth, food consumption, neurological findings, haematological parameters, biochemical parameters, fasting body weights, organ weights and their ratios, gross pathology and histopathology.

In light of the results discussed above, as no changes of toxicological significance were noted among the animals that received a concentration of 20000 mg/kg Bwt/day, this level is considered to be the No Observed Adverse Effect Level (NOAEL) of enzyme preparation of *Aspergillus niger* (GEP44) in Wistar rats, under the test conditions and the doses employed.

REFERENCES

1. *Games, P.A. and Howell, J.F. (1976), J.Ed. Statist., 1: 113-125*
2. *Scheffe, H. (1953), Biometrika, 40 : 87 - 104.*
3. *Snedecor,G.W. and Cochran, W.G. (1987): Statistical Methods, 7th ed.(Reprint) Iowa State University Press, Ames, IA.*
4. *Sokal, R.R. and Rohlf, F.F. (1981): Biometry, Freeman,San Francisco.*

ARCHIVING

Rallis will archive at the archives of the test facility the following for thirty years after completion of the study: the study plan, raw data, draft and final reports. A sample of test item had been sent from test item stores to the archives at the time of receipt of test item. This sample shall be stored for a period of 2 years from the date of this report or till the next GLP inspection, whichever is later, however not beyond 30 years. All the 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.

REPORT DISTRIBUTION

Archives: One signed original final report

Sponsor: Three signed original final reports (Two unbound and One bound)

TABLE 1

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

DETAILS OF EXPERIMENTAL LAYOUT, TREATMENT AND SACRIFICE SCHEDULE

Group No.	Dose (mg/kg Bwt/day)	No. of rats/group		Treatment period (days)	Neurological examinations	Laboratory investigations		Pathology			Sacrifice Schedule	
		Males	Females			Haema-tology	Clinical chemistry	Organ weights	Gross	Histo	Males 92nd day	Females 93rd day
G1	0	10	10	90	+	+	+	+	+	+	+	+
G2	2000	10	10	90	+	+	+	+	+	a	+	+
G3	7000	10	10	90	+	+	+	+	+	a	+	+
G4	20000	10	10	90	+	+	+	+	+	+	+	+

+: Yes

a: Lesions and lungs from low and mid dose groups

TABLE 2

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF VETERINARY AND OPHTHALMOLOGICAL EXAMINATIONS, CLINICAL SIGNS 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	2000	7000	20000	0	2000	7000	20000
	No. of rats	10	10	10	10	10	10	10	10
1. GENERAL AFFECTIONS		0	0	0	0	0	0	0	0
2. NEUROLOGICAL AFFECTIONS		0	0	0	0	0	0	0	0
3. RESPIRATORY AFFECTIONS		0	0	0	0	0	0	0	0
4. EYE AFFECTIONS		0	0	0	0	0	0	0	0
5. GASTRO INTESTINAL AFFECTIONS		0	0	0	0	0	0	0	0
6. SKIN AFFECTIONS									
- Hair thinning with hair regrowth		0	1	1	1	8	2	5	3
- Injury		0	0	0	0	1	1	0	0
7. UROGENITAL AFFECTIONS		0	0	0	0	0	0	0	0
8. PRE-TERMINAL DEATHS		0	0	0	0	0	0	0	0

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TABLE 3

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF CLINICAL EXAMINATION

Ref.App.: 1 & 2

PARAMETERS	Sex	Males				Females			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
	Dose (mg/kg Bwt/day)	0	2000	7000	20000	0	2000	7000	20000
	No. of rats	10	10	10	10	10	10	10	10
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

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TABLE 4

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY - MALES
(Incidence of parameters observed)

Ref. App. : 3

Group No.	No.	Home cage observations			Handling observations		
Dose	of	Convulsions	Tremors	Palpebral closure	Ease of removal from the cage	Ease of handling animal in hand	Lacrimation
(mg/kg Bwt/day)	rats	Absent	Absent	Eyelids wide open	Very easy	No resistance, animal is easy to handle	None
G1 0	10	10	10	10	10	10	10
G2 2000	10	10	10	10	10	10	10
G3 7000	10	10	10	10	10	10	10
G4 20000	10	10	10	10	10	10	10

contd.

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TABLE 4 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY - MALES
(Incidence of parameters observed)

Ref. App. : 3

Group No. Dose (mg/kg Bwt/day)	No. of rats	Handling observations contd.						
		Chromodacryorrhea	Salivation	Piloerection	Palpebral closure	Respiratory character	Eye Prominence	Muscle tone
		Absent	Normal	None	Eyelids wide open	Normal	Normal	Muscle is firm but not hard(normal)
G1 0	10	10	10	10	10	10	10	10
G2 2000	10	10	10	10	10	10	10	10
G3 7000	10	10	10	10	10	10	10	10
G4 20000	10	10	10	10	10	10	10	10

contd.

TABLE 4 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY - MALES
(Incidence of parameters observed)

Ref. App. : 3

Group No. Dose (mg/kg Bwt/day)	No. of rats	Open field observations						
		Mobility	Backing	Grooming	Gait	Convulsions	Tremors	Arousal
		Normal	(counts)	(counts)	Normal	Absent	Absent	Normal
G1 0	10	10	0	0	10	10	10	10
G2 2000	10	10	0	0	10	10	10	10
G3 7000	10	10	0	0	10	10	10	10
G4 20000	10	10	0	0	10	10	10	10

contd.

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TABLE 4 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY - MALES
(Incidence of parameters observed)

Ref. App. : 3

Group No. Dose (mg/kg Bwt/day)	No. of rats	Sensory observations					
		Startle response	Touch response	Pupil response	Response to Nociceptive stimuli	Righting reflex	
		Normal reaction	Animal slowly turned, walked away	present	Animal turned or walked away	Onback Present	Dropped Present
G1 0	10	10	10	10	10	10	10
G2 2000	10	10	10	10	10	10	10
G3 7000	10	10	10	10	10	10	10
G4 20000	10	10	10	10	10	10	10

contd.

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TABLE 4 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY - MALES

Ref. App. : 3

Group No. Dose (mg/kg Bwt/day)		Physiological observation		Neuromuscular observations		
					Grip strength (g)	
		Body temperature(°C)	Motor activity score	Hind limb foot splay (cms)	Fore limbs	Hind limbs
G1	Mean	36.6	693	7.2	1013	623
0	SD	0.61	92.47	0.95	102.37	50.55
	N	10	10	30	30	30
G2	Mean	36.8	640	6.7	1002	612
2000	SD	0.88	100.80	1.22	81.68	45.33
	N	10	10	30	30	30
G3	Mean	36.6	682	6.3 -	998	632
7000	SD	0.64	112.60	1.17	97.71	71.27
	N	10	10	30	30	30
G4	Mean	37.1	665	6.3 -	1003	642
20000	SD	0.58	121.37	0.76	85.92	87.95
	N	10	10	30	30	30

N: No. of observations

-: Significantly lower(-) than the control group

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TABLE 5

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY - FEMALES
(Incidence of parameters observed)

Ref. App. : 4

Group No.	No.	Home cage observations			Handling observations		
Dose	of	Convulsions	Tremors	Palpebral closure	Ease of removal from the cage	Ease of handling animal in hand	Lacrimation
(mg/kg Bwt/day)	rats	Absent	Absent	Eyelids wide open	Very easy	No resistance, animal is easy to handle	None
G1 0	10	10	10	10	10	10	10
G2 2000	10	10	10	10	10	10	10
G3 7000	10	10	10	10	10	10	10
G4 20000	10	10	10	10	10	10	10

contd.

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TABLE 5 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY - FEMALES
(Incidence of parameters observed)

Ref. App. : 4

Group No. Dose (mg/kg Bwt/day)	No. of rats	Handling observations contd.						
		Chromodacryorrhea	Salivation	Piloerection	Palpebral closure	Respiratory character	Eye Prominence	Muscle tone
		Absent	Normal	None	Eyelids wide open	Normal	Normal	Muscle is firm but not hard(normal)
G1 0	10	10	10	10	10	10	10	10
G2 2000	10	10	10	10	10	10	10	10
G3 7000	10	10	10	10	10	10	10	10
G4 20000	10	10	10	10	10	10	10	10

contd.

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TABLE 5 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY - FEMALES
(Incidence of parameters observed)

Ref. App. : 4

Group No. Dose (mg/kg Bwt/day)	No. of rats	Open field observations						
		Mobility	Backing	Grooming	Gait	Convulsions	Tremors	Arousal
		Normal	(counts)	(counts)	Normal	Absent	Absent	Normal
G1 0	10	10	0	0	10	10	10	10
G2 2000	10	10	0	0	10	10	10	10
G3 7000	10	10	0	0	10	10	10	10
G4 20000	10	10	0	0	10	10	10	10

contd.

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TABLE 5 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY - FEMALES
(Incidence of parameters observed)

Ref. App. : 4

Group No. Dose (mg/kg Bwt/day)	No. of rats	Sensory observations					
		Startle response	Touch response	Pupil response	Response to Nociceptive stimuli	Righting reflex	
		Normal reaction	Animal slowly turned, walked away	present	Animal turned or walked away	Onback Present	Dropped Present
G1 0	10	10	10	10	10	10	10
G2 2000	10	10	10	10	10	10	10
G3 7000	10	10	10	10	10	10	10
G4 20000	10	10	10	10	10	10	10

contd.

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TABLE 5 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF FUNCTIONAL OBSERVATION BATTERY - FEMALES

Ref. App. : 4

Group No. Dose (mg/kg Bwt/day)		Physiological observation		Neuromuscular observations		
					Grip strength (g)	
		Body temperature(°C)	Motor activity score	Hind limb foot splay (cms)	Fore limbs	Hind limbs
G1	Mean	37.1	804	5.8	988	605
0	SD	0.98	151.14	0.63	67.43	52.10
	N	10	10	30	30	30
G2	Mean	37.5	806	5.7	997	603
2000	SD	0.76	231.07	0.68	82.02	57.62
	N	10	10	30	30	30
G3	Mean	37.8	851	5.2 -	1005	605
7000	SD	0.44	165.07	0.65	75.24	49.29
	N	10	10	30	30	30
G4	Mean	37.8	839	5.2 -	1012	592
20000	SD	0.37	156.72	0.78	66.05	67.37
	N	10	10	30	30	30

N: No. of observations

-: Significantly lower(-) than the control group

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TABLE 6

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF WEEKLY BODY WEIGHTS (g) - MALES

Values: Mean ± SD

Ref.App.: 5

G. No. Dose (mg/kg Bwt/day)	No. of rats	Weeks													
		$	1	2	3	4	5	6	7	8	9	10	11	12	13
G1	10	194	248	295	331	357	380	403	418	434	448	455	464	471	480
0		7.8	9.4	11.8	13.5	16.9	18.3	22.5	23.7	25.0	28.3	33.9	32.9	35.3	34.5
G2	10	194	250	297	327	357	379	402	418	433	444	448	456	463	475
2000		8.6	9.5	10.5	15.4	21.0	20.8	24.0	24.3	28.1	27.7	32.5	34.0	33.2	32.3
G3	10	192	251	298	334	364	389	412	432	450	463	473	481	488	499
7000		13.3	14.3	25.9	20.4	32.0	34.7	38.4	38.8	38.4	37.6	37.4	42.1	44.4	47.3
G4	10	196	254	300	335	366	387	410	428	438	447	455	460	468	477
20000		10.8	14.7	20.5	24.0	25.0	26.8	29.5	31.8	34.6	35.7	38.5	38.9	40.4	39.3

$: Day 1of treatment period

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TABLE 7

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF CUMULATIVE WEEKLY NET BODY WEIGHT GAINS (g) - MALES

Values: Mean ± SD

Ref.App.: 6

G. No. Dose (mg/kg Bwt/day)	No. of rats	Weeks												
		1	2	3	4	5	6	7	8	9	10	11	12	13
G1	10	55	101	137	163	186	209	225	241	255	261	270	278	286
0		6.1	9.8	12.8	16.9	18.8	22.9	25.0	26.7	30.8	36.9	36.1	38.4	37.6
G2	10	56	103	132	162	185	207	224	239	249	253	261	269	280
2000		5.6	9.3	13.5	19.2	19.6	22.7	21.7	26.9	26.3	31.4	33.7	32.7	32.2
G3	10	60	106	142	173	197	220	241	259	271	282	289	297	308
7000		5.7	16.6	14.7	22.8	26.2	29.7	31.3	31.1	31.2	31.5	35.5	38.0	40.7
G4	10	57	104	139	169	190	213	232	242	251	259	264	272	281
20000		6.6	12.3	15.8	16.6	18.6	21.1	23.8	26.9	27.6	30.8	32.1	33.9	33.0

TABLE 8

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF WEEKLY BODY WEIGHTS (g) - FEMALES

Values: Mean ± SD

Ref.App.: 7

G. No. Dose (mg/kg Bwt/day)	No. of rats	Weeks													
		$	1	2	3	4	5	6	7	8	9	10	11	12	13
G1	10	157	174	193	204	212	219	226	233	237	238	244	247	249	249
0		6.3	7.5	8.0	8.9	10.4	11.6	9.3	11.6	11.3	12.5	12.3	12.5	13.2	11.8
G2	10	156	178	195	205	215	223	232	238	241	246	252	255	256	259
2000		7.1	9.5	14.1	14.3	14.0	18.5	17.4	17.3	19.1	18.2	19.7	19.1	19.4	21.2
G3	10	155	175	187	199	212	223	227	231	237	238	244	245	249	249
7000		8.9	11.0	11.9	13.5	15.3	15.2	14.8	13.5	14.5	15.4	15.5	15.2	17.1	15.6
								+		+	+	+			
G4	10	157	180	198	213	226	236	245	248	255	260	263	264	267	268
20000		7.7	13.7	10.9	12.5	14.4	13.9	16.2	16.3	16.9	17.8	18.3	21.5	21.7	20.1

$: Day 1of treatment period

+: Significantly higher(+) than the control group

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TABLE 9

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF CUMULATIVE WEEKLY NET BODY WEIGHT GAINS (g) - FEMALES

Values: Mean ± SD Ref.App.: 8

G. No. Dose (mg/kg Bwt/day)	No. of rats	Weeks 1	2	3	4	5	6	7	8	9	10	11	12	13
G1	10	17	36	48	55	62	69	77	80	82	87	90	92	92
0		6.8	7.0	7.2	8.2	9.9	7.7	8.9	9.3	10.5	10.7	10.4	10.5	9.7
G2	10	21	38	48	58	67	76	82	85	90	96	98	100	103
2000		7.4	11.1	11.8	11.1	15.7	15.4	14.9	15.3	15.9	17.1	16.2	16.1	18.3
G3	10	20	32	44	57	68	72	76	82	84	89	90	94	94
7000		6.3	10.0	9.0	9.8	10.0	10.7	9.5	9.3	9.4	10.2	9.5	11.7	10.3
					+	+	+	+	+	+	+	+	+	+
G4	10	23	41	56	70	79	88	91	98	103	106	107	110	111
20000		7.7	7.2	8.9	9.5	9.2	12.3	12.9	12.5	12.9	13.6	16.7	16.8	15.6

+: Significantly higher(+) than the control group

TABLE 10

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF CAGEWISE AVERAGE FOOD INTAKE (g/rat/day) - MALES

Values: Mean ± SD — Ref.App.: 9

G. No. Dose (mg/kg Bwt/day)	No. of cages	No. of rats / cage	Weeks 1	2	3	4	5	6	7	8	9	10	11	12	13
G1	5	2	26.4	28.7	29.0	28.0	27.6	27.6	27.6	28.4	28.0	27.9	28.0	26.7	26.8
0			0.86	0.90	0.43	0.82	0.89	0.93	0.46	0.79	0.76	0.76	1.08	0.70	0.74
G2	5	2	26.6	28.8	28.6	27.7	27.4	27.4	27.5	27.9	26.7	26.9	27.0	26.6	26.8
2000			1.12	0.49	0.45	0.62	0.63	0.59	1.06	0.73	0.78	0.82	1.42	0.79	0.69
G3	5	2	23.7 -	29.1	29.5	28.8	28.2	27.8	28.0	28.7	28.5	28.4	27.7	27.0	27.9
7000			1.63	2.68	1.40	2.17	2.72	2.76	2.18	1.91	1.48	1.42	2.58	1.86	1.61
G4	5	2	22.2 -	27.8	28.9	27.7	26.8	26.1	26.4	26.0 -	25.9 -	25.6 -	24.9 -	25.0	24.7 -
20000			1.50	0.46	1.13	1.13	1.09	0.73	1.06	1.13	0.63	0.87	1.45	1.53	1.30

-: Significantly lower(-) than the control group

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TABLE 11

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF CAGEWISE AVERAGE FOOD INTAKE (g/rat/day) - FEMALES

Values: Mean ± SD Ref.App.: 10

G. No. Dose (mg/kg Bwt/day)	No. of cages	No. of rats / cage	Weeks												
			1	2	3	4	5	6	7	8	9	10	11	12	13
G1	5	2	17.6	18.0	18.8	17.7	18.5	18.5	18.6	18.8	18.5	19.2	18.9	17.8	17.5
0			0.85	0.94	0.57	0.29	0.92	0.76	0.69	0.86	0.73	0.40	0.32	0.72	0.78
G2	5	2	18.5	18.9	19.2	18.6	19.0	18.7	18.0	19.2	18.8	19.1	18.8	17.6	17.4
2000			1.50	1.77	1.88	1.19	1.65	1.43	1.24	1.62	2.19	0.98	0.68	1.47	1.10
G3	5	2	13.7 -	17.6	18.8	18.5	18.3	18.2	18.3	18.4	18.5	18.8	18.8	17.7	17.4
7000			0.64	0.79	0.84	0.33	1.28	1.56	1.13	0.29	0.55	0.63	0.43	0.91	0.51
G4	5	2	13.7 -	17.9	19.3	18.6	18.5	18.5	18.2	18.3	18.4	18.2	18.5	17.3	17.1
20000			0.84	0.38	0.70	0.30	0.53	0.34	0.30	0.84	0.77	0.53	1.49	0.65	1.12

-: Significantly lower(-) than the control group

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TABLE 12

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF HAEMATOLOGICAL VALUES AT TERMINATION - MALES

Values: Mean ± SD — Ref.App.: 11

G. 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	10	7.8	8.43	159	0.423	50.2	18.9	376	878	14.5	15.0	83.2	1.3	0.5	0.0
0		1.58	0.47	3.50	0.019	1.60	0.73	11.21	97.53	1.27	7.51	7.79	1.57	0.85	0.00
G2	10	5.8 -	8.27	156	0.418	50.6	18.9	373	922	15.3	18.3	79.3	1.8	0.6	0.0
2000		1.09	0.37	4.12	0.016	1.15	0.64	8.43	69.75	1.06	7.18	7.23	1.03	0.84	0.00
G3	10	6.3 -	8.33	156	0.413	49.6	18.8	379	932	15.8	14.1	83.0	2.2	0.7	0.0
7000		1.39	0.37	3.89	0.021	1.55	0.76	14.04	122.08	0.98	4.12	4.55	1.99	0.67	0.00
G4	10	6.4	8.03	152	0.402	50.1	19.1	381	953	14.8	12.6	84.6	2.4	0.4	0.0
20000		1.37	0.65	7.72	0.032	1.68	0.96	15.99	90.55	1.48	3.17	4.58	1.96	0.70	0.00

-: Significantly lower(-) than the control group

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TABLE 13

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF HAEMATOLOGICAL VALUES AT TERMINATION - FEMALES

Values: Mean ± SD — Ref.App.: 12

G. 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	10	4.4	8.66	160	0.439	50.6	18.5	367	1197	15.0	13.6	84.3	0.9	1.2	0.0
0		1.86	0.45	5.30	0.029	1.18	0.52	15.58	84.98	0.54	4.74	5.10	1.20	1.32	0.00
										-				-	
G2	10	4.2	8.96	163	0.448	50.1	18.2	363	1232	14.2	12.6	85.7	1.4	0.3	0.0
2000		1.33	0.49	5.21	0.025	1.23	0.69	15.09	260.04	0.22	7.12	7.38	1.65	0.48	0.00
							+		-					-	
G3	10	3.8	8.18	159	0.424	51.8	19.4	375	931	14.8	11.8	87.0	1.0	0.2	0.0
7000		1.15	0.40	5.57	0.026	1.24	0.40	10.58	114.93	0.48	5.61	5.46	1.25	0.42	0.00
			-				+		-					-	
G4	10	3.7	8.03	158	0.415	51.7	19.6	380	927	14.9	13.1	85.1	1.0	0.8	0.0
20000		1.17	0.45	7.25	0.026	1.74	0.66	10.84	189.37	0.56	7.81	8.85	1.05	0.63	0.00

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

TABLE 14

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF CLINICAL CHEMISTRY VALUES AT TERMINATION - MALES

Values: Mean ± SD

Ref.App.: 13

G. 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	GGT U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
G1	10	10.58	3.18	6.80	65.9	64	47	0.7	3.28	59	33.9	2.31	2.79	2.54	104	144.4	4.43
0		0.63	0.33	0.71	1.32	6.02	3.24	1.06	0.56	3.41	1.02	0.26	0.09	0.27	2.53	1.15	0.39
G2	10	10.25	3.27	7.01	64.6	61	45	0.3	3.45	- 56	33.8	2.51	2.81	2.27	103	144.3	4.35
2000		1.09	0.32	0.69	2.19	4.77	3.87	0.48	0.43	1.32	1.01	0.24	0.08	0.23	1.57	0.99	0.30
G3	10	10.00	3.02	6.46	66.3	63	45	0.8	3.77	- 56	33.8	2.36	2.79	2.52	105	144.8	4.33
7000		1.09	0.31	0.67	2.05	6.93	4.11	0.92	0.52	2.78	1.19	0.18	0.05	0.36	2.18	0.80	0.31
G4	10	10.15	3.23	6.91	65.1	61	43	1.5	+ 3.83	57	33.9	2.47	2.82	2.44	105	144.9	4.24
20000		0.67	0.29	0.61	1.36	8.61	7.65	1.58	0.29	2.67	0.88	0.27	0.09	0.28	2.59	0.87	0.44

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

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TABLE 15

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF CLINICAL CHEMISTRY VALUES AT TERMINATION - FEMALES

Values: Mean ± SD

Ref.App.: 14

G. 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	GGT U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
G1	10	7.95	2.78	5.95	62.9	73	41	0.0	4.60	61	33.3	1.96	2.82	1.65	99	142.0	3.85
0		0.98	0.17	0.35	2.01	8.86	9.17	0.00	0.65	4.18	1.18	0.39	0.75	0.29	1.14	1.71	0.29
G2	10	8.50	2.21 -	4.72 -	65.0	71	40	0.0	5.48	59	34.3	2.11	2.67	1.72	99	141.8	4.08
2000		0.68	0.26	0.55	3.12	11.06	10.42	0.00	1.86	2.78	1.33	0.27	0.10	0.41	1.56	3.24	0.20
G3	10	9.32 +	2.52	5.39	64.9	68	41	0.0	5.12	61	34.0	1.82	2.64	1.82	101	143.2	4.12
7000		1.51	0.16	0.35	1.82	17.11	10.30	0.00	2.10	3.80	1.83	0.30	0.14	0.30	2.15	2.77	0.34
G4	10	9.14 +	2.62	5.61	64.9	67	40	0.1	5.01	58	34.2	1.97	2.67	2.19 +	100	142.6	3.99
20000		0.79	0.40	0.86	1.95	14.04	11.60	0.32	1.01	2.41	1.08	0.38	0.08	0.33	1.48	1.10	0.42

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

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TABLE 16

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF TERMINAL FASTING BODY WEIGHTS, ORGAN WEIGHTS AND ORGAN WEIGHT RATIOS - MALES

Values: Mean ± SD

Ref.App.: 15

G. 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	10	464	0.049	3.626	2.766	13.807	1.395	2.027	1.440	0.555	0.723	0.011	0.783	0.597	2.977	0.302	0.439	0.311	0.120	0.156
0		34.76	0.004	0.517	0.214	1.248	0.065	0.037	0.139	0.080	0.080	0.001	0.099	0.023	0.145	0.018	0.030	0.021	0.017	0.014
G2	10	459	0.048	3.706	2.767	13.427	1.367	2.076	1.492	0.526	0.726	0.010	0.809	0.604	2.927	0.299	0.454	0.326	0.115	0.158
2000		32.55	0.003	0.494	0.185	0 918	0.099	0.092	0.135	0.087	0.101	0.001	0.109	0.024	0.094	0.025	0.030	0.032	0.022	0.021
G3	10	482	0.049	3.541	2.985	15.021	1.366	2.042	1.535	0.513	0.694	0.010	0.739	0.621	3.100	0.284	0.427	0.321	0.105	0.144
7000		46.03	0.004	0.310	0.265	2.224	0.111	0.058	0.157	0.116	0.112	0.001	0.078	0.045	0.226	0.017	0.043	0.049	0.015	0.017
G4	10	460	0.049	3.731	2.897	14.598	1.367	2.046	1.489	0.465	0.755	0.011	0.816	0.630	3.169 +	0.298	0.448	0.326	0.102	0.164
20000		41.24	0.005	0.410	0.274	1.682	0.148	0.055	0.128	0.072	0.099	0.001	0.105	0.031	0.142	0.031	0.032	0.040	0.019	0.020

+: Significantly higher(+) than the control group

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TABLE 17

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF TERMINAL FASTING BODY WEIGHTS, ORGAN WEIGHTS AND ORGAN WEIGHT RATIOS - FEMALES

Values: Mean ± SD

Ref.App.: 16

G. No. Dose (mg/kg Bwt/day)	No. of rats	Fasting Bwt (g)	Organ weights(g)									Organ weight ratios(%)								
			Adrenals	Ovaries	Kidneys	Liver	Heart	Brain	Thymus	Spleen	Uterus	Adrenals	Ovaries	Kidneys	Liver	Heart	Brain	Thymus	Spleen	Uterus
G1	10	238	0.067	0.127	1.582	6.344	0.918	1.906	0.377	0.526	0.766	0.028	0.054	0.664	2.665	0.386	0.801	0.159	0.221	0.323
0		10.23	0.008	0.014	0.111	0.300	0.022	0.051	0.053	0.105	0.148	0.004	0.006	0.034	0.131	0.020	0.041	0.025	0.041	0.074
G2	10	247	0.071	0.136	1.590	6.413	0.922	1.920	0.388	0.500	0.839	0.029	0.055	0.645	2.610	0.376	0.783	0.157	0.203	0.340
2000		19.99	0.008	0.023	0.119	0.486	0.044	0.052	0.059	0.101	0.265	0.003	0.009	0.026	0.196	0.032	0.066	0.017	0.036	0.104
G3	10	238	0.067	0.135	1.555	6.730	0.903	1.886	0.362	0.510	1.096	0.028	0.057	0.655	2.837	0.380	0.797	0.153	0.214	0.468
7000		15.32	0.008	0.012	0.101	0.531	0.065	0.052	0.063	0.082	0.627	0.004	0.006	0.037	0.190	0.021	0.056	0.027	0.029	0.280
						+									+					
G4	10	256	0.066	0.145	1.639	7.397	0.958	1.902	0.391	0.538	0.978	0.026	0.057	0.641	2.890	0.375	0.747	0.152	0.211	0.384
20000		21.69	0.007	0.020	0.151	0.997	0.106	0.076	0.061	0.080	0.323	0.003	0.011	0.029	0.253	0.027	0.048	0.015	0.032	0.125

+: Significantly higher(+) than the control group

TABLE 18

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

SUMMARY OF GROSS PATHOLOGY FINDINGS

Ref. App.: 17 & 18

PARAMETERS	Sex	Males				Females			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
	Dose (mg/kg Bwt/day)	0	2000	7000	20000	0	2000	7000	20000
	No. of rats	10	10	10	10	10	10	10	10
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		10	10	10	10	10	10	10	10
4. No. examined for gross pathology		10	10	10	10	10	10	10	10
5. No. showing gross pathology		1	3	1	2	8	2	6	6
A. No. showing external pathology		0	0	1	1	8	2	5	4
i. Skin hair thinning with hair regrowth focal/multifocal		0	0	1	1	8	2	5	4
ii. Wound		0	0	0	0	1	1	0	0
B. No. showing visceral organ pathology		1	3	1	1	0	0	3	2
i. Kidney (a) unilateral/bilateral pelvis dilated		0	1	0	0	0	0	1	0
(b) unilateral cyst		0	1	0	0	0	0	0	0
ii. Thymus petechiae		1	1	1	1	0	0	0	0
iii. Epididymides unilateral mass		1	0	0	0	NA	NA	NA	NA
iv. Uterus dilatation focal/multifocal		NA	NA	NA	NA	0	0	2	2

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TABLE 19

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE
WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

SUMMARY OF HISTOPATHOLOGICAL FINDINGS

Number in (): No. of Tissues evaluated/group — Ref.App.: 17 & 18

	Sex	MALES				FEMALES			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
TISSUE AND	Dose (mg/kg Bwt/day)	0	2000	7000	20000	0	2000	7000	20000
OBSERVATION	No. of rats	10	10	10	10	10	10	10	10
	No. of rats examined	10	10	10	10	10	10	10	10
1. SALIVARY GLAND		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Lymphocytic infiltration		2	-	-	1	1	-	-	2
Vacuolation		0	-	-	0	1	-	-	0
2. ESOPHAGUS		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
3. STOMACH		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Cystic gland(s)		4	-	-	2	1	-	-	1
Hypertrophy-mucus glands		0	-	-	1	0	-	-	1
4. DUODENUM		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
5. ILEUM WITH PEYER'S PATCHES		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
6. COLON		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Lymphoid hyperplasia		0	-	-	0	0	-	-	1
Parasite(s)		0	-	-	1	0	-	-	0

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE
WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

SUMMARY OF HISTOPATHOLOGICAL FINDINGS

Number in (): No. of Tissues evaluated/group Ref.App.: 17 & 18

TISSUE AND OBSERVATION	Sex	MALES				FEMALES			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
	Dose (mg/kg Bwt/day)	0	2000	7000	20000	0	2000	7000	20000
	No. of rats	10	10	10	10	10	10	10	10
	No. of rats examined	10	10	10	10	10	10	10	10
7. PANCREAS		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Inflammation-chronic		1	-	-	0	0	-	-	0
Lymphocytic infiltration		0	-	-	2	0	-	-	0
Inflammation		1	-	-	0	0	-	-	0
Adipocytes		1	-	-	0	0	-	-	0
3. LIVER		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Lymphocytic infiltration		1	-	-	0	0	-	-	2
Necrobiotic focus(i)		4	-	-	6	9	-	-	4
9. LUNGS		(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Lymphocytic infiltration		1	1	0	3	2	3	0	2
Mineralisation-pulmonary vessels		1	5	5	0	1	3	1	1
Pneumonic foci		5	7	8	2	6	2	4	2
Osseous metaplasia		0	0	0	0	1	0	0	0
10. TRACHEA		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
11. HEART		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
12. AORTA		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)

contd.

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TABLE 19 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE
WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

SUMMARY OF HISTOPATHOLOGICAL FINDINGS

Number in (): No. of Tissues evaluated/group Ref.App.: 17 & 18

	Sex	MALES				FEMALES			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
TISSUE AND	Dose (mg/kg Bwt/day)	0	2000	7000	20000	0	2000	7000	20000
OBSERVATION	No. of rats	10	10	10	10	10	10	10	10
	No. of rats examined	10	10	10	10	10	10	10	10
13. SPLEEN		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Increased hemosiderosis		0	-	-	0	4	-	-	4
14. MESENTERIC LYMPH NODES		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
15. KIDNEYS		(10)	(2)	(-)	(10)	(10)	(-)	(1)	(10)
Cyst(s)		0	1	-	0	0	-	0	0
Lymphocytic infiltration		4	3	-	1	1	-	1	0
Mineralisation		0	1	-	0	1	-	0	0
Dilatation of pelvis		1	1	-	0	0	-	1	0
Urothelial hyperplasia		0	1	-	1	1	-	0	0
Dilatation-collecting ducts		2	0	-	2	1	-	0	0
Basophilic tubules		3	0	-	4	0	-	1	0
Proteinaceous material in tubules		7	0	-	2	0	-	0	0
Hyaline droplets-tubular epithelium		2	0	-	2	0	-	0	0
16. URINARY BLADDER		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Lymphocytic infiltration-submucosa		1	-	-	1	1	-	-	0
17. TESTES		(10)	(-)	(-)	(10)	NA	NA	NA	NA
Atrophy-seminiferous tubules		1	-	-	0	NA	NA	NA	NA

contd.

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TABLE 19 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger*(GEP44) IN WISTAR RATS

SUMMARY OF HISTOPATHOLOGICAL FINDINGS

Number in (): No. of Tissues evaluated/group — Ref.App.: 17 & 18

TISSUE AND OBSERVATION	Sex	MALES				FEMALES			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
	Dose (mg/kg Bwt/day)	0	2000	7000	20000	0	2000	7000	20000
	No. of rats	10	10	10	10	10	10	10	10
	No. of rats examined	10	10	10	10	10	10	10	10
18. EPIDIDYMIDES		(10)	(-)	(-)	(10)	NA	NA	NA	NA
Lymphocytic infiltration		2	-	-	-	NA	NA	NA	NA
Spermatic granuloma		1	-	-	-	NA	NA	NA	NA
Cell debris in lumen		1	-	-	-	NA	NA	NA	NA
19. PROSTATE		(10)	(-)	(-)	(10)	NA	NA	NA	NA
20. SEMINAL VESICLES		(10)	(-)	(-)	(10)	NA	NA	NA	NA
21. COAGULATING GLANDS		(10)	(-)	(-)	(10)	NA	NA	NA	NA
22. OVARIES		NA	NA	NA	NA	(10)	(-)	(-)	(10)
Hemocyst		NA	NA	NA	NA	1	-	-	0
Luteal cyst(s)		NA	NA	NA	NA	2	-	-	2
Dilated tubules-hilus		NA	NA	NA	NA	2	-	-	1
23. UTERUS		NA	NA	NA	NA	(10)	(-)	(2)	(10)
Dilatation		NA	NA	NA	NA	1	-	2	2
24. THYROIDS		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Ultimobranchial cyst		0	-	-	1	0	-	-	0
Ectopic thymus		2	-	-	1	2	-	-	1

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE
WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

SUMMARY OF HISTOPATHOLOGICAL FINDINGS

Number in (): No. of Tissues evaluated/group — Ref.App.: 17 & 18

TISSUE AND OBSERVATION	Sex	MALES				FEMALES			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
	Dose (mg/kg Bwt/day)	0	2000	7000	20000	0	2000	7000	20000
	No. of rats	10	10	10	10	10	10	10	10
	No. of rats examined	10	10	10	10	10	10	10	10
25. PARATHYROIDS		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Connective tissue proliferation		0	-	-	0	0	-	-	1
26. PITUITARY		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Cyst(s)		1	-	-	1	1	-	-	0
Dilated Rathke's cleft		6	-	-	9	1	-	-	1
27. ADRENALS		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Accessory adrenal		0	-	-	1	0	-	-	0
Vacuolation-cortical cells		2	-	-	1	0	-	-	0
28. EYES WITH RETINA AND OPTIC NERVE		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
29. BONE MARROW (SMEAR)		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
30. SKIN		(10)	(-)	(1)	(10)	(10)	(2)	(5)	(10)
Epidermal hyperplasia		1	-	1	3	6	1	5	2
Hyperkeratosis		2	-	0	0	0	0	0	0
Necrotising dermatitis		0	-	0	0	1	1	0	0
31. NOSE		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)

contd.

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TABLE 19 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE
WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

SUMMARY OF HISTOPATHOLOGICAL FINDINGS

Number in (): No. of Tissues evaluated/group — Ref.App.: 17 & 18

TISSUE AND OBSERVATION	Sex	MALES				FEMALES			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
	Dose (mg/kg Bwt/day)	0	2000	7000	20000	0	2000	7000	20000
	No. of rats	10	10	10	10	10	10	10	10
	No. of rats examined	10	10	10	10	10	10	10	10
32. THYMUS		(10)	(1)	(1)	(10)	(10)	(-)	(-)	(10)
Hemorrhage		5	1	1	2	0	-	-	1
Epithelial cyst(s)		0	0	0	1	1	-	-	0
Epithelial hyperplasia		3	0	0	1	3	-	-	1
33. SPINAL CORD		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
34. SCIATIC NERVES		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
35. MAMMARY GLAND		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
36. JEJUNUM		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
37. CECUM		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
38. RECTUM		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Parasite(s)		1	-	-	0	1	0	0	0
39. STERNUM WITH MARROW		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
Cartilage degeneration		2	-	-	5	3	0	0	3
40. AXILLARY LYMPH NODE		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)

contd.

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TABLE 19 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE
WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

SUMMARY OF HISTOPATHOLOGICAL FINDINGS

Number in (): No. of Tissues evaluated/group Ref.App.: 17 & 18

TISSUE AND OBSERVATION	Sex	MALES				FEMALES			
	Group No.	G1	G2	G3	G4	G1	G2	G3	G4
	Dose (mg/kg Bwt/day)	0	2000	7000	20000	0	2000	7000	20000
	No. of rats	10	10	10	10	10	10	10	10
	No. of rats examined	10	10	10	10	10	10	10	10
41. BRAIN-CEREBRAL CORTEX		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
42. BRAIN-CEREBELLAR CORTEX		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
43. BRAIN-MEDULLA/PONS		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
44. LESION		(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
45. PHARYNX		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)
46. LARYNX		(10)	(-)	(-)	(10)	(10)	(-)	(-)	(10)

APPENDIX 1

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL VETERINARY AND OPHTHALMOLOGICAL EXAMINATIONS, CLINICAL SIGNS AND PRE-TERMINAL DEATHS - MALES

Group No. Dose (mg/kg Bwt/day)	Rat No.	Veterinary examination & clinical signs	Clinical examination	Ophthalmological findings End of treatment period
G1	Rf2311	NAD	NAD	NAD
0	Rf2312	NAD	NAD	NAD
	Rf2313	NAD	NAD	NAD
	Rf2314	NAD	NAD	NAD
	Rf2315	NAD	NAD	NAD
	Rf2316	NAD	NAD	NAD
	Rf2317	NAD	NAD	NAD
	Rf2318	NAD	NAD	NAD
	Rf2319	NAD	NAD	NAD
	Rf2320	NAD	NAD	NAD
G2	Rf2321	NAD	NAD	NAD
2000	Rf2322	NAD	NAD	NAD
	Rf2323	NAD	NAD	NAD
	Rf2324	NAD	NAD	NAD
	Rf2325	Hair thinning with hair regrowth	NAD	NAD
	Rf2326		NAD	NAD
	Rf2327	NAD	NAD	NAD
	Rf2328	NAD	NAD	NAD
	Rf2329	NAD	NAD	NAD
	Rf2330	NAD	NAD	NAD

NAD: No Abnormality Detected

Note: Veterinary and ophthalmological examinations carried out during acclimatization period for all animals did not reveal any abnormalities.

contd.

APPENDIX 1 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL VETERINARY AND OPHTHALMOLOGICAL EXAMINATIONS, CLINICAL SIGNS AND PRE-TERMINAL DEATHS - MALES

Group No. Dose (mg/kg Bwt/day)	Rat No.	Veterinary examination & clinical signs	Clinical examination	Ophthalmological findings End of treatment period
G3 7000	Rf2331	NAD	NAD	NAD
	Rf2332	NAD	NAD	NAD
	Rf2333	NAD	NAD	NAD
	Rf2334	NAD	NAD	NAD
	Rf2335	NAD	NAD	NAD
	Rf2336	NAD	NAD	NAD
	Rf2337	NAD	NAD	NAD
	Rf2338	Hair thinning with hair regrowth	NAD	NAD
	Rf2339	NAD	NAD	NAD
	Rf2340	NAD	NAD	NAD
G4 20000	Rf2341	NAD	NAD	NAD
	Rf2342	NAD	NAD	NAD
	Rf2343	NAD	NAD	NAD
	Rf2344	NAD	NAD	NAD
	Rf2345	Hair thinning with hair regrowth	NAD	NAD
	Rf2346	NAD	NAD	NAD
	Rf2347	NAD	NAD	NAD
	Rf2348	NAD	NAD	NAD
	Rf2349	NAD	NAD	NAD
	Rf2350	NAD	NAD	NAD

NAD: No Abnormality Detected

Note: Veterinary and ophthalmological examinations carried out during acclimatization period for all animals did not reveal any abnormalities.

APPENDIX 2

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL VETERINARY AND OPHTHALMOLOGICAL EXAMINATIONS, CLINICAL SIGNS AND PRE-TERMINAL DEATHS - FEMALES

Group No. Dose (mg/kg Bwt/day)	Rat No.	Veterinary examination & clinical signs	Clinical examination	Ophthalmological findings End of treatment period
G1	Rf2351	NAD	NAD	NAD
0	Rf2352	Hair thinning with hair regrowth	NAD	NAD
	Rf2353	Hair thinning with hair regrowth	NAD	NAD
	Rf2354	Hair thinning with hair regrowth	NAD	NAD
	Rf2355	Hair thinning with hair regrowth	NAD	NAD
	Rf2356	Hair thinning with hair regrowth	NAD	NAD
	Rf2357	Hair thinning with hair regrowth	NAD	NAD
	Rf2358	Hair thinning with hair regrowth	NAD	NAD
	Rf2359	Hair thinning with hair regrowth, Skin injury	NAD	NAD
	Rf2360	NAD	NAD	NAD
G2	Rf2361	NAD	NAD	NAD
2000	Rf2362	Hair thinning with hair regrowth, Skin injury	NAD	NAD
	Rf2363	NAD	NAD	NAD
	Rf2364	NAD	NAD	NAD
	Rf2365	Hair thinning with hair regrowth	NAD	NAD
	Rf2366	NAD	NAD	NAD
	Rf2367	NAD	NAD	NAD
	Rf2368	NAD	NAD	NAD
	Rf2369	NAD	NAD	NAD
	Rf2370	NAD	NAD	NAD

NAD: No Abnormality Detected

Note: Veterinary and ophthalmological examinations carried out during acclimatization period for all animals did not reveal any abnormalities.

contd.

APPENDIX 2 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL VETERINARY AND OPHTHALMOLOGICAL EXAMINATIONS, CLINICAL SIGNS AND PRE-TERMINAL DEATHS - FEMALES

Group No. Dose (mg/kg Bwt/day)	Rat No.	Veterinary examination & clinical signs	Clinical examination	Ophthalmological findings End of treatment period
G3 7000	Rf2371	Hair thinning with hair regrowth	NAD	NAD
	Rf2372	NAD	NAD	NAD
	Rf2373	NAD	NAD	NAD
	Rf2374	Hair thinning with hair regrowth	NAD	NAD
	Rf2375	Hair thinning with hair regrowth	NAD	NAD
	Rf2376	NAD	NAD	NAD
	Rf2377	NAD	NAD	NAD
	Rf2378	NAD	NAD	NAD
	Rf2379	Hair thinning with hair regrowth	NAD	NAD
	Rf2380	Hair thinning with hair regrowth	NAD	NAD
G4 20000	Rf2381	NAD	NAD	NAD
	Rf2382	Hair thinning with hair regrowth	NAD	NAD
	Rf2383	NAD	NAD	NAD
	Rf2384	NAD	NAD	NAD
	Rf2385	NAD	NAD	NAD
	Rf2386	Hair thinning with hair regrowth	NAD	NAD
	Rf2387	NAD	NAD	NAD
	Rf2388	Hair thinning with hair regrowth	NAD	NAD
	Rf2389	NAD	NAD	NAD
	Rf2390	NAD	NAD	NAD

NAD: No Abnormality Detected

Note: Veterinary and ophthalmological examinations carried out during acclimatization period for all animals did not reveal any abnormalities.

APPENDIX 3

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - MALES

G.No.	Rat	Home cage observations			Handling observations		
Dose (mg/kg Bwt/day)	No.	Convulsions 1 = Absent 2 = Present	Tremors 1 = Absent 2 = Present	Palpebral closure 1 = Eyelids wide open 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut	Ease of removal from the cage 1 = Very easy 2 = Easy 3 = Moderately difficult 4 = Difficult 5 = Very difficult	Ease of handling animal in hand 1 = No resistance, animal is easy to handle 2 = Slight resistance 3 = Moderate resistance 4 = High resistance	Lacrimation 1 = None 2 = Slight 3 = Severe
G1	Rf2311	1	1	1	1	1	1
0	Rf2312	1	1	1	1	1	1
	Rf2313	1	1	1	1	1	1
	Rf2314	1	1	1	1	1	1
	Rf2315	1	1	1	1	1	1
	Rf2316	1	1	1	1	1	1
	Rf2317	1	1	1	1	1	1
	Rf2318	1	1	1	1	1	1
	Rf2319	1	1	1	1	1	1
	Rf2320	1	1	1	1	1	1
G2	Rf2321	1	1	1	1	1	1
2000	Rf2322	1	1	1	1	1	1
	Rf2323	1	1	1	1	1	1
	Rf2324	1	1	1	1	1	1
	Rf2325	1	1	1	1	1	1
	Rf2326	1	1	1	1	1	1
	Rf2327	1	1	1	1	1	1
	Rf2328	1	1	1	1	1	1
	Rf2329	1	1	1	1	1	1
	Rf2330	1	1	1	1	1	1

contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - MALES

G.No.	Rat	Handling observations contd.						
Dose (mg/kg Bwt/day)	No.	Chromodacryorrhea 1= Absent 2 = Present	Salivation 1= Normal 2 = Slight 3 = Severe	Piloerection 1 = None 2 = Slight 3 = Severe	Palpebral closure 1 = Eyelids wide open 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut	Respiratory character 1 = Normal 2 = Rales 3 = Retching 4 = Dyspnoeic 5 = Gasping	Eye Prominence 1 = Normal 2 = Exophthalmus 3 = Enophthalmus	Muscle tone 1 = Muscle is firm but not hard(normal) 2 = muscle is soft & flabby 3 = Muscle is tense & hard
G1	Rf2311	1	1	1	1	1	1	1
0	Rf2312	1	1	1	1	1	1	1
	Rf2313	1	1	1	1	1	1	1
	Rf2314	1	1	1	1	1	1	1
	Rf2315	1	1	1	1	1	1	1
	Rf2316	1	1	1	1	1	1	1
	Rf2317	1	1	1	1	1	1	1
	Rf2318	1	1	1	1	1	1	1
	Rf2319	1	1	1	1	1	1	1
	Rf2320	1	1	1	1	1	1	1
G2	Rf2321	1	1	1	1	1	1	1
2000	Rf2322	1	1	1	1	1	1	1
	Rf2323	1	1	1	1	1	1	1
	Rf2324	1	1	1	1	1	1	1
	Rf2325	1	1	1	1	1	1	1
	Rf2326	1	1	1	1	1	1	1
	Rf2327	1	1	1	1	1	1	1
	Rf2328	1	1	1	1	1	1	1
	Rf2329	1	1	1	1	1	1	1
	Rf2330	1	1	1	1	1	1	1

contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - MALES

G.No. Dose (mg/kg Bw/day)	Rat No.	Open field observations						
		Mobility 1 = Normal 2 = Moderately impaired 3 = Totally impaired locomotion impossible	Backing (counts)	Grooming (counts)	Gait 1 = Normal 2 = Walks on tiptoes 3 = Body drags 4 = Hindlimbs splayed 5 = Hunched body 6 = Ataxia	Convulsions 1 = Absent 2 = Present	Tremors 1 = Absent 2 = Present	Arousal 1 = Very low 2 = Low 3 = Normal 4 = Moderately high 5 = Very high
G1	Rf2311	1	0	0	1	1	1	3
0	Rf2312	1	0	0	1	1	1	3
	Rf2313	1	0	0	1	1	1	3
	Rf2314	1	0	0	1	1	1	3
	Rf2315	1	0	0	1	1	1	3
	Rf2316	1	0	0	1	1	1	3
	Rf2317	1	0	0	1	1	1	3
	Rf2318	1	0	0	1	1	1	3
	Rf2319	1	0	0	1	1	1	3
	Rf2320	1	0	0	1	1	1	3
G2	Rf2321	1	0	0	1	1	1	3
2000	Rf2322	1	0	0	1	1	1	3
	Rf2323	1	0	0	1	1	1	3
	Rf2324	1	0	0	1	1	1	3
	Rf2325	1	0	0	1	1	1	3
	Rf2326	1	0	0	1	1	1	3
	Rf2327	1	0	0	1	1	1	3
	Rf2328	1	0	0	1	1	1	3
	Rf2329	1	0	0	1	1	1	3
	Rf2330	1	0	0	1	1	1	3

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - MALES

G.No.	Rat	Sensory observations					
Dose (mg/kg Bwt/day)	No.	Startle response 1 = No reaction 2 = Normal reaction 3 = Exaggerated reaction	Touch response 1 = No reaction 2 = Animal slowly turned, walked away 3 = More energetic response than (2) 4 = Freezes, actual muscle contraction 5 = Bizarre reaction	Pupil response 1 = No pupil response 2 = Pupil response present	Response to Nociceptive stimuli 1 = No reaction 2 = Animal turned or walked away 3 = More energetic response than (2) 4 = Freezes, actual muscle contraction 5 = Bizarre reaction	Righting reflex 1 = Present, 2 = Slow, 3 = Absent On back	 Dropped
G1	Rf2311	2	2	2	2	1	1
0	Rf2312	2	2	2	2	1	1
	Rf2313	2	2	2	2	1	1
	Rf2314	2	2	2	2	1	1
	Rf2315	2	2	2	2	1	1
	Rf2316	2	2	2	2	1	1
	Rf2317	2	2	2	2	1	1
	Rf2318	2	2	2	2	1	1
	Rf2319	2	2	2	2	1	1
	Rf2320	2	2	2	2	1	1
G2	Rf2321	2	2	2	2	1	1
2000	Rf2322	2	2	2	2	1	1
	Rf2323	2	2	2	2	1	1
	Rf2324	2	2	2	2	1	1
	Rf2325	2	2	2	2	1	1
	Rf2326	2	2	2	2	1	1
	Rf2327	2	2	2	2	1	1
	Rf2328	2	2	2	2	1	1
	Rf2329	2	2	2	2	1	1
	Rf2330	2	2	2	2	1	1

contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - MALES

G.No. Dose (mg/kg Bwt/day)	Rat No.	Physiological observation		Neuromuscular observations								
		Body temperature (°C)	Motor activity score	Hind limb foot splay (cms)			Grip strength (g)					
							Fore limbs			Hind limbs		
				R1	R2	R3	R1	R2	R3	R1	R2	R3
G1	Rf2311	36.8	723	9.0	9.0	8.2	1053	1104	724	633	528	609
0	Rf2312	37.8	652	8.4	8.3	8.5	1157	1008	963	609	538	612
	Rf2313	37.1	613	8.0	7.1	7.0	1049	1063	986	572	562	580
	Rf2314	36.7	828	6.5	6.2	6.4	1124	819	1112	734	619	588
	Rf2315	36.7	730	6.5	7.1	8.3	890	992	1102	609	633	599
	Rf2316	36.1	642	8.0	6.3	6.7	1106	1090	940	587	620	657
	Rf2317	36.2	507	7.1	7.0	6.7	1061	1143	914	659	649	588
	Rf2318	35.8	780	6.5	6.2	6.1	990	980	926	639	580	702
	Rf2319	35.9	753	7.2	7.5	7.4	997	895	1102	712	678	607
	Rf2320	36.4	698	6.0	6.5	5.5	1130	1036	942	606	712	658
G2	Rf2321	36.2	814	5.6	8.7	8.9	1087	1103	1129	594	622	652
2000	Rf2322	35.9	546	5.7	6.5	7.5	979	1008	919	587	684	624
	Rf2323	36.5	683	5.3	4.2	5.5	1058	1117	991	621	554	560
	Rf2324	36.1	485	5.4	7.2	4.8	959	1091	919	526	644	705
	Rf2325	37.6	728	6.2	8.5	7.3	1054	967	819	584	671	641
	Rf2326	36.7	550	7.2	9.2	8.2	1071	959	1008	589	600	617
	Rf2327	35.9	620	5.7	6.0	5.8	851	904	1102	655	631	602
	Rf2328	36.6	680	6.5	6.7	7.0	907	1032	1042	611	547	643
	Rf2329	38.3	579	6.5	7.1	7.3	896	999	1037	551	622	670
	Rf2330	38.0	710	7.0	6.5	7.4	1072	948	1034	540	635	565

R: Reading

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - MALES

G.No.	Rat	Home cage observations			Handling observations		
Dose (mg/kg Bwt/day)	No.	Convulsions 1 = Absent 2 = Present	Tremors 1 = Absent 2 = Present	Palpebral closure 1 = Eyelids wide open 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut	Ease of removal from the cage 1 = Very easy 2 = Easy 3 = Moderately difficult 4 = Difficult 5 = Very difficult	Ease of handling animal in hand 1 = No resistance, animal is easy to handle 2 = Slight resistance 3 = Moderate resistance 4 = High resistance	Lacrimation 1 = None 2 = Slight 3 = Severe
G3	Rf2331	1	1	1	1	1	1
7000	Rf2332	1	1	1	1	1	1
	Rf2333	1	1	1	1	1	1
	Rf2334	1	1	1	1	1	1
	Rf2335	1	1	1	1	1	1
	Rf2336	1	1	1	1	1	1
	Rf2337	1	1	1	1	1	1
	Rf2338	1	1	1	1	1	1
	Rf2339	1	1	1	1	1	1
	Rf2340	1	1	1	1	1	1
G4	Rf2341	1	1	1	1	1	1
20000	Rf2342	1	1	1	1	1	1
	Rf2343	1	1	1	1	1	1
	Rf2344	1	1	1	1	1	1
	Rf2345	1	1	1	1	1	1
	Rf2346	1	1	1	1	1	1
	Rf2347	1	1	1	1	1	1
	Rf2348	1	1	1	1	1	1
	Rf2349	1	1	1	1	1	1
	Rf2350	1	1	1	1	1	1

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - MALES

G.No. Dose (mg/kg Bwt/day)	Rat No.	Handling observations contd.						
		Chromodacryorrhea 1= Absent 2 = Present	Salivation 1= Normal 2 = Slight 3 = Severe	Piloerection 1 = None 2 = Slight 3 = Severe	Palpebral closure 1 = Eyelids wide open 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut	Respiratory character 1 = Normal 2 = Rales 3 = Retching 4 = Dyspnoeic 5 = Gasping	Eye Prominence 1 = Normal 2 = Exophthalmus 3 = Enophthalmus	Muscle tone 1 = Muscle is firm but not hard(normal) 2 = muscle is soft & flabby 3 = Muscle is tense & hard
G3	Rf2331	1	1	1	1	1	1	1
7000	Rf2332	1	1	1	1	1	1	1
	Rf2333	1	1	1	1	1	1	1
	Rf2334	1	1	1	1	1	1	1
	Rf2335	1	1	1	1	1	1	1
	Rf2336	1	1	1	1	1	1	1
	Rf2337	1	1	1	1	1	1	1
	Rf2338	1	1	1	1	1	1	1
	Rf2339	1	1	1	1	1	1	1
	Rf2340	1	1	1	1	1	1	1
G4	Rf2341	1	1	1	1	1	1	1
20000	Rf2342	1	1	1	1	1	1	1
	Rf2343	1	1	1	1	1	1	1
	Rf2344	1	1	1	1	1	1	1
	Rf2345	1	1	1	1	1	1	1
	Rf2346	1	1	1	1	1	1	1
	Rf2347	1	1	1	1	1	1	1
	Rf2348	1	1	1	1	1	1	1
	Rf2349	1	1	1	1	1	1	1
	Rf2350	1	1	1	1	1	1	1

contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - MALES

G.No.	Rat	Open field observations						
Dose (mg/kg Bwt/day)	No.	Mobility 1 = Normal 2 = Moderately impaired 3 = Totally impaired locomotion impossible	Backing (counts)	Grooming (counts)	Gait 1 = Normal 2 = Walks on tiptoes 3 = Body drags 4 = Hindlimbs splayed 5 = Hunched body 6 = Ataxia	Convulsions 1 = Absent 2 = Present	Tremors 1 = Absent 2 = Present	Arousal 1 = Very low 2 = Low 3 = Normal 4 = Moderately high 5 = Very high
G3	Rf2331	1	0	0	1	1	1	3
7000	Rf2332	1	0	0	1	1	1	3
	Rf2333	1	0	0	1	1	1	3
	Rf2334	1	0	0	1	1	1	3
	Rf2335	1	0	0	1	1	1	3
	Rf2336	1	0	0	1	1	1	3
	Rf2337	1	0	0	1	1	1	3
	Rf2338	1	0	0	1	1	1	3
	Rf2339	1	0	0	1	1	1	3
	Rf2340	1	0	0	1	1	1	3
G4	Rf2341	1	0	0	1	1	1	3
20000	Rf2342	1	0	0	1	1	1	3
	Rf2343	1	0	0	1	1	1	3
	Rf2344	1	0	0	1	1	1	3
	Rf2345	1	0	0	1	1	1	3
	Rf2346	1	0	0	1	1	1	3
	Rf2347	1	0	0	1	1	1	3
	Rf2348	1	0	0	1	1	1	3
	Rf2349	1	0	0	1	1	1	3
	Rf2350	1	0	0	1	1	1	3

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - MALES

G.No.	Rat	Sensory observations					
Dose	No.	Startle response	Touch response	Pupil response	Response to Nociceptive stimuli	Righting reflex	
(mg/kg Bwt/day)		1 = No reaction	1 = No reaction	1 = No pupil response	1 = No reaction	1 = Present,	
		2 = Normal reaction	2 = Animal slowly turned, walked away	2 = Pupil response present	2 = Animal turned or walked away	2 = Slow, 3 = Absent	
		3 = Exaggerated reaction	3 = More energetic response than (2)		3 = More energetic response than (2)	On back	Dropped
			4 = Freezes, actual muscle contraction		4 = Freezes, actual muscle contraction		
			5 = Bizarre reaction		5 = Bizarre reaction		
G3	Rf2331	2	2	2	2	1	1
7000	Rf2332	2	2	2	2	1	1
	Rf2333	2	2	2	2	1	1
	Rf2334	2	2	2	2	1	1
	Rf2335	2	2	2	2	1	1
	Rf2336	2	2	2	2	1	1
	Rf2337	2	2	2	2	1	1
	Rf2338	2	2	2	2	1	1
	Rf2339	2	2	2	2	1	1
	Rf2340	2	2	2	2	1	1
G4	Rf2341	2	2	2	2	1	1
20000	Rf2342	2	2	2	2	1	1
	Rf2343	2	2	2	2	1	1
	Rf2344	2	2	2	2	1	1
	Rf2345	2	2	2	2	1	1
	Rf2346	2	2	2	2	1	1
	Rf2347	2	2	2	2	1	1
	Rf2348	2	2	2	2	1	1
	Rf2349	2	2	2	2	1	1
	Rf2350	2	2	2	2	1	1

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - MALES

G.No. Dose (mg/kg Bwt/day)	Rat No.	Physiological observation		Neuromuscular observations								
		Body temperature (°C)	Motor activity score	Hind limb foot splay (cms)			Grip strength (g)					
							Fore limbs			Hind limbs		
				R1	R2	R3	R1	R2	R3	R1	R2	R3
G3	Rf2331	36.3	443	6.0	5.0	4.5	894	963	1003	541	604	579
7000	Rf2332	35.8	738	6.0	7.0	6.0	982	1156	1065	685	621	588
	Rf2333	36.7	711	5.0	6.0	5.5	913	934	1019	535	680	570
	Rf2334	36.7	682	5.0	6.1	7.2	878	1045	1069	644	586	704
	Rf2335	35.9	578	8.5	8.7	9.0	1122	804	1128	604	701	722
	Rf2336	36.7	824	5.6	6.0	4.7	1112	993	1043	700	681	590
	Rf2337	36.2	666	5.0	5.3	7.4	1049	1052	1115	640	556	715
	Rf2338	36.3	695	5.1	6.3	6.9	1105	821	800	513	623	684
	Rf2339	37.1	827	7.5	6.5	6.3	985	1013	1019	517	741	690
	Rf2340	38.0	658	6.5	6.5	7.0	1025	942	894	778	600	564
G4	Rf2341	38.1	859	6.1	7.1	8.2	1091	1055	843	722	668	622
20000	Rf2342	36.3	604	7.0	6.5	5.5	949	1131	937	601	642	779
	Rf2343	37.2	640	6.0	7.5	6.5	1010	915	849	739	664	732
	Rf2344	37.6	560	5.7	5.5	6.8	953	1024	986	501	546	658
	Rf2345	37.6	822	5.5	7.3	5.6	1078	906	930	594	528	587
	Rf2346	36.5	793	6.3	6.2	6.2	1124	1059	853	707	577	596
	Rf2347	36.7	559	5.2	5.2	5.0	971	1107	1051	577	699	796
	Rf2348	37.2	604	5.4	6.2	6.4	937	963	982	610	553	797
	Rf2349	36.7	693	6.5	6.5	7.3	1010	1097	1002	566	551	552
	Rf2350	36.6	514	6.5	6.0	6.1	1039	1106	1136	597	693	813

R: Reading

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APPENDIX 4

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - FEMALES

G.No.	Rat	Home cage observations			Handling observations		
Dose (mg/kg Bwt/day)	No.	Convulsions 1 = Absent 2 = Present	Tremors 1 = Absent 2 = Present	Palpebral closure 1 = Eyelids wide open 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut	Ease of removal from the cage 1 = Very easy 2 = Easy 3 = Moderately difficult 4 = Difficult 5 = Very difficult	Ease of handling animal in hand 1 = No resistance, animal is easy to handle 2 = Slight resistance 3 = Moderate resistance 4 = High resistance	Lacrimation 1 = None 2 = Slight 3 = Severe
G1	Rf2351	1	1	1	1	1	1
0	Rf2352	1	1	1	1	1	1
	Rf2353	1	1	1	1	1	1
	Rf2354	1	1	1	1	1	1
	Rf2355	1	1	1	1	1	1
	Rf2356	1	1	1	1	1	1
	Rf2357	1	1	1	1	1	1
	Rf2358	1	1	1	1	1	1
	Rf2359	1	1	1	1	1	1
	Rf2360	1	1	1	1	1	1
G2	Rf2361	1	1	1	1	1	1
2000	Rf2362	1	1	1	1	1	1
	Rf2363	1	1	1	1	1	1
	Rf2364	1	1	1	1	1	1
	Rf2365	1	1	1	1	1	1
	Rf2366	1	1	1	1	1	1
	Rf2367	1	1	1	1	1	1
	Rf2368	1	1	1	1	1	1
	Rf2369	1	1	1	1	1	1
	Rf2370	1	1	1	1	1	1

contd.

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APPENDIX 4 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - FEMALES

G.No. Dose (mg/kg Bwt/day)	Rat No.	Handling observations contd.						
		Chromodacryorrhea 1= Absent 2 = Present	Salivation 1= Normal 2 = Slight 3 = Severe	Piloerection 1 = None 2 = Slight 3 = Severe	Palpebral closure 1 = Eyelids wide open 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut	Respiratory character 1 = Normal 2 = Rales 3 = Retching 4 = Dyspnoeic 5 = Gasping	Eye Prominence 1 = Normal 2 = Exophthalmus 3 = Enophthalmus	Muscle tone 1 = Muscle is firm but not hard(normal) 2 = muscle is soft & flabby 3 = Muscle is tense & hard
G1	Rf2351	1	1	1	1	1	1	1
0	Rf2352	1	1	1	1	1	1	1
	Rf2353	1	1	1	1	1	1	1
	Rf2354	1	1	1	1	1	1	1
	Rf2355	1	1	1	1	1	1	1
	Rf2356	1	1	1	1	1	1	1
	Rf2357	1	1	1	1	1	1	1
	Rf2358	1	1	1	1	1	1	1
	Rf2359	1	1	1	1	1	1	1
	Rf2360	1	1	1	1	1	1	1
G2	Rf2361	1	1	1	1	1	1	1
2000	Rf2362	1	1	1	1	1	1	1
	Rf2363	1	1	1	1	1	1	1
	Rf2364	1	1	1	1	1	1	1
	Rf2365	1	1	1	1	1	1	1
	Rf2366	1	1	1	1	1	1	1
	Rf2367	1	1	1	1	1	1	1
	Rf2368	1	1	1	1	1	1	1
	Rf2369	1	1	1	1	1	1	1
	Rf2370	1	1	1	1	1	1	1

contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - FEMALES

G.No.	Rat	Open field observations						
Dose (mg/kg Bwt/day)	No.	Mobility 1 = Normal 2 = Moderately impaired 3 = Totally impaired locomotion impossible	Backing (counts)	Grooming (counts)	Gait 1 = Normal 2 = Walks on tiptoes 3 = Body drags 4 = Hindlimbs splayed 5 = Hunched body 6 = Ataxia	Convulsions 1 = Absent 2 = Present	Tremors 1 = Absent 2 = Present	Arousal 1 = Very low 2 = Low 3 = Normal 4 = Moderately high 5 = Very high
G1	Rf2351	1	0	0	1	1	1	3
0	Rf2352	1	0	0	1	1	1	3
	Rf2353	1	0	0	1	1	1	3
	Rf2354	1	0	0	1	1	1	3
	Rf2355	1	0	0	1	1	1	3
	Rf2356	1	0	0	1	1	1	3
	Rf2357	1	0	0	1	1	1	3
	Rf2358	1	0	0	1	1	1	3
	Rf2359	1	0	0	1	1	1	3
	Rf2360	1	0	0	1	1	1	3
G2	Rf2361	1	0	0	1	1	1	3
2000	Rf2362	1	0	0	1	1	1	3
	Rf2363	1	0	0	1	1	1	3
	Rf2364	1	0	0	1	1	1	3
	Rf2365	1	0	0	1	1	1	3
	Rf2366	1	0	0	1	1	1	3
	Rf2367	1	0	0	1	1	1	3
	Rf2368	1	0	0	1	1	1	3
	Rf2369	1	0	0	1	1	1	3
	Rf2370	1	0	0	1	1	1	3

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - FEMALES

G.No. Dose (mg/kg Bwt/day)	Rat No.	Sensory observations					
		Startle response 1 = No reaction 2 = Normal reaction 3 = Exaggerated reaction	Touch response 1 = No reaction 2 = Animal slowly turned, walked away 3 = More energetic response than (2) 4 = Freezes, actual muscle contraction 5 = Bizarre reaction	Pupil response 1 = No pupil response 2 = Pupil response present	Response to Nociceptive stimuli 1 = No reaction 2 = Animal turned or walked away 3 = More energetic response than (2) 4 = Freezes, actual muscle contraction 5 = Bizarre reaction	Righting reflex 1 = Present, 2 = Slow, 3 = Absent On back	Dropped
G1	Rf2351	2	2	2	2	1	1
0	Rf2352	2	2	2	2	1	1
	Rf2353	2	2	2	2	1	1
	Rf2354	2	2	2	2	1	1
	Rf2355	2	2	2	2	1	1
	Rf2356	2	2	2	2	1	1
	Rf2357	2	2	2	2	1	1
	Rf2358	2	2	2	2	1	1
	Rf2359	2	2	2	2	1	1
	Rf2360	2	2	2	2	1	1
G2	Rf2361	2	2	2	2	1	1
2000	Rf2362	2	2	2	2	1	1
	Rf2363	2	2	2	2	1	1
	Rf2364	2	2	2	2	1	1
	Rf2365	2	2	2	2	1	1
	Rf2366	2	2	2	2	1	1
	Rf2367	2	2	2	2	1	1
	Rf2368	2	2	2	2	1	1
	Rf2369	2	2	2	2	1	1
	Rf2370	2	2	2	2	1	1

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - FEMALES

G.No. Dose (mg/kg Bwt/day)	Rat No.	Physiological observation		Neuromuscular observations								
		Body temperature (°C)	Motor activity score	Hind limb foot splay (cms)			Grip strength (g)					
							Fore limbs			Hind limbs		
				R1	R2	R3	R1	R2	R3	R1	R2	R3
G1	Rf2351	36.5	703	5.5	5.0	5.3	1007	1005	940	576	600	614
0	Rf2352	38.4	732	6.0	5.2	5.4	1142	1088	1102	615	528	629
	Rf2353	37.6	662	5.2	5.2	5.5	964	871	997	635	675	661
	Rf2354	35.8	1045	6.5	5.3	6.0	992	950	1005	582	526	524
	Rf2355	35.9	972	5.7	6.7	7.5	948	1013	950	634	601	658
	Rf2356	36.3	953	5.2	5.2	6.0	1056	918	935	616	711	600
	Rf2357	37.9	854	6.0	6.1	6.6	1060	980	900	589	571	534
	Rf2358	36.9	577	5.0	5.5	6.0	987	966	1093	568	582	600
	Rf2359	38.3	720	5.1	6.0	6.5	1053	919	869	667	540	715
	Rf2360	37.8	825	5.2	6.6	6.3	977	946	1012	540	619	635
G2	Rf2361	37.2	709	6.5	5.7	6.2	1107	1002	879	540	598	693
2000	Rf2362	37.4	739	6.0	6.1	6.5	849	956	1144	597	544	629
	Rf2363	37.6	844	7.5	6.3	6.3	1009	1012	1053	545	661	555
	Rf2364	35.9	719	5.5	5.1	5.0	907	1019	1012	519	564	580
	Rf2365	38.5	575	5.3	4.7	4.7	953	879	1111	584	619	602
	Rf2366	38.1	1179	5.1	5.0	4.9	983	919	1002	652	576	550
	Rf2367	38.1	884	5.1	6.2	6.0	897	1092	1104	550	527	632
	Rf2368	37.8	1091	4.8	5.7	5.8	1012	1105	993	661	735	692
	Rf2369	36.7	400	5.2	6.5	6.1	1034	912	963	699	541	615
	Rf2370	37.3	920	5.6	5.9	6.3	1126	912	978	597	565	653

R: Reading

contd.

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APPENDIX 4 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - FEMALES

G.No.	Rat	Home cage observations			Handling observations		
Dose (mg/kg Bwt/day)	No.	Convulsions 1 = Absent 2 = Present	Tremors 1 = Absent 2 = Present	Palpebral closure 1 = Eyelids wide open 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut	Ease of removal from the cage 1 = Very easy 2 = Easy 3 = Moderately difficult 4 = Difficult 5 = Very difficult	Ease of handling animal in hand 1 = No resistance, animal is easy to handle 2 = Slight resistance 3 = Moderate resistance 4 = High resistance	Lacrimation 1 = None 2 = Slight 3 = Severe
G3	Rf2371	1	1	1	1	1	1
7000	Rf2372	1	1	1	1	1	1
	Rf2373	1	1	1	1	1	1
	Rf2374	1	1	1	1	1	1
	Rf2375	1	1	1	1	1	1
	Rf2376	1	1	1	1	1	1
	Rf2377	1	1	1	1	1	1
	Rf2378	1	1	1	1	1	1
	Rf2379	1	1	1	1	1	1
	Rf2380	1	1	1	1	1	1
G4	Rf2381	1	1	1	1	1	1
20000	Rf2382	1	1	1	1	1	1
	Rf2383	1	1	1	1	1	1
	Rf2384	1	1	1	1	1	1
	Rf2385	1	1	1	1	1	1
	Rf2386	1	1	1	1	1	1
	Rf2387	1	1	1	1	1	1
	Rf2388	1	1	1	1	1	1
	Rf2389	1	1	1	1	1	1
	Rf2390	1	1	1	1	1	1

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - FEMALES

G.No. Dose (mg/kg Bwt/day)	Rat No.	Handling observations contd.						
		Chromodacryorrhea 1= Absent 2 = Present	Salivation 1= Normal 2 = Slight 3 = Severe	Piloerection 1 = None 2 = Slight 3 = Severe	Palpebral closure 1 = Eyelids wide open 2 = Eyelids slightly drooping 3 = Drooping eyelids (half closed) 4 = Eyelids completely shut	Respiratory character 1 = Normal 2 = Rales 3 = Retching 4 = Dyspnoeic 5 = Gasping	Eye Prominence 1 = Normal 2 = Exophthalmus 3 = Enophthalmus	Muscle tone 1 = Muscle is firm but not hard(normal) 2 = muscle is soft & flabby 3 = Muscle is tense & hard
G3	Rf2371	1	1	1	1	1	1	1
7000	Rf2372	1	1	1	1	1	1	1
	Rf2373	1	1	1	1	1	1	1
	Rf2374	1	1	1	1	1	1	1
	Rf2375	1	1	1	1	1	1	1
	Rf2376	1	1	1	1	1	1	1
	Rf2377	1	1	1	1	1	1	1
	Rf2378	1	1	1	1	1	1	1
	Rf2379	1	1	1	1	1	1	1
	Rf2380	1	1	1	1	1	1	1
G4	Rf2381	1	1	1	1	1	1	1
20000	Rf2382	1	1	1	1	1	1	1
	Rf2383	1	1	1	1	1	1	1
	Rf2384	1	1	1	1	1	1	1
	Rf2385	1	1	1	1	1	1	1
	Rf2386	1	1	1	1	1	1	1
	Rf2387	1	1	1	1	1	1	1
	Rf2388	1	1	1	1	1	1	1
	Rf2389	1	1	1	1	1	1	1
	Rf2390	1	1	1	1	1	1	1

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - FEMALES

G.No.	Rat	Open field observations						
Dose (mg/kg Bwt/day)	No.	Mobility 1 = Normal 2 = Moderately impaired 3 = Totally impaired locomotion impossible	Backing (counts)	Grooming (counts)	Gait 1 = Normal 2 = Walks on tiptoes 3 = Body drags 4 = Hindlimbs splayed 5 = Hunched body 6 = Ataxia	Convulsions 1 = Absent 2 = Present	Tremors 1 = Absent 2 = Present	Arousal 1 = Very low 2 = Low 3 = Normal 4 = Moderately high 5 = Very high
G3	Rf2371	1	0	0	1	1	1	3
7000	Rf2372	1	0	0	1	1	1	3
	Rf2373	1	0	0	1	1	1	3
	Rf2374	1	0	0	1	1	1	3
	Rf2375	1	0	0	1	1	1	3
	Rf2376	1	0	0	1	1	1	3
	Rf2377	1	0	0	1	1	1	3
	Rf2378	1	0	0	1	1	1	3
	Rf2379	1	0	0	1	1	1	3
	Rf2380	1	0	0	1	1	1	3
G4	Rf2381	1	0	0	1	1	1	3
20000	Rf2382	1	0	0	1	1	1	3
	Rf2383	1	0	0	1	1	1	3
	Rf2384	1	0	0	1	1	1	3
	Rf2385	1	0	0	1	1	1	3
	Rf2386	1	0	0	1	1	1	3
	Rf2387	1	0	0	1	1	1	3
	Rf2388	1	0	0	1	1	1	3
	Rf2389	1	0	0	1	1	1	3
	Rf2390	1	0	0	1	1	1	3

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - FEMALES

G.No.	Rat	Sensory observations					
Dose	No.	Startle response	Touch response	Pupil response	Response to Nociceptive stimuli	Righting reflex	
(mg/kg Bwt/day)		1 = No reaction	1 = No reaction	1 = No pupil response	1 = No reaction	1 = Present,	
		2 = Normal reaction	2 = Animal slowly turned, walked away	2 = Pupil response present	2 = Animal turned or walked away	2 = Slow, 3 = Absent	
		3 = Exaggerated reaction	3 = More energetic response than (2)		3 = More energetic response than (2)	On back	Dropped
			4 = Freezes, actual muscle contraction		4 = Freezes, actual muscle contraction		
			5 = Bizarre reaction		5 = Bizarre reaction		
G3	Rf2371	2	2	2	2	1	1
7000	Rf2372	2	2	2	2	1	1
	Rf2373	2	2	2	2	1	1
	Rf2374	2	2	2	2	1	1
	Rf2375	2	2	2	2	1	1
	Rf2376	2	2	2	2	1	1
	Rf2377	2	2	2	2	1	1
	Rf2378	2	2	2	2	1	1
	Rf2379	2	2	2	2	1	1
	Rf2380	2	2	2	2	1	1
G4	Rf2381	2	2	2	2	1	1
20000	Rf2382	2	2	2	2	1	1
	Rf2383	2	2	2	2	1	1
	Rf2384	2	2	2	2	1	1
	Rf2385	2	2	2	2	1	1
	Rf2386	2	2	2	2	1	1
	Rf2387	2	2	2	2	1	1
	Rf2388	2	2	2	2	1	1
	Rf2389	2	2	2	2	1	1
	Rf2390	2	2	2	2	1	1

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

FUNCTIONAL OBSERVATION BATTERY - FEMALES

G.No. Dose (mg/kg Bwt/day)	Rat No.	Physiological observation		Neuromuscular observations								
		Body temperature (°C)	Motor activity score	Hind limb foot splay (cms)			Grip strength (g)					
							Fore limbs			Hind limbs		
				R1	R2	R3	R1	R2	R3	R1	R2	R3
G3	Rf2371	38.3	844	4.5	4.5	4.5	1089	919	1101	610	650	651
7000	Rf2372	37.6	840	5.0	4.5	5.5	1078	942	1126	547	596	600
	Rf2373	37.8	732	5.5	5.5	6.9	886	1002	983	705	653	588
	Rf2374	38.4	1059	4.7	5.7	4.8	963	958	966	651	605	591
	Rf2375	37.3	612	5.0	6.0	4.3	900	1071	1104	631	601	663
	Rf2376	37.6	884	5.1	6.3	5.4	996	1084	1065	679	619	643
	Rf2377	37.7	1066	5.5	4.7	5.6	908	981	1012	517	527	533
	Rf2378	38.5	988	5.1	5.3	6.1	946	919	1086	577	546	574
	Rf2379	37.3	889	5.2	5.5	6.0	1128	994	926	586	640	587
	Rf2380	37.6	600	4.4	4.4	4.8	968	1093	948	657	617	517
G4	Rf2381	37.1	821	4.5	4.0	4.2	1038	1087	990	576	591	546
20000	Rf2382	37.6	1132	5.0	4.6	5.4	944	1029	907	573	545	633
	Rf2383	37.5	909	5.5	5.0	5.5	1014	1102	1074	539	506	520
	Rf2384	37.6	641	4.5	5.5	6.0	1000	992	1082	693	591	566
	Rf2385	37.8	1014	5.6	7.4	6.4	1081	1097	949	583	731	666
	Rf2386	37.9	618	6.6	5.6	6.0	931	1091	902	551	577	521
	Rf2387	37.8	765	5.3	4.6	5.1	981	1099	937	532	519	590
	Rf2388	38.5	840	4.4	4.2	4.3	1049	1052	1086	573	590	517
	Rf2389	38.1	879	5.5	5.0	4.7	1029	1023	884	751	728	578
	Rf2390	37.7	774	5.0	5.2	4.6	987	962	957	611	677	571

R: Reading

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APPENDIX 5

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL WEEKLY BODY WEIGHTS (g) - MALES

G. No. Dose (mg/kg Bwt/day)	Rat No.	Weeks													
		$	1	2	3	4	5	6	7	8	9	10	11	12	13
G1	Rf2311	193	258	305	348	374	398	428	452	470	488	502	512	512	526
0	Rf2312	188	237	278	311	331	350	365	384	400	413	419	432	437	440
	Rf2313	187	250	306	343	376	399	430	450	469	491	509	520	533	534
	Rf2314	204	258	304	331	358	374	403	406	416	422	421	430	438	451
	Rf2315	207	262	314	353	379	399	421	432	447	457	457	466	479	484
	Rf2316	196	246	291	329	354	381	402	419	434	451	456	461	471	478
	Rf2317	200	250	289	320	340	364	383	401	416	423	425	432	429	439
	Rf2318	187	247	293	333	364	398	424	438	457	472	487	488	504	513
	Rf2319	186	235	286	322	357	371	393	409	422	439	445	455	459	472
	Rf2320	188	238	282	320	337	361	381	393	413	426	428	443	451	460
G2	Rf2321	186	240	289	318	349	377	396	408	422	427	429	444	446	458
2000	Rf2322	184	240	293	323	353	374	399	409	441	450	453	468	475	490
	Rf2323	190	244	291	314	341	361	384	408	418	430	439	452	460	475
	Rf2324	193	249	307	343	369	396	424	436	456	467	470	478	482	493
	Rf2325	188	253	294	318	344	366	382	397	410	421	425	428	437	454
	Rf2326	208	259	302	334	369	387	404	435	444	454	455	453	461	473
	Rf2327	205	271	321	361	406	426	457	473	495	505	519	533	540	548
	Rf2328	198	251	286	311	342	357	376	392	401	421	403	414	424	434
	Rf2329	203	251	294	320	334	361	387	402	408	413	421	423	433	442
	Rf2330	188	244	291	323	360	383	406	424	439	448	461	464	473	480

$: Day 1 of treatment period

contd.

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APPENDIX 5 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL WEEKLY BODY WEIGHTS (g) - MALES

G. No. Dose (mg/kg Bwt/day)	Rat No.	Weeks													
		$	1	2	3	4	5	6	7	8	9	10	11	12	13
G3	Rf2331	193	256	304	339	376	406	431	452	474	479	483	486	499	515
7000	Rf2332	190	257	312	353	387	414	443	464	484	492	508	509	528	535
	Rf2333	158	214	232	287	281	300	313	340	360	380	397	395	397	400
	Rf2334	201	248	282	310	343	365	385	399	416	426	437	435	441	449
	Rf2335	199	259	326	352	389	420	441	476	493	512	527	548	553	566
	Rf2336	192	258	305	341	377	402	429	447	462	478	487	496	501	517
	Rf2337	185	246	298	332	365	396	419	446	460	479	487	490	503	520
	Rf2338	191	248	295	336	368	385	411	421	439	444	447	460	463	472
	Rf2339	205	263	313	343	375	393	422	437	454	461	473	485	490	503
	Rf2340	201	261	309	345	381	404	423	440	459	475	488	501	505	517
G4	Rf2341	203	268	325	361	384	405	432	455	468	482	482	491	493	506
20000	Rf2342	198	246	288	316	345	362	381	394	403	411	413	415	420	429
	Rf2343	214	279	335	373	412	441	465	489	507	520	539	540	551	560
	Rf2344	177	228	265	294	324	343	364	382	388	398	403	407	412	428
	Rf2345	190	248	297	331	360	384	407	426	442	444	455	463	480	493
	Rf2346	195	261	307	348	382	398	427	448	458	461	473	488	499	498
	Rf2347	198	259	308	348	372	392	415	426	435	450	455	453	460	466
	Rf2348	195	247	297	328	354	383	398	416	421	434	445	446	451	462
	Rf2349	185	240	279	311	346	365	383	402	413	419	430	441	452	456
	Rf2350	208	260	303	340	376	392	424	441	445	454	458	457	465	473

$: Day 1 of treatment period

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APPENDIX 6

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL CUMULATIVE WEEKLY NET BODY WEIGHT GAINS (g) - MALES

G. No. Dose (mg/kg Bwt/day)	Rat No.	1	2	3	4	5	6	7	8	9	10	11	12	13
G1	Rf2311	65	112	155	181	205	235	259	277	295	309	319	319	333
0	Rf2312	49	90	123	143	162	177	196	212	225	231	244	249	252
	Rf2313	63	119	156	189	212	243	263	282	304	322	333	346	347
	Rf2314	54	100	127	154	170	199	202	212	218	217	226	234	247
	Rf2315	55	107	146	172	192	214	225	240	250	250	259	272	277
	Rf2316	50	95	133	158	185	206	223	238	255	260	265	275	282
	Rf2317	50	89	120	140	164	183	201	216	223	225	232	229	239
	Rf2318	60	106	146	177	211	237	251	270	285	300	301	317	326
	Rf2319	49	100	136	171	185	207	223	236	253	259	269	273	286
	Rf2320	50	94	132	149	173	193	205	225	238	240	255	263	272
G2	Rf2321	54	103	132	163	191	210	222	236	241	243	258	260	272
2000	Rf2322	56	109	139	169	190	215	225	257	266	269	284	291	306
	Rf2323	54	101	124	151	171	194	218	228	240	249	262	270	285
	Rf2324	56	114	150	176	203	231	243	263	274	277	285	289	300
	Rf2325	65	106	130	156	178	194	209	222	233	237	240	249	266
	Rf2326	51	94	126	161	179	196	227	236	246	247	245	253	265
	Rf2327	66	116	156	201	221	252	268	290	300	314	328	335	343
	Rf2328	53	88	113	144	159	178	194	203	223	205	216	226	236
	Rf2329	48	91	117	131	158	184	199	205	210	218	220	230	239
	Rf2330	56	103	135	172	195	218	236	251	260	273	276	285	292

contd.

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APPENDIX 6 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergilius niger* (GEP44) IN WISTAR RATS

INDIVIDUAL CUMULATIVE WEEKLY NET BODY WEIGHT GAINS (g) - MALES

G. No. Dose (mg/kg Bwt/day)	Rat No.	1	2	3	4	5	6	7	8	9	10	11	12	13
G3	Rf2331	63	111	146	183	213	238	259	281	286	290	293	306	322
7000	Rf2332	67	122	163	197	224	253	274	294	302	318	319	338	345
	Rf2333	56	74	129	123	142	155	182	202	222	239	237	239	242
	Rf2334	47	81	109	142	164	184	198	215	225	236	234	240	248
	Rf2335	60	127	153	190	221	242	277	294	313	326	349	354	367
	Rf2336	66	113	149	185	210	237	255	270	286	295	304	309	325
	Rf2337	61	113	147	180	211	234	261	275	294	302	305	318	335
	Rf2338	57	104	145	177	194	220	230	248	253	256	269	272	281
	Rf2339	58	108	138	170	188	217	232	249	256	268	280	285	298
	Rf2340	60	108	144	180	203	222	239	258	274	287	300	304	316
G4	Rf2341	65	122	158	181	202	229	252	265	279	279	288	290	303
20000	Rf2342	48	90	118	147	164	183	196	205	213	215	217	222	231
	Rf2343	65	121	159	198	227	251	275	293	306	325	326	337	346
	Rf2344	51	88	117	147	166	187	205	211	221	226	230	235	251
	Rf2345	58	107	141	170	194	217	236	252	254	265	273	290	303
	Rf2346	66	112	153	187	203	232	253	263	266	278	293	304	303
	Rf2347	61	110	150	174	194	217	228	237	252	257	255	262	268
	Rf2348	52	102	133	159	188	203	221	226	239	250	251	256	267
	Rf2349	55	94	126	161	180	198	217	228	234	245	256	267	271
	Rf2350	52	95	132	168	184	216	233	237	246	250	249	257	265

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APPENDIX 7

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL WEEKLY BODY WEIGHTS (g) - FEMALES

G. No. Dose (mg/kg Bwt/day)	Rat No.	Weeks													
		$	1	2	3	4	5	6	7	8	9	10	11	12	13
G1	Rf2351	167	178	205	218	228	235	242	253	257	262	266	269	273	271
0	Rf2352	162	178	202	212	221	221	231	244	245	244	256	258	260	261
	Rf2353	153	160	182	197	197	215	221	227	243	233	238	241	248	250
	Rf2354	153	175	189	197	204	217	227	229	230	244	246	245	240	249
	Rf2355	159	180	199	209	215	222	221	236	234	234	239	248	249	250
	Rf2356	151	161	181	189	197	195	206	213	216	214	222	223	227	231
	Rf2357	154	173	191	206	210	215	225	232	228	234	242	248	245	248
	Rf2358	165	181	189	207	217	229	229	239	239	242	243	248	256	247
	Rf2359	148	178	197	211	221	231	231	240	243	246	253	255	258	250
	Rf2360	156	177	191	197	210	210	223	221	232	231	234	236	236	232
G2	Rf2361	161	189	223	216	231	242	250	247	255	265	264	264	263	266
2000	Rf2362	156	180	194	200	218	227	231	231	238	246	252	253	257	255
	Rf2363	158	172	189	203	211	232	229	246	247	246	258	260	262	262
	Rf2364	149	178	195	213	218	231	241	248	247	253	256	264	268	276
	Rf2365	147	155	169	171	181	181	197	199	200	208	213	215	214	216
	Rf2366	166	178	197	205	217	216	227	236	242	239	248	251	254	262
	Rf2367	160	184	203	221	227	243	259	263	266	275	284	285	281	292
	Rf2368	154	181	199	211	221	226	239	244	249	249	265	260	261	264
	Rf2369	166	185	198	212	220	229	232	241	251	248	251	261	269	264
	Rf2370	147	173	181	193	204	206	215	224	218	231	228	232	232	233

$: Day 1 of treatment period

contd.

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APPENDIX 7 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL WEEKLY BODY WEIGHTS (g) - FEMALES

G. No. Dose (mg/kg Bwt/day)	Rat No.	Weeks													
		$	1	2	3	4	5	6	7	8	9	10	11	12	13
G3	Rf2371	146	166	172	188	203	206	217	223	225	222	231	235	236	242
7000	Rf2372	154	171	186	190	210	220	224	227	231	236	235	241	238	238
	Rf2373	166	187	198	209	227	238	247	242	255	261	260	264	273	271
	Rf2374	141	156	169	174	187	199	203	203	212	215	216	215	219	221
	Rf2375	163	188	200	217	232	243	239	250	253	257	264	262	271	270
	Rf2376	160	177	191	200	213	220	227	232	238	240	250	250	251	255
	Rf2377	143	175	200	203	210	224	231	233	238	236	245	246	255	250
	Rf2378	155	164	173	190	195	207	206	219	221	222	228	231	237	235
	Rf2379	155	175	187	205	210	228	236	242	244	241	251	249	248	251
	Rf2380	164	189	195	215	234	240	241	236	251	252	256	258	263	258
G4	Rf2381	168	202	218	230	245	250	267	267	277	280	280	288	290	289
20000	Rf2382	161	181	196	202	217	233	238	236	244	252	255	256	264	261
	Rf2383	167	191	209	231	250	255	262	273	280	287	292	302	303	304
	Rf2384	151	178	196	209	229	239	252	245	257	261	262	267	277	275
	Rf2385	158	191	209	228	235	247	257	265	263	274	282	279	281	276
	Rf2386	156	180	195	209	225	240	242	247	257	259	260	255	261	259
	Rf2387	150	168	181	196	206	209	211	218	224	227	232	227	227	230
	Rf2388	145	153	194	205	214	220	232	242	238	241	241	246	247	256
	Rf2389	162	180	196	210	231	238	243	243	253	259	261	257	264	266
	Rf2390	151	171	188	205	212	230	241	246	257	257	263	259	259	261

$: Day 1 of treatment period

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APPENDIX 8

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL CUMULATIVE WEEKLY NET BODY WEIGHT GAINS (g) - FEMALES

G. No. Dose (mg/kg Bwt/day)	Rat No.	1	2	3	4	5	6	7	8	9	10	11	12	13
G1	Rf2351	11	38	51	61	68	75	86	90	95	99	102	106	104
0	Rf2352	16	40	50	59	59	69	82	83	82	94	96	98	99
	Rf2353	7	29	44	44	62	68	74	90	80	85	88	95	97
	Rf2354	22	36	44	51	64	74	76	77	91	93	92	87	96
	Rf2355	21	40	50	56	63	62	77	75	75	80	89	90	91
	Rf2356	10	30	38	46	44	55	62	55	63	71	72	76	80
	Rf2357	19	37	52	56	61	71	78	74	80	88	94	91	94
	Rf2358	16	24	42	52	64	64	74	74	77	78	83	91	82
	Rf2359	30	49	63	73	83	83	92	95	98	105	107	110	102
	Rf2360	21	35	41	54	54	67	65	76	75	78	80	80	76
G2	Rf2361	28	62	55	70	81	89	86	94	104	103	103	102	105
2000	Rf2362	24	38	44	62	71	75	75	82	90	96	97	101	99
	Rf2363	14	31	45	53	74	71	88	89	88	100	102	104	104
	Rf2364	29	46	64	69	82	92	99	98	104	107	115	119	127
	Rf2365	8	22	24	34	34	50	52	53	61	66	68	67	69
	Rf2366	12	31	39	51	50	61	70	76	73	82	85	88	96
	Rf2367	24	43	61	67	83	99	103	106	115	124	125	121	132
	Rf2368	27	45	57	67	72	85	90	95	95	111	106	107	110
	Rf2369	19	32	46	54	63	66	75	85	82	85	95	103	98
	Rf2370	26	34	46	57	59	68	77	71	84	81	85	85	86

contd.

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APPENDIX 8 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL CUMULATIVE WEEKLY NET BODY WEIGHT GAINS (g) - FEMALES

G. No. Dose (mg/kg Bwt/day)	Rat No.	1	2	3	4	5	6	7	8	9	10	11	12	13
G3	Rf2371	20	26	42	57	60	71	77	79	76	85	89	90	96
7000	Rf2372	17	32	36	56	66	70	73	77	82	81	87	84	84
	Rf2373	21	32	43	61	72	81	76	89	95	94	98	107	105
	Rf2374	15	28	33	46	58	62	62	71	74	75	74	78	80
	Rf2375	25	37	54	69	80	76	87	90	94	101	99	108	107
	Rf2376	17	31	40	53	60	67	72	78	80	90	90	91	95
	Rf2377	32	57	60	67	81	88	90	95	93	102	103	112	107
	Rf2378	9	18	35	40	52	51	64	66	67	73	76	82	80
	Rf2379	20	32	50	55	73	81	87	89	86	96	94	93	96
	Rf2380	25	31	51	70	76	77	72	87	88	92	94	99	94
G4	Rf2381	34	50	62	77	82	99	99	109	112	112	120	122	121
20000	Rf2382	20	35	41	56	72	77	75	83	91	94	95	103	100
	Rf2383	24	42	64	83	88	95	106	113	120	125	135	136	137
	Rf2384	27	45	58	78	88	101	94	106	110	111	116	126	124
	Rf2385	33	51	70	77	89	99	107	105	116	124	121	123	118
	Rf2386	24	39	53	69	84	86	91	101	103	104	99	105	103
	Rf2387	18	31	46	56	59	61	68	74	77	82	77	77	80
	Rf2388	8	49	60	69	75	87	97	93	96	96	101	102	111
	Rf2389	18	34	48	69	76	81	81	91	97	99	95	102	104
	Rf2390	20	37	54	61	79	90	95	106	106	112	108	108	110

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APPENDIX 9

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

CAGEWISE AVERAGE FOOD INTAKE (g/rat/day) - MALES

G. No. Dose (mg/kg Bwt/day)	Rat Nos. From	Rat Nos. To	Cage No.	Weeks 1	2	3	4	5	6	7	8	9	10	11	12	13
G1	Rf2311	Rf2312	1	26.8	28.7	28.8	27.3	26.5	26.7	26.9	28.1	28.4	28.4	28.5	26.3	27.0
0	Rf2313	Rf2314	2	26.6	29.5	29.1	28.5	28.1	28.3	27.7	28.1	27.1	27.4	27.5	26.9	26.8
	Rf2315	Rf2316	3	26.4	29.6	29.4	28.9	27.9	28.1	28.1	27.9	27.4	27.0	26.4	26.4	26.3
	Rf2317	Rf2318	4	27.1	28.4	29.2	28.4	28.6	28.3	27.9	29.8	28.9	28.9	29.0	27.9	28.0
	Rf2319	Rf2320	5	24.9	27.4	28.3	27.0	26.8	26.4	27.5	28.1	28.4	27.9	28.8	26.2	26.1
G2	Rf2321	Rf2322	6	25.9	28.4	28.5	27.7	27.9	27.2	27.2	28.1	27.1	26.9	26.9	26.6	26.4
2000	Rf2323	Rf2324	7	26.2	29.6	28.2	28.2	27.4	27.5	28.9	28.7	27.8	27.7	27.8	27.2	27.5
	Rf2325	Rf2326	8	26.2	28.4	28.1	26.9	26.5	26.5	26.1	27.0	26.4	26.4	25.4	25.6	26.2
	Rf2327	Rf2328	9	28.6	28.9	29.2	28.4	28.1	28.1	28.1	28.3	25.9	27.8	28.9	27.5	27.6
	Rf2329	Rf2330	10	26.1	28.9	28.8	27.3	27.2	27.6	27.1	27.2	26.1	25.9	25.9	26.0	26.3
G3	Rf2331	Rf2332	11	25.0	31.2	30.0	29.3	30.1	29.7	30.1	30.5	30.2	28.7	28.1	28.6	29.3
7000	Rf2333	Rf2334	12	21.4	24.4	27.1	25.0	23.6	23.0	24.3	25.6	26.8	26.8	23.4	24.3	25.4
	Rf2335	Rf2336	13	25.0	30.3	30.6	30.4	30.4	29.6	28.6	29.9	29.6	30.0	29.6	28.9	29.3
	Rf2337	Rf2338	14	22.6	29.8	30.3	29.8	28.4	28.2	28.5	29.1	27.2	27.1	27.5	26.4	27.5
	Rf2339	Rf2340	15	24.6	29.6	29.6	29.6	28.4	28.4	28.6	28.3	28.7	29.5	29.8	26.8	27.9
G4	Rf2341	Rf2342	16	22.3	27.7	27.3	26.4	25.4	25.5	27.1	25.6	25.6	24.4	24.1	23.3	24.0
20000	Rf2343	Rf2344	17	22.4	27.9	28.8	28.4	28.1	26.3	26.6	27.0	26.6	25.9	24.9	24.9	26.0
	Rf2345	Rf2346	18	23.9	28.6	30.4	29.3	27.7	27.3	27.6	27.4	26.6	26.5	27.1	27.5	26.3
	Rf2347	Rf2348	19	22.8	27.6	28.6	27.3	26.3	25.7	25.5	25.1	25.3	26.2	23.2	24.7	23.6
	Rf2349	Rf2350	20	19.8	27.4	29.3	27.2	26.6	25.7	25.1	24.9	25.5	25.0	25.0	24.6	23.8

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APPENDIX 10

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

CAGEWISE AVERAGE FOOD INTAKE (g/rat/day) - FEMALES

G. No. Dose (mg/kg Bwt/day)	Rat Nos. From	Rat Nos. To	Cage No.	Weeks 1	2	3	4	5	6	7	8	9	10	11	12	13
G1	Rf2351	Rf2352	21	17.9	18.4	18.8	17.6	18.6	19.1	18.9	18.4	18.2	19.0	18.6	16.9	16.8
0	Rf2353	Rf2354	22	16.8	16.7	18.7	17.9	19.7	19.4	18.8	20.1	19.7	19.9	18.7	18.2	18.7
	Rf2355	Rf2356	23	16.7	17.5	18.0	17.2	17.1	17.5	17.7	17.8	17.8	18.9	19.3	18.8	17.6
	Rf2357	Rf2358	24	18.0	18.5	19.6	17.9	18.5	18.3	19.4	18.6	18.4	19.3	19.1	17.8	17.6
	Rf2359	Rf2360	25	18.7	19.1	18.9	17.8	18.4	18.2	18.0	19.0	18.2	19.1	18.6	17.5	16.8
G2	Rf2361	Rf2362	26	13.9	19.1	19.4	20.0	18.9	19.0	17.7	20.1	18.5	19.4	19.1	17.0	16.4
2000	Rf2363	Rf2364	27	20.4	21.3	21.9	18.9	21.3	20.7	19.9	21.5	22.4	20.0	18.8	18.9	18.8
	Rf2365	Rf2366	28	16.3	16.4	16.6	16.7	16.9	17.0	16.5	17.4	16.7	17.4	17.6	15.4	16.7
	Rf2367	Rf2368	29	18.9	19.4	19.2	18.7	19.6	19.1	18.4	19.1	18.8	19.3	19.1	18.9	18.4
	Rf2369	Rf2370	30	18.0	18.4	19.1	18.6	18.1	17.7	17.7	18.1	17.5	19.2	19.3	17.9	16.8
G3	Rf2371	Rf2372	31	13.3	16.6	18.3	18.1	17.0	17.4	16.9	17.9	17.6	18.4	18.4	16.5	16.8
7000	Rf2373	Rf2374	32	13.0	17.2	17.8	18.3	17.4	18.2	17.6	18.5	18.5	18.0	18.4	18.8	17.3
	Rf2375	Rf2376	33	13.4	18.5	19.1	18.7	17.9	17.0	18.4	18.7	18.7	19.2	18.6	17.6	17.5
	Rf2377	Rf2378	34	14.0	17.4	18.6	18.3	19.1	17.6	18.9	18.4	18.6	18.9	19.0	17.3	18.2
	Rf2379	Rf2380	35	14.6	18.3	20.0	18.9	20.1	20.9	19.8	18.4	19.1	19.6	19.4	18.4	17.3
G4	Rf2381	Rf2382	36	14.1	17.6	19.1	18.7	18.6	18.4	18.1	18.6	19.2	17.9	19.0	17.6	18.7
20000	Rf2383	Rf2384	37	14.4	18.1	20.4	18.9	19.0	19.1	18.6	18.5	18.6	19.1	20.5	18.2	16.7
	Rf2385	Rf2386	38	13.1	18.3	18.5	18.1	18.7	18.2	18.0	18.6	17.1	17.9	19.0	16.6	16.0
	Rf2387	Rf2388	39	14.3	18.1	19.5	18.5	17.6	18.4	17.8	16.9	18.5	17.9	16.6	16.8	17.9
	Rf2389	Rf2390	40	12.5	17.4	19.1	18.6	18.6	18.6	18.3	19.1	18.4	18.4	17.6	17.1	16.4

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APPENDIX 11

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL HAEMATOLOGICAL VALUES AT TERMINATION - MALES

G.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	Rf2311	9.8	8.33	161	0.439	52.7	19.3	367	967	14.4	15	84	1	0	0
0	Rf2312	7.6	9.19	163	0.450	49.0	17.7	362	809	15.5	5	95	0	0	0
	Rf2313	7.7	9.18	162	0.448	48.8	17.6	362	818	13.3	9	89	1	1	0
	Rf2314	9.2	8.71	163	0.440	50.5	18.7	370	652	13.5	24	75	1	0	0
	Rf2315	7.9	8.43	158	0.421	49.9	18.7	375	924	13.2	10	87	3	0	0
	Rf2316	8.7	8.16	157	0.407	49.9	19.2	386	896	14.0	26	74	0	0	0
	Rf2317	9.8	7.83	156	0.417	53.3	19.9	374	895	13.8	19	76	5	0	0
	Rf2318	5.6	7.86	152	0.397	50.5	19.3	383	990	15.7	23	74	1	2	0
	Rf2319	6.0	8.35	158	0.407	48.7	18.9	388	927	17.2	8	90	0	2	0
	Rf2320	5.9	8.27	160	0.406	49.1	19.3	394	902	14.6	11	88	1	0	0
G2	Rf2321	4.8	8.78	160	0.440	50.1	18.2	364	1072	15.9	20	78	2	0	0
2000	Rf2322	5.7	7.89	146	0.394	49.9	18.5	371	976	14.5	18	82	0	0	0
	Rf2323	6.5	8.70	158	0.428	49.2	18.2	369	873	16.1	36	62	2	0	0
	Rf2324	8.0	7.78	156	0.413	53.1	20.1	378	852	17.2	13	86	1	0	0
	Rf2325	6.0	8.43	156	0.427	50.7	18.5	365	867	16.2	19	78	2	1	0
	Rf2326	5.3	8.34	158	0.415	49.8	18.9	381	869	15.2	21	75	4	0	0
	Rf2327	6.0	8.18	156	0.422	51.6	19.1	370	913	13.5	9	88	2	1	0
	Rf2328	6.0	8.16	158	0.421	51.6	19.4	375	937	14.8	14	83	1	2	0
	Rf2329	3.8	7.78	152	0.389	50.0	19.5	391	884	14.6	17	79	2	2	0
	Rf2330	5.8	8.63	159	0.435	50.4	18.4	366	981	15.1	16	82	2	0	0

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL HAEMATOLOGICAL VALUES AT TERMINATION - MALES

G.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 %
G3	Rf2331	6.3	8.23	153	0.412	50.1	18.6	371	883	13.9	14	83	2	1	0
7000	Rf2332	6.0	8.37	155	0.428	51.1	18.5	362	959	15.0	18	77	3	2	0
	Rf2333	5.2	8.32	157	0.407	48.9	18.9	386	1119	15.9	20	75	5	0	0
	Rf2334	5.3	8.44	157	0.401	47.5	18.6	392	881	16.3	8	89	2	1	0
	Rf2335	9.5	8.82	163	0.445	50.5	18.5	366	678	16.8	13	85	1	1	0
	Rf2336	5.8	8.00	148	0.378	47.2	18.5	392	1028	15.5	7	89	4	0	0
	Rf2337	8.0	8.23	156	0.401	48.7	19.0	389	1006	15.7	17	82	0	1	0
	Rf2338	5.8	8.32	158	0.419	50.4	19.0	377	965	15.3	16	84	0	0	0
	Rf2339	5.2	8.91	158	0.440	49.4	17.7	359	978	17.0	15	85	0	0	0
	Rf2340	5.9	7.62	158	0.397	52.1	20.7	398	827	17.0	13	81	5	1	0
G4	Rf2341	4.7	7.76	152	0.396	51.0	19.6	384	949	17.6	9	90	0	1	0
20000	Rf2342	8.1	7.29	150	0.358	49.1	20.6	419	965	16.4	10	88	2	0	0
	Rf2343	5.8	7.69	142	0.378	49.2	18.5	376	1112	12.9	15	84	1	0	0
	Rf2344	5.7	7.65	145	0.376	49.2	19.0	386	1096	12.9	14	86	0	0	0
	Rf2345	7.4	8.07	147	0.388	48.1	18.2	379	918	15.3	17	79	4	0	0
	Rf2346	6.6	8.15	153	0.401	49.2	18.8	382	956	13.6	13	81	6	0	0
	Rf2347	8.1	7.23	150	0.389	53.8	20.7	386	933	15.3	12	85	3	0	0
	Rf2348	7.6	9.06	163	0.442	48.8	18.0	369	829	14.8	16	78	4	2	0
	Rf2349	4.9	9.12	167	0.463	50.8	18.3	361	857	14.7	7	92	1	0	0
	Rf2350	4.8	8.26	155	0.424	51.3	18.8	366	912	14.3	13	83	3	1	0

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APPENDIX 12

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL HAEMATOLOGICAL VALUES AT TERMINATION - FEMALES

G.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	Rf2351	3.2	8.54	164	0.441	51.6	19.2	372	1132	15.7	14	82	4	0	0
0	Rf2352	2.4	8.68	161	0.444	51.2	18.5	363	1002	15.9	10	89	1	0	0
	Rf2353	5.2	8.66	157	0.431	49.8	18.1	364	1213	14.8	13	85	0	2	0
	Rf2354	2.7	8.84	160	0.454	51.4	18.1	352	1173	15.1	15	85	0	0	0
	Rf2355	4.1	8.68	159	0.442	50.9	18.3	360	1234	14.1	24	74	1	1	0
	Rf2356	4.1	8.33	159	0.429	51.5	19.1	371	1162	14.7	12	86	0	2	0
	Rf2357	4.4	8.61	161	0.424	49.2	18.7	380	1280	14.9	16	82	1	1	0
	Rf2358	5.7	8.78	160	0.449	51.1	18.2	356	1282	15.5	16	80	0	4	0
	Rf2359	8.8	7.83	151	0.377	48.1	19.3	401	1247	14.7	7	92	1	0	0
	Rf2360	3.5	9.64	172	0.495	51.3	17.8	347	1249	14.8	9	88	1	2	0
G2	Rf2361	5.5	8.70	159	0.446	51.3	18.3	357	1264	14.1	11	89	0	0	0
2000	Rf2362	3.8	9.01	160	0.449	49.8	17.8	356	1392	14.5	11	88	1	0	0
	Rf2363	3.3	8.44	162	0.435	51.5	19.2	372	1081	14.3	8	91	0	1	0
	Rf2364	4.6	9.13	161	0.460	50.4	17.6	350	1224	14.0	7	91	2	0	0
	Rf2365	4.5	9.09	160	0.459	50.5	17.6	349	1219	14.2	32	66	2	0	0
	Rf2366	3.5	9.30	167	0.460	49.5	18.0	363	1344	14.6	12	82	5	1	0
	Rf2367	3.2	8.65	162	0.445	51.4	18.7	364	1147	14.4	12	87	0	1	0
	Rf2368	3.3	8.98	159	0.430	47.9	17.7	370	1708	14.1	13	87	0	0	0
	Rf2369	7.3	10.01	176	0.498	49.8	17.6	353	674	14.0	8	89	3	0	0
	Rf2370	3.1	8.30	161	0.402	48.4	19.4	400	1267	14.0	12	87	1	0	0

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL HAEMATOLOGICAL VALUES AT TERMINATION - FEMALES

G.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 %
G3	Rf2371	3.2	8.36	157	0.420	50.2	18.8	374	984	14.2	15	85	0	0	0
7000	Rf2372	3.1	8.13	157	0.416	51.2	19.3	377	975	14.7	8	92	0	0	0
	Rf2373	5.9	7.52	151	0.399	53.1	20.1	378	836	15.3	11	88	1	0	0
	Rf2374	5.7	8.80	168	0.469	53.3	19.1	358	696	15.3	12	87	0	1	0
	Rf2375	3.7	8.41	165	0.441	52.4	19.6	374	1013	14.7	24	75	1	0	0
	Rf2376	3.4	8.35	162	0.437	52.3	19.4	371	994	15.1	6	90	4	0	0
	Rf2377	2.6	7.82	153	0.386	49.4	19.6	396	1042	15.0	13	85	1	1	0
	Rf2378	4.0	8.51	162	0.444	52.2	19.0	365	1029	15.0	7	91	2	0	0
	Rf2379	3.1	7.70	153	0.395	51.3	19.9	387	800	14.9	16	83	1	0	0
	Rf2380	2.9	8.21	160	0.429	52.3	19.5	373	941	13.8	6	94	0	0	0
G4	Rf2381	2.7	7.55	149	0.402	53.2	19.7	371	802	14.0	7	91	1	1	0
20000	Rf2382	2.7	7.69	154	0.398	51.8	20.0	387	805	14.6	20	76	3	1	0
	Rf2383	2.3	7.66	150	0.394	51.4	19.6	381	801	14.9	15	83	0	2	0
	Rf2384	5.1	7.98	161	0.412	51.6	20.2	391	1049	14.7	30	67	2	1	0
	Rf2385	3.7	7.79	155	0.389	49.9	19.9	398	1073	14.3	9	91	0	0	0
	Rf2386	5.5	7.95	166	0.442	55.6	20.9	376	557	15.5	8	92	0	0	0
	Rf2387	4.6	8.34	162	0.426	51.1	19.4	380	965	15.8	6	92	1	1	0
	Rf2388	2.7	7.83	148	0.386	49.3	18.9	383	1210	15.5	5	95	0	0	0
	Rf2389	3.1	8.91	168	0.463	52.0	18.9	363	938	15.1	17	80	2	1	0
	Rf2390	4.7	8.62	162	0.441	51.2	18.8	367	1074	14.9	14	84	1	1	0

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APPENDIX 13

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL CLINICAL CHEMISTRY VALUES AT TERMINATION - MALES

G.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	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
G1	Rf2311	9.46	3.08	6.60	63.4	58	47	0	3.13	61	32.6	1.82	2.76	2.27	105	142.3	4.16
0	Rf2312	10.82	3.15	6.75	64.0	69	47	0	3.94	55	33.4	2.37	2.84	2.10	102	142.6	4.37
	Rf2313	10.61	3.82	8.18	67.0	55	41	0	2.04	57	34.6	2.48	2.89	2.72	98	145.1	4.39
	Rf2314	11.79	2.89	6.19	65.7	63	41	0	3.67	59	33.9	2.63	2.86	2 64	102	145 1	4.66
	Rf2315	10.34	3.05	6.53	67.2	71	49	1	3.47	65	35.5	2.23	2.79	2.39	105	144.8	4.26
	Rf2316	10.16	2.86	6.12	66.9	61	47	1	2.99	61	35.0	2.16	2.74	2.97	105	144.4	4.23
	Rf2317	10.37	3.44	7.37	66.5	74	46	0	3.19	59	33.4	2.56	2.81	2.47	104	144.9	5.33
	Rf2318	11.27	3.47	7.43	66.9	63	51	0	2.92	63	34.8	2.24	2.76	2.43	105	146.0	4.05
	Rf2319	10.30	3.27	7.00	66.3	63	47	3	3.81	60	33.3	2.59	2.87	2.55	105	145.0	4.79
	Rf2320	10.66	2.74	5.87	65.3	59	49	2	3.67	54	32.6	2.06	2.57	2.86	107	144.2	4.10
G2	Rf2321	11.02	3.17	6.79	64.1	55	41	0	2.79	56	34.0	2.44	2.74	2.03	103	145.2	4.30
2000	Rf2322	11.03	2.88	6.17	65.3	69	52	1	3.19	57	33.1	2.68	2.87	2.39	103	145.2	4.74
	Rf2323	8.83	3.51	7.52	66.1	61	43	0	3.81	57	33.8	2.96	2.89	2.33	102	144.9	3.95
	Rf2324	9.67	3.01	6.45	62.0	59	46	0	2.92	56	32.9	2.27	2.74	2.27	105	145.1	4.02
	Rf2325	8.88	3.45	7.39	64.9	59	43	0	3.53	57	34.4	2.29	2.70	1.91	103	144.4	4.40
	Rf2326	12.44	3.20	6.85	69.4	63	49	0	4.08	56	35.6	2.59	2.96	2.15	103	145.5	4.78
	Rf2327	10.05	3.42	7.32	63.3	63	39	0	3.53	56	32.5	2.43	2.84	2.28	104	143.1	4.63
	Rf2328	10.77	2.81	6.02	62.4	66	47	0	3.94	53	32.6	2.18	2.76	2.68	102	142.8	4.05
	Rf2329	9.91	3.86	8.27	62.8	61	46	1	3.60	54	34.7	2.74	2.85	2.13	103	143.5	4.28
	Rf2330	9.91	3.43	7.34	65.4	53	43	1	3.13	56	34.3	2.48	2.74	2.50	99	143.7	4.33

contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL CLINICAL CHEMISTRY VALUES AT TERMINATION - MALES

G.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	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
G3	Rf2331	10.85	2.96	6.34	68.5	64	40	0	3.40	54	35.1	2.68	2.83	2.61	103	145.5	4.33
7000	Rf2332	10.35	3.52	7.54	65.6	59	46	2	4.21	58	32.5	2.28	2.83	3.15	106	145.5	4.34
	Rf2333	8.23	3.12	6.68	65.6	65	41	1	3.40	54	34.9	2.15	2.77	1.84	106	142.9	3.78
	Rf2334	10.16	3.39	7.26	68.6	78	53	0	3.33	55	35.0	2.44	2.85	2.53	106	145.4	4.92
	Rf2335	10.75	3.08	6.60	68.1	57	43	2	3.81	59	34.2	2.55	2.76	2.85	101	144.7	4.43
	Rf2336	11.27	3.18	6.81	66.7	62	46	0	3.33	61	34.4	2.30	2.81	2.49	108	145.5	4.34
	Rf2337	10.97	2.93	6.27	64.3	65	45	0	3.87	57	32.2	2.23	2.74	2.27	106	144.4	4.50
	Rf2338	8.79	2.86	6.12	64.6	66	49	1	3.47	58	32.8	2.09	2.72	2.24	105	144.5	3.96
	Rf2339	10.09	2.59	5.55	68.0	59	40	0	4.96	53	34.2	2.49	2.72	2.79	102	144.7	4.46
	Rf2340	8.53	2.55	5.46	62.6	52	44	2	3.94	53	32.2	2.38	2.85	2.44	106	144.7	4.22
G4	Rf2341	9.63	3.29	7.04	64.6	60	42	0	3.60	55	34.2	2.39	2.69	2.29	105	144.5	4.80
20000	Rf2342	10.15	3.41	7.30	64.4	56	34	0	3.81	53	34.2	2.68	2.69	2.41	102	143.7	4.09
	Rf2343	10.13	2.60	5.57	63.9	54	34	1	3.87	57	31.9	2.54	2.87	3.00	105	144.0	4.46
	Rf2344	11.17	3.24	6.94	65.2	54	41	1	3.40	56	34.2	2.29	2.86	2.09	103	144.5	3.90
	Rf2345	10.40	3.14	6.72	65.3	79	57	1	3.53	55	34.6	2.35	2.78	2.71	105	144.5	3.86
	Rf2346	10.27	3.28	7.02	65.9	62	47	3	3.94	61	33.8	2.08	2.91	2.64	103	146.1	3.84
	Rf2347	9.83	3.12	6.68	63.3	65	50	1	3.60	61	33.9	2.12	2.80	2.10	109	144.4	3.86
	Rf2348	9.59	3.64	7.79	64.1	68	44	4	4.08	59	33.0	2.73	2.74	2.32	106	145.0	4.83
	Rf2349	11.20	3.52	7.54	68.0	64	43	0	4.15	59	35.1	2.58	2.93	2.41	100	146.1	4.83
	Rf2350	9.10	3.05	6.53	66.2	49	33	4	4.28	57	33.9	2.91	2.90	2.43	107	145.9	3.90

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APPENDIX 14

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL CLINICAL CHEMISTRY VALUES AT TERMINATION - FEMALES

G.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	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
G1	Rf2351	7.88	2.67	5.72	63.7	79	34	0	4.01	70	32.4	1.24	2.50	1.49	99	142.3	3.70
0	Rf2352	7.43	2.80	6.00	61.0	62	34	0	5.57	56	32.9	1.59	4.94	2.00	100	144.3	3.75
	Rf2353	9.52	2.38	5.10	59.3	61	34	0	4.35	58	31.6	1.84	2.39	1.79	100	140.0	4.08
	Rf2354	6.53	2.86	6.12	64.4	77	37	0	3.90	62	35.2	2.08	2.57	1.29	99	143.8	3.31
	Rf2355	7.87	2.79	5.97	64.1	78	54	0	5.12	60	34.8	1.89	2.78	1.68	97	139.6	3.80
	Rf2356	7.14	2.75	5.89	63.5	78	48	0	3.96	64	33.3	2.37	2.64	1.30	98	143.3	4.06
	Rf2357	8.01	2.89	6.19	61.6	77	37	0	5.00	59	32.2	2.55	2.51	1.72	99	143.7	4.23
	Rf2358	9.68	2.82	6.04	61.6	58	35	0	3.84	58	33.0	1.98	2.65	1.37	100	140.9	3.55
	Rf2359	7.43	3.00	6.42	63.1	83	59	0	5.18	58	33.2	1.73	2.54	2.11	101	141.0	4.12
	Rf2360	7.97	2.84	6.08	66.3	72	40	0	5.07	64	34.5	2.32	2.66	1.78	99	141.0	3.91
G2	Rf2361	8.80	2.39	5.12	64.6	75	50	0	4.36	62	33.3	2.18	2.70	1.29	101	142.6	3.94
2000	Rf2362	7.97	2.02	4.33	60.7	67	34	0	4.24	58	33.6	1.96	2.59	1.65	99	143.7	4.17
	Rf2363	7.92	2.22	4.75	66.7	64	37	0	6.13	60	36.9	2.17	2.61	1.47	96	143.6	3.97
	Rf2364	7.59	2.04	4.37	64.4	64	31	0	5.19	56	34.1	2.19	2.71	1.55	99	143.2	4.15
	Rf2365	9.29	2.21	4.73	64.5	66	46	0	5.19	55	34.1	2.03	2.69	1.80	98	142.1	3.97
	Rf2366	9.68	2.32	4.97	65.8	81	39	0	5.95	62	36.6	2.28	2.75	1.49	100	142.8	3.87
	Rf2367	8.24	2.64	5.65	62.0	69	33	0	4.13	57	33.5	1.67	2.56	1.65	100	143.1	3.80
	Rf2368	8.78	1.97	4.22	72.2	91	44	0	5.01	63	33.9	1.81	2.89	2.42	100	132.8	4.14
	Rf2369	7.90	1.78	3.81	63.1	52	23	0	10.38	58	33.1	2.18	2.64	1.36	100	141.2	4.31
	Rf2370	8.84	2.46	5.27	65.5	80	59	0	4.24	57	34.1	2.67	2.59	2.48	97	142.8	4.44

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL CLINICAL CHEMISTRY VALUES AT TERMINATION - FEMALES

G.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	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
G3	Rf2371	8.78	2.53	5.42	62.6	58	35	0	4.60	57	33.4	2.04	2.40	1.97	101	140.2	3.89
7000	Rf2372	11.20	2.73	5.85	64.1	50	40	0	4.30	57	34.2	1.61	2.64	1.96	102	145.6	4.18
	Rf2373	9.16	2.46	5.27	66.6	73	45	0	4.60	64	34.4	2.04	2.83	2.13	101	145.7	3.80
	Rf2374	6.43	2.34	5.01	64.2	74	32	0	10.91	60	34.3	2.48	2.79	1.24	99	143.5	4.63
	Rf2375	8.57	2.32	4.97	66.9	78	45	0	4.95	65	37.2	1.64	2.73	2.32	101	145.9	4.04
	Rf2376	10.01	2.30	4.93	63.7	61	32	0	3.60	55	34.0	1.83	2.62	1.68	98	142.5	3.47
	Rf2377	8.67	2.61	5.59	62.0	109	65	0	4.78	60	33.2	1.43	2.43	1.77	103	142.3	4.39
	Rf2378	8.95	2.47	5.29	66.1	60	34	0	5.19	61	29.9	1.74	2.72	1.68	103	137.9	4.47
	Rf2379	11.91	2.71	5.80	67.2	69	47	0	4.60	67	35.2	1.61	2.65	1.75	103	146.4	4.06
	Rf2380	9.47	2.69	5.76	65.1	52	33	0	3.65	61	34.6	1.73	2.56	1.67	97	142.1	4.24
G4	Rf2381	10.30	2.80	6.00	67.4	58	43	0	4.19	58	35.5	1.60	2.56	2.03	98	143.4	3.51
20000	Rf2382	10.69	3.29	7.04	65.5	99	68	0	4.66	58	34.4	2.08	2.70	1.77	100	143.3	4.96
	Rf2383	8.69	3.00	6.42	68.4	70	41	0	5.66	60	35.0	1.06	2.67	2.67	99	140.4	3.68
	Rf2384	9.41	2.48	5.31	65.0	74	48	1	4.01	59	35.6	1.94	2.74	2.17	100	142.7	3.89
	Rf2385	8.40	1.89	4.05	64.5	59	38	0	4.01	59	34.6	2.07	2.54	2.76	102	141.7	3.90
	Rf2386	8.69	2.60	5.57	61.4	72	31	0	7.13	53	32.3	2.38	2.69	2.27	99	142.7	3.99
	Rf2387	9.19	2.68	5.74	63.8	72	37	0	5.07	59	33.2	2.22	2.65	1.77	102	142.1	4.38
	Rf2388	8.46	2.57	5.50	64.8	59	35	0	4.24	60	33.9	2.12	2.60	2.22	99	144.2	3.70
	Rf2389	9.09	2.11	4.52	63.7	50	27	0	5.90	54	33.1	2.06	2.77	2.06	98	141.9	3.81
	Rf2390	8.51	2.77	5.93	64.4	55	32	0	5.19	57	34.1	2.20	2.73	2.22	101	143.5	4.10

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APPENDIX 15

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL TERMINAL FASTING BODY WEIGHTS, ORGAN WEIGHTS AND ORGAN WEIGHT RATIOS - MALES

G.No.	Rat	Fasting	Organ weights(g)									Organ weight ratios(%)								
Dose	No.	Bwt																		
(mg/kg Bwt/day)		(g)	Adrenals	Testes	Kidneys	Liver	Heart	Brain	Epididym	Thymus	Spleen	Adrenals	Testes	Kidneys	Liver	Heart	Brain	Epididym	Thymus	Spleen
G1	Rf2311	508	0.051	4.476	2.913	14.817	1.449	2.005	1.595	0.544	0.873	0.010	0.881	0.573	2.917	0.285	0.395	0.314	0.107	0.172
0	Rf2312	429	0.048	3.179	2.530	11.861	1.271	2.052	1.294	0.501	0.634	0.011	0.741	0.590	2.765	0.296	0.478	0.302	0.117	0.148
	Rf2313	526	0.052	3.850	3.135	15.345	1.404	2.097	1.642	0.641	0.745	0.010	0.732	0.596	2.917	0.267	0.399	0.312	0.122	0.142
	Rf2314	433	0.052	3.723	2.503	12.627	1.445	1.982	1.306	0.530	0.765	0.012	0.860	0.578	2.916	0.334	0.458	0.302	0.122	0.177
	Rf2315	467	0.041	2.728	2.823	14.892	1 391	2.050	1.391	0.469	0.669	0.009	0.584	0.604	3.189	0.298	0.439	0.298	0.100	0.143
	Rf2316	462	0.047	3.553	2.882	12.941	1.380	2.041	1.308	0.681	0.669	0.010	0.769	0.624	2.801	0.299	0.442	0.283	0.147	0.145
	Rf2317	424	0.051	3.902	2.582	12.633	1.353	1.999	1.483	0.579	0.678	0.012	0.920	0.609	2.979	0.319	0.471	0.350	0.137	0.160
	Rf2318	491	0.052	4.203	2.941	15.246	1.493	1.984	1.612	0.570	0.771	0.011	0.856	0.599	3.105	0.304	0.404	0.328	0.116	0.157
	Rf2319	455	0.054	3.239	2.549	13.657	1.434	2.054	1.302	0.615	0.799	0.012	0.712	0.560	3.002	0.315	0.451	0.286	0.135	0.176
	Rf2320	442	0.046	3.403	2.799	14.046	1.328	2.007	1.462	0.419	0.630	0.010	0.770	0.633	3.178	0.300	0.454	0.331	0.095	0.143
G2	Rf2321	441	0.050	4.184	2.626	13.748	1.345	2.010	1.660	0.535	0.614	0.011	0.949	0.595	3.117	0.305	0.456	0.376	0.121	0.139
2000	Rf2322	471	0.048	3.881	2.883	13.824	1.545	2.066	1.565	0.455	0.810	0.010	0.824	0.612	2.935	0.328	0.439	0.332	0.097	0.172
	Rf2323	456	0.048	2.873	2.623	13.796	1.315	1.966	1.255	0.506	0.663	0.011	0.630	0.575	3.025	0.288	0.431	0.275	0.111	0.145
	Rf2324	480	0.055	4.470	2.891	13.722	1.353	2.170	1.606	0.535	0.963	0.011	0.931	0.602	2.859	0.282	0.452	0.335	0.111	0.201
	Rf2325	440	0.049	3.820	2.722	12.628	1.390	2.117	1.607	0.416	0.647	0.011	0.868	0.619	2.870	0.316	0.481	0.365	0.095	0.147
	Rf2326	456	0.046	3.701	2.600	13.477	1.245	2.136	1.358	0.526	0.675	0.010	0.812	0.570	2.955	0.273	0.468	0.298	0.115	0.148
	Rf2327	533	0.049	3.727	3.178	15.305	1.493	2.164	1.534	0.602	0.746	0.009	0.699	0.596	2.871	0.280	0.406	0.288	0.113	0.140
	Rf2328	418	0.043	2.951	2.749	12.471	1.357	1.933	1.419	0.507	0.718	0.010	0.706	0.658	2.983	0.325	0.462	0.339	0.121	0.172
	Rf2329	427	0.045	3.914	2.574	12.014	1.400	2.192	1.357	0.726	0.748	0.011	0.917	0.603	2.814	0.328	0.513	0.318	0.170	0.175
	Rf2330	467	0.046	3.537	2.825	13.283	1.224	2.008	1.560	0.455	0.674	0.010	0.757	0.605	2.844	0.262	0.430	0.334	0.097	0.144

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APPENDIX 15 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL TERMINAL FASTING BODY WEIGHTS, ORGAN WEIGHTS AND ORGAN WEIGHT RATIOS - MALES

G.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
G3	Rf2331	495	0.051	4.098	3.089	16.288	1.379	2.162	1.530	0.479	0.946	0.010	0.828	0.624	3.291	0.279	0.437	0.309	0.097	0.191
7000	Rf2332	527	0.048	3.741	3.170	17.388	1.411	2.008	1.747	0.700	0.734	0.009	0.710	0.602	3.299	0.268	0.381	0.331	0.133	0.139
	Rf2333	385	0.041	3.334	2.413	9.632	1.118	2.022	1.577	0.327	0.539	0.011	0.866	0.627	2.502	0.290	0.525	0.410	0.085	0.140
	Rf2334	435	0.056	3.491	3.132	13.418	1.340	1.990	1.664	0.388	0.611	0.013	0.803	0.720	3.085	0.308	0.457	0.383	0.089	0.140
	Rf2335	545	0.053	3.768	3.240	17.153	1.522	2.086	1.645	0.691	0.781	0.010	0.691	0.594	3.147	0.279	0.383	0.302	0.127	0.143
	Rf2336	499	0.048	3.477	2.826	15.187	1.402	2.065	1.558	0.514	0.714	0.010	0.697	0.568	3.043	0.281	0.414	0.312	0.103	0.143
	Rf2337	498	0.048	3.225	2.892	15.459	1.379	1.995	1.315	0.516	0.636	0.010	0.648	0.581	3.104	0.277	0.401	0.264	0.104	0.128
	Rf2338	460	0.049	3.509	2.730	14.506	1.373	2.019	1.638	0.471	0.650	0.011	0.763	0.593	3.153	0.298	0.439	0.356	0.102	0.141
	Rf2339	481	0.047	3.018	3.221	15.494	1.466	2.096	1.271	0.531	0.636	0.010	0.627	0.670	3.221	0.305	0.436	0.264	0.110	0.132
	Rf2340	498	0.051	3.744	3.124	15.686	1.267	1.980	1.408	0.511	0.694	0.010	0.752	0.627	3.150	0.254	0.398	0.283	0.103	0.139
G4	Rf2341	482	0.055	4.614	3.254	15.383	1.735	2.077	1.631	0.554	0.776	0.011	0.957	0.675	3.191	0.360	0.431	0.338	0.115	0.161
20000	Rf2342	411	0.042	3.231	2.549	12.581	1.205	2.008	1.316	0.467	0.644	0.010	0.786	0.620	3.061	0.293	0.489	0.320	0.114	0.157
	Rf2343	549	0.050	3.428	3.416	17.893	1.386	2.113	1.474	0.464	0.848	0.009	0.624	0.622	3.259	0.252	0.385	0.268	0.085	0.154
	Rf2344	409	0.041	3.610	2.633	12.203	1.267	1.929	1.594	0.489	0.563	0.010	0.883	0.644	2.984	0.310	0.472	0.390	0.120	0.138
	Rf2345	475	0.053	3.611	2.937	15.346	1.412	2.065	1.554	0.537	0.698	0.011	0.760	0.618	3.231	0.297	0.435	0.327	0.113	0.147
	Rf2346	486	0.054	3.499	2.879	15.488	1.221	2.015	1.432	0.337	0.704	0.011	0.720	0.592	3.187	0.251	0.415	0.295	0.069	0.145
	Rf2347	451	0.044	4.152	2.856	13.823	1.327	2.106	1.365	0.400	0.803	0.010	0.921	0.633	3.065	0.294	0.467	0.303	0.089	0.178
	Rf2348	443	0.051	3.561	3.015	13.242	1.353	2.037	1.434	0.525	0.870	0.012	0.804	0.681	2.989	0.305	0.460	0.324	0.119	0.196
	Rf2349	435	0.054	4.019	2.762	14.841	1.380	2.087	1.710	0.496	0.824	0.012	0.924	0.635	3.412	0.317	0.480	0.393	0.114	0.189
	Rf2350	459	0.049	3.587	2.671	15.182	1.380	2.026	1.383	0.379	0.820	0.011	0.781	0.582	3.308	0.301	0.441	0.301	0.083	0.179

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APPENDIX 16

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL TERMINAL FASTING BODY WEIGHTS, ORGAN WEIGHTS AND ORGAN WEIGHT RATIOS - FEMALES

G.No.	Rat	Fasting	Organ weights(g)									Organ weight ratios(%)								
Dose	No.	Bwt																		
(mg/kg Bwt/day)		(g)	Adrenals	Ovaries	Kidneys	Liver	Heart	Brain	Thymus	Spleen	Uterus	Adrenals	Ovaries	Kidneys	Liver	Heart	Brain	Thymus	Spleen	Uterus
G1	Rf2351	254	0.069	0.155	1.665	6.305	0.884	1.892	0.313	0.756	0.641	0.027	0.061	0.656	2.482	0.348	0.745	0.123	0.298	0.252
0	Rf2352	250	0.058	0.125	1.685	6.545	0.908	1.895	0.334	0.514	0.675	0.023	0.050	0.674	2.618	0.363	0.758	0.134	0.206	0.270
	Rf2353	235	0.074	0.109	1.753	6.850	0.917	1.919	0.503	0.662	0.766	0.031	0.046	0.746	2.915	0.390	0.817	0.214	0.282	0.326
	Rf2354	234	0.078	0.138	1.483	6.305	0.907	1.993	0.398	0.477	0.744	0.033	0.059	0.634	2.694	0.388	0.852	0.170	0.204	0.318
	Rf2355	245	0.072	0.105	1.585	6.044	0.925	1.940	0.394	0.423	0.752	0.029	0.043	0.647	2.467	0.378	0.792	0.161	0.173	0.307
	Rf2356	223	0.069	0.125	1.461	6.075	0.946	1.931	0.359	0.546	1.164	0.031	0.056	0.655	2.724	0.424	0.866	0.161	0.245	0.522
	Rf2357	234	0.065	0.126	1.572	6.410	0.919	1.930	0.379	0.474	0.710	0.028	0.054	0.672	2.739	0.393	0.825	0.162	0.203	0.303
	Rf2358	242	0.061	0.132	1.594	6.582	0.952	1.835	0.331	0.500	0.806	0.025	0.055	0.659	2.720	0.393	0.758	0.137	0.207	0.333
	Rf2359	242	0.074	0.130	1.632	6.493	0.933	1.912	0.394	0.434	0.729	0.031	0.054	0.674	2.683	0.386	0.790	0.163	0.179	0.301
	Rf2360	224	0.051	0.129	1.391	5.831	0.887	1.815	0.363	0.477	0.675	0.023	0.058	0.621	2.603	0.396	0.810	0.162	0.213	0.301
G2	Rf2361	252	0.084	0.127	1.671	6.624	0.927	2.003	0.435	0.513	1.452	0.033	0.050	0.663	2.629	0.368	0.795	0.173	0.204	0.576
2000	Rf2362	244	0.070	0.110	1.570	5.831	0.906	1.873	0.318	0.491	0.849	0.029	0.045	0.643	2.390	0.371	0.768	0.130	0.201	0.348
	Rf2363	251	0.072	0.148	1.579	6.816	0.970	1.875	0.322	0.485	1.112	0.029	0.059	0.629	2.716	0.386	0.747	0.128	0.193	0.443
	Rf2364	259	0.078	0.160	1.674	6.610	0.927	1.948	0.449	0.436	0.692	0.030	0.062	0.646	2.552	0.358	0.752	0.173	0.168	0.267
	Rf2365	206	0.057	0.143	1.379	6.062	0.880	1.946	0.337	0.401	0.615	0.028	0.069	0.669	2.943	0.427	0.945	0.164	0.195	0.299
	Rf2366	248	0.076	0.152	1.522	6.139	0.974	1.897	0.393	0.449	0.620	0.031	0.061	0.614	2.475	0.393	0.765	0.158	0.181	0.250
	Rf2367	279	0.060	0.161	1.830	7.314	0.949	1.941	0.495	0.520	0.812	0.022	0.058	0.656	2.622	0.340	0.696	0.177	0.186	0.291
	Rf2368	252	0.069	0.122	1.611	6.750	0.936	1.974	0.409	0.749	0.602	0.027	0.048	0.639	2.679	0.371	0.783	0.162	0.297	0.239
	Rf2369	254	0.074	0.141	1.536	5.791	0.825	1.904	0.368	0.556	0.788	0.029	0.056	0.605	2.280	0.325	0.750	0.145	0.219	0.310
	Rf2370	222	0.070	0.092	1.532	6.241	0.929	1.834	0.351	0.401	0.846	0.032	0.041	0.690	2.811	0.418	0.826	0.158	0.181	0.381

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

INDIVIDUAL TERMINAL FASTING BODY WEIGHTS, ORGAN WEIGHTS AND ORGAN WEIGHT RATIOS - FEMALES

G.No.	Rat	Fasting	Organ weights(g)									Organ weight ratios(%)								
Dose	No.	Bwt																		
(mg/kg Bwt/day)		(g)	Adrenals	Ovaries	Kidneys	Liver	Heart	Brain	Thymus	Spleen	Uterus	Adrenals	Ovaries	Kidneys	Liver	Heart	Brain	Thymus	Spleen	Uterus
G3	Rf2371	230	0.065	0.137	1.499	6.139	0.822	1.893	0.369	0.425	2.558	0.028	0.060	0.652	2.669	0.357	0.823	0.160	0.185	1.112
7000	Rf2372	231	0.056	0.131	1.507	7.015	0.895	1.832	0.438	0.494	0.941	0.024	0.057	0.652	3.037	0.387	0.793	0.190	0.214	0.407
	Rf2373	257	0.071	0.124	1.485	6.603	0.999	1.818	0.379	0.577	0.690	0.028	0.048	0.578	2.569	0.389	0.707	0.147	0.225	0.268
	Rf2374	210	0.066	0.125	1.352	6.030	0.862	1.842	0.363	0.447	1.364	0.031	0.060	0.644	2.871	0.410	0.877	0.173	0.213	0.650
	Rf2375	257	0.071	0.152	1.700	6.828	0.969	1.909	0.351	0.584	0.733	0.028	0.059	0.661	2.657	0.377	0.743	0.137	0.227	0.285
	Rf2376	235	0.058	0.148	1.605	6.675	0.848	1.856	0.276	0.470	0.660	0.025	0.063	0.683	2.840	0.361	0.790	0.117	0.200	0.281
	Rf2377	237	0.082	0.153	1.636	6.341	0.836	1.955	0.244	0.404	0.818	0.035	0.065	0.690	2.676	0.353	0.825	0.103	0.170	0.345
	Rf2378	224	0.076	0.133	1.604	6.879	0.924	1.973	0.373	0.485	0.638	0.034	0.059	0.716	3.071	0.413	0.881	0.167	0.217	0.285
	Rf2379	239	0.066	0.116	1.526	6.880	0.882	1.876	0.382	0.665	1.762	0.028	0.049	0.638	2.879	0.369	0.785	0.160	0.278	0.737
	Rf2380	255	0.058	0.134	1.633	7.911	0.990	1.910	0.449	0.549	0.795	0.023	0.053	0.640	3.102	0.388	0.749	0.176	0.215	0.312
G4	Rf2381	282	0.064	0.114	1.916	9.219	1.029	1.900	0.451	0.593	1.323	0.023	0.040	0.679	3.269	0.365	0.674	0.160	0.210	0.469
20000	Rf2382	263	0.074	0.160	1.637	8.790	1.081	1.931	0.417	0.611	0.582	0.028	0.061	0.622	3.342	0.411	0.734	0.159	0.232	0.221
	Rf2383	293	0.071	0.150	1.807	7.946	1.131	2.017	0.482	0.509	1.026	0.024	0.051	0.617	2.712	0.386	0.688	0.165	0.174	0.350
	Rf2384	256	0.068	0.162	1.524	7.026	0.901	1.861	0.446	0.413	0.685	0.027	0.063	0.595	2.745	0.352	0.727	0.174	0.161	0.268
	Rf2385	262	0.071	0.153	1.678	7.524	0.976	1.965	0.390	0.537	0.860	0.027	0.058	0.640	2.872	0.373	0.750	0.149	0.205	0.328
	Rf2386	248	0.062	0.135	1.560	6.437	0.912	1.966	0.310	0.570	0.812	0.025	0.054	0.629	2.596	0.368	0.793	0.125	0.230	0.327
	Rf2387	217	0.055	0.161	1.417	6.207	0.871	1.766	0.311	0.485	0.863	0.025	0.074	0.653	2.860	0.401	0.814	0.143	0.224	0.398
	Rf2388	235	0.073	0.170	1.529	7.105	0.861	1.916	0.323	0.452	1.037	0.031	0.072	0.651	3.023	0.366	0.815	0.137	0.192	0.441
	Rf2389	252	0.072	0.118	1.750	7.197	1.019	1.896	0.370	0.685	1.693	0.029	0.047	0.694	2.856	0.404	0.752	0.147	0.272	0.672
	Rf2390	248	0.054	0.131	1.571	6.518	0.802	1.802	0.409	0.528	0.903	0.022	0.053	0.633	2.628	0.323	0.727	0.165	0.213	0.364

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APPENDIX 17

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-MALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G1	Rf2311	0	NAD	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Proteinaceous material in tubules 1a PANCREAS: Inflammation 1a STOMACH: Cystic gland(s) 1a THYMUS: Epithelial hyperplasia 1a Hemorrhage 1a PITUITARY: Dilated Rathke's cleft
G1	Rf2312	0	NAD	STOMACH: Cystic gland(s) 1a THYMUS: Hemorrhage 1a PITUITARY: Cyst(s)
G1	Rf2313	0	NAD	LIVER: Lymphocytic infiltration 1a KIDNEYS: Proteinaceous material in tubules 1a Basophilic tubules 1a Lymphocytic infiltration 1a LUNGS: Pneumonic foci 2 SALIVARY GLAND: Lymphocytic infiltration 1a THYMUS: Epithelial hyperplasia 1a URINARY BLADDER: Lymphocytic infiltration-submucosa 1a
G1	Rf2314	0	NAD	KIDNEYS: Proteinaceous material in tubules 1a Dilatation-collecting ducts 1 LUNGS: Pneumonic foci 1 Mineralisation-pulmonary vessels 1a PITUITARY: Dilated Rathke's cleft SKIN: Epidermal hyperplasia 1a

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

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-MALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G1	Rf2314			SKIN: Hyperkeratosis 1 STERNUM WITH MARROW: Cartilage degeneration 1a
G1	Rf2315	0	THYMUS:Petechiae EPIDIDYMES(Unilateral): :Mass(es)-0.7 cm -White -Soft -Round	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Dilatation of pelvis 2-unilateral Hyaline droplets-tubular epithelium 2a Basophilic tubules 1a Lymphocytic infiltration 1a THYMUS: Hemorrhage 3a TESTES: Atrophy-seminiferous tubules 3-unilateral EPIDIDYMIDES: Spermatic granuloma Lymphocytic infiltration 1a Cell debris in lumen PITUITARY: Dilated Rathke's cleft
G1	Rf2316	0	NAD	LIVER: Necrobiotic focus(i) 1 LUNGS: Pneumonic foci 2 ADRENALS: Vacuolation-cortical cells 2d THYROIDS: Ectopic thymus PITUITARY: Dilated Rathke's cleft

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

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-MALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G1	Rf2317	0	NAD	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Proteinaceous material in tubules 2a Basophilic tubules 1a Hyaline droplets-tubular epithelium 2a LUNGS: Pneumonic foci 2 PANCREAS: Adipocytes 1a THYMUS: Epithelial hyperplasia 1a Hemorrhage 1a ADRENALS: Vacuolation-cortical cells 1d EPIDIDYMIDES: Lymphocytic infiltration 1a
G1	Rf2318	0	NAD	KIDNEYS: Proteinaceous material in tubules 1a Lymphocytic infiltration 1a Dilatation-collecting ducts 3 LUNGS: Pneumonic foci 2 STOMACH: Cystic gland(s) 1a PITUITARY: Dilated Rathke's cleft STERNUM WITH MARROW: Cartilage degeneration 2a
G1	Rf2319	0	NAD	KIDNEYS: Proteinaceous material in tubules 1a Lymphocytic infiltration 1a LUNGS: Lymphocytic infiltration 2a SALIVARY GLAND: Lymphocytic infiltration 1a PANCREAS: Inflammation-chronic 1a STOMACH: Cystic gland(s) 2a

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

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-MALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G1	Rf2319			RECTUM: Parasite(s) THYMUS: Hemorrhage 1a PITUITARY: Dilated Rathke's cleft
G1	Rf2320	0	NAD	KIDNEYS: Proteinaceous material in tubules 1a THYROIDS: Ectopic thymus SKIN: Hyperkeratosis 1
G2	Rf2321	2000	NAD	LUNGS: Mineralisation-pulmonary vessels 1a
G2	Rf2322	2000	NAD	LUNGS: Pneumonic foci 1 Mineralisation-pulmonary vessels 1a
G2	Rf2323	2000	THYMUS:Petechiae	LUNGS: Pneumonic foci 1 THYMUS: Hemorrhage 2a
G2	Rf2324	2000	NAD	LUNGS: Lymphocytic infiltration 2a
G2	Rf2325	2000	KIDNEY(Unilateral):Pelvis dilated	LUNGS: Pneumonic foci 2 KIDNEYS: Dilatation of pelvis 2-unilateral Urothelial hyperplasia 1a Mineralisation 1a
G2	Rf2326	2000	NAD	LUNGS: Pneumonic foci 1 Mineralisation-pulmonary vessels 1a

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

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-MALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G2	Rf2327	2000	NAD	LUNGS: Pneumonic foci 2
G2	Rf2328	2000	KIDNEY(Unilateral):Cyst-0.3 cm	LUNGS: Pneumonic foci 2 KIDNEYS: Cyst(s)
G2	Rf2329	2000	NAD	LUNGS: Mineralisation-pulmonary vessels 1a
G2	Rf2330	2000	NAD	LUNGS: Pneumonic foci 2 Mineralisation-pulmonary vessels 1a
G3	Rf2331	7000	NAD	LUNGS: Pneumonic foci 3 Mineralisation-pulmonary vessels 1a
G3	Rf2332	7000	NAD	LUNGS: Pneumonic foci 1 Mineralisation-pulmonary vessels 1a
G3	Rf2333	7000	NAD	LUNGS: Mineralisation-pulmonary vessels 1a
G3	Rf2334	7000	NAD	LUNGS: Tissue present no change
G3	Rf2335	7000	NAD	LUNGS: Pneumonic foci 3
G3	Rf2336	7000	NAD	LUNGS: Pneumonic foci 2
G3	Rf2337	7000	NAD	LUNGS: Pneumonic foci 4

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

contd.

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INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-MALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G3	Rf2338	7000	SKIN:Hair thinning with hair regrowth-Multifocal THYMUS:Petechiae	LUNGS: Pneumonic foci 1 Mineralisation-pulmonary vessels 1a SKIN: Epidermal hyperplasia 2a THYMUS: Hemorrhage 2a
G3	Rf2339	7000	NAD	LUNGS: Pneumonic foci 3 Mineralisation-pulmonary vessels 1a
G3	Rf2340	7000	NAD	LUNGS: Pneumonic foci 2
G4	Rf2341	20000	NAD	ADRENALS: Accessory adrenal PITUITARY: Dilated Rathke's cleft SKIN: Epidermal hyperplasia 1d STERNUM WITH MARROW: Cartilage degeneration 1a
G4	Rf2342	20000	NAD	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Dilatation-collecting ducts 1 LUNGS: Lymphocytic infiltration 1a PITUITARY: Dilated Rathke's cleft SKIN: Epidermal hyperplasia 1a
G4	Rf2343	20000	NAD	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Proteinaceous material in tubules 1a Basophilic tubules 1a LUNGS: Lymphocytic infiltration 1a

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

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-MALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G4	Rf2343			PANCREAS: Lymphocytic infiltration 1a THYMUS: Epithelial hyperplasia 1a PITUITARY: Dilated Rathke's cleft STERNUM WITH MARROW: Cartilage degeneration 1a
G4	Rf2344	20000	NAD	LIVER: Necrobiotic focus(i) 1 STOMACH: Cystic gland(s) 1a THYROIDS: Ectopic thymus Ultimobranchial cyst PITUITARY: Dilated Rathke's cleft STERNUM WITH MARROW: Cartilage degeneration 1a
G4	Rf2345	20000	SKIN(Cervical region):Hair thinning with hair regrowth	KIDNEYS: Urothelial hyperplasia 1a PANCREAS: Lymphocytic infiltration 1a PITUITARY: Dilated Rathke's cleft SKIN: Epidermal hyperplasia 1a
G4	Rf2346	20000	NAD	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Proteinaceous material in tubules 1a Basophilic tubules 1a THYMUS: Hemorrhage 1a PITUITARY: Dilated Rathke's cleft
G4	Rf2347	20000	NAD	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Basophilic tubules 1a Lymphocytic infiltration 1a Dilatation-collecting ducts 2

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

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-MALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G4	Rf2347			LUNGS: Pneumonic foci 3 SALIVARY GLAND: Lymphocytic infiltration 1a STOMACH: Hypertrophy-mucus glands 2 THYMUS: Epithelial cyst(s) PITUITARY: Dilated Rathke's cleft
G4	Rf2348	20000	THYMUS:Petechiae	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Basophilic tubules 1a Hyaline droplets-tubular epithelium 2a LUNGS: Pneumonic foci 3 COLON: Parasite(s) THYMUS: Hemorrhage 3a ADRENALS: Vacuolation-cortical cells 1d URINARY BLADDER: Lymphocytic infiltration-submucosa 1a
G4	Rf2349	20000	NAD	KIDNEYS: Hyaline droplets-tubular epithelium 2d LUNGS: Lymphocytic infiltration 1a PITUITARY: Dilated Rathke's cleft STERNUM WITH MARROW: Cartilage degeneration 1a
G4	Rf2350	20000	NAD	STOMACH: Cystic gland(s) 1a PITUITARY: Dilated Rathke's cleft Cyst(s)

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

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APPENDIX 18

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-FEMALES

G. No	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G1	Rf2351	0	NAD	LIVER: Necrobiotic focus(i) 1 LUNGS: Pneumonic foci 3 RECTUM: Parasite(s) OVARIES: Dilated tubules-hilus 1 THYROIDS: Ectopic thymus
G1	Rf2352	0	SKIN:Hair thinning with hair regrowth-Multifocal	LIVER: Necrobiotic focus(i) 1 STOMACH: Cystic gland(s) 1a THYMUS: Epithelial hyperplasia 1a Epithelial cyst(s) SKIN: Epidermal hyperplasia 2d
G1	Rf2353	0	SKIN:Hair thinning with hair regrowth-Multifocal	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Urothelial hyperplasia 1a Lymphocytic infiltration 2a LUNGS: Pneumonic foci 2 OVARIES: Hemocyst PITUITARY: Dilated Rathke's cleft SKIN: Epidermal hyperplasia 1d STERNUM WITH MARROW: Cartilage degeneration 1a
G1	Rf2354	0	SKIN:Hair thinning with hair regrowth-Multifocal	LIVER: Necrobiotic focus(i) 1 LUNGS: Lymphocytic infiltration 2a THYROIDS: Ectopic thymus SKIN: Epidermal hyperplasia 2d

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

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-FEMALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G1	Rf2355	0	SKIN(Cervical region):Hair thinning with hair regrowth-Focal	LIVER: Necrobiotic focus(i) 1 LUNGS: Osseous metaplasia 1a, Lymphocytic infiltration 1a SPLEEN: Increased hemosiderosis 1 OVARIES: Luteal cyst(s) SKIN: Tissue present no change
G1	Rf2356	0	SKIN(Cervical region):Hair thinning with hair regrowth-Focal	LUNGS: Pneumonic foci 2 THYMUS: Epithelial hyperplasia 1a UTERUS: Dilatation 3 URINARY BLADDER: Lymphocytic infiltration-submucosa 1a SKIN: Epidermal hyperplasia 1d
G1	Rf2357	0	SKIN(Cervical region):Hair thinning with hair regrowth-Focal	LIVER: Necrobiotic focus(i) 1 LUNGS: Pneumonic foci 3 Mineralisation-pulmonary vessels 1a SPLEEN: Increased hemosiderosis 2 THYMUS: Epithelial hyperplasia 1a SKIN: Tissue present no change
G1	Rf2358	0	SKIN(Cervical region):Hair thinning with hair regrowth-Focal	LIVER: Necrobiotic focus(i) 1 LUNGS: Pneumonic foci 2 SALIVARY GLAND: Vacuolation 2a SPLEEN: Increased hemosiderosis 2 PITUITARY: Cyst(s) SKIN: Epidermal hyperplasia 1a STERNUM WITH MARROW: Cartilage degeneration 1a

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

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-FEMALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G1	Rf2359	0	SKIN(Lumbar region):Wound :Hair thinning with hair regrowth-Multifocal	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Mineralisation 1a SPLEEN: Increased hemosiderosis 2 OVARIES: Luteal cyst(s) SKIN: Epidermal hyperplasia 2d Necrotising dermatitis 2a STERNUM WITH MARROW: Cartilage degeneration 1a
G1	Rf2360	0	NAD	LIVER: Necrobiotic focus(i) 1 KIDNEYS: Dilatation-collecting ducts 2 LUNGS: Pneumonic foci 2 SALIVARY GLAND: Lymphocytic infiltration 1a OVARIES: Dilated tubules-hilus 2
G2	Rf2361	2000	NAD	LUNGS: Mineralisation-pulmonary vessels 1a Lymphocytic infiltration 2a
G2	Rf2362	2000	SKIN(Cervical region):Wound :Hair thinning with hair regrowth-Multifocal	LUNGS: Tissue present no change SKIN: Epidermal hyperplasia 2d Necrotising dermatitis 2a
G2	Rf2363	2000	NAD	LUNGS: Pneumonic foci 2 Mineralisation-pulmonary vessels 1a
G2	Rf2364	2000	NAD	LUNGS: Lymphocytic infiltration 1a

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

contd.

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APPENDIX 18 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-FEMALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G2	Rf2365	2000	SKIN(Pelvic region):Hair thinning with hair regrowth-Focal	LUNGS: Tissue present no change SKIN: Tissue present no change
G2	Rf2366	2000	NAD	LUNGS: Tissue present no change
G2	Rf2367	2000	NAD	LUNGS: Pneumonic foci 1 Mineralisation-pulmonary vessels 1a
G2	Rf2368	2000	NAD	LUNGS: Lymphocytic infiltration 2a
G2	Rf2369	2000	NAD	LUNGS: Tissue present no change
G2	Rf2370	2000	NAD	LUNGS: Tissue present no change
G3	Rf2371	7000	SKIN:Hair thinning with hair regrowth-Multifocal UTERUS:Dilatation-Multifocal	LUNGS: Pneumonic foci 1 SKIN: Epidermal hyperplasia 1d UTERUS: Dilatation 4
G3	Rf2372	7000	NAD	LUNGS: Tissue present no change
G3	Rf2373	7000	NAD	LUNGS: Pneumonic foci 1
G3	Rf2374	7000	SKIN(Cervical region):Hair thinning with hair regrowth-Focal UTERUS:Dilatation-Multifocal	LUNGS: Tissue present no change UTERUS: Dilatation 4 SKIN: Epidermal hyperplasia 1d

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

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-FEMALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G3	Rf2375	7000	SKIN(Cervical region):Hair thinning with hair regrowth-Focal	LUNGS: Pneumonic foci 3 Mineralisation-pulmonary vessels 1a SKIN: Epidermal hyperplasia 1a
G3	Rf2376	7000	KIDNEY(Bilateral):Pelvis dilated	LUNGS: Tissue present no change KIDNEYS: Dilatation of pelvis 4-unilateral Lymphocytic infiltration 1a Basophilic tubules 1a
G3	Rf2377	7000	NAD	LUNGS: Tissue present no change
G3	Rf2378	7000	NAD	LUNGS: Tissue present no change
G3	Rf2379	7000	SKIN(Cervical region):Hair thinning with hair regrowth-Focal	LUNGS: Pneumonic foci 2 SKIN: Epidermal hyperplasia 1a
G3	Rf2380	7000	SKIN(Cervical region):Hair thinning with hair regrowth-Focal	LUNGS: Tissue present no change SKIN: Epidermal hyperplasia 1d
G4	Rf2381	20000	UTERUS:Dilatation-Focal	LUNGS: Mineralisation-pulmonary vessels 1a STOMACH: Cystic gland(s) 1a THYROIDS: Ectopic thymus UTERUS: Dilatation 4

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

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-FEMALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G4	Rf2382	20000	SKIN:Hair thinning with hair regrowth-Multifocal	OVARIES: Dilated tubules-hilus 2 PITUITARY: Dilated Rathke s cleft STERNUM WITH MARROW: Cartilage degeneration 1a SKIN: Tissue present no change
G4	Rf2383	20000	NAD	LIVER: Necrobiotic focus(i) 1 LUNGS: Lymphocytic infiltration 1a SPLEEN: Increased hemosiderosis 2 PARATHYROIDS: Connective tissue proliferation 1a
G4	Rf2384	20000	NAD	LUNGS: Lymphocytic infiltration 3a STOMACH: Hypertrophy-mucus glands 2
G4	Rf2385	20000	NAD	SALIVARY GLAND: Lymphocytic infiltration 1a SPLEEN: Increased hemosiderosis 2 THYMUS: Epithelial hyperplasia 2a OVARIES: Luteal cyst(s) STERNUM WITH MARROW: Cartilage degeneration 1a
G4	Rf2386	20000	SKIN:Hair thinning with hair regrowth-Multifocal	LIVER: Necrobiotic focus(i) 1 SALIVARY GLAND: Lymphocytic infiltration 1a COLON: Lymphoid hyperplasia 2 SKIN: Epidermal hyperplasia 1d
G4	Rf2387	20000	NAD	LIVER: Lymphocytic infiltration 1a LUNGS: Pneumonic foci 3 SPLEEN: Increased hemosiderosis 2

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

contd.

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REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF Aspergillus niger(GEP44) IN WISTAR RATS

INDIVIDUAL GROSS PATHOLOGICAL AND HISTOPATHOLOGICAL FINDINGS-FEMALES

G. No.	Rat No.	Dose (mg/kg Bwt/day)	Gross	Microscopic
G4	Rf2388	20000	SKIN(Cervical region):Hair thinning with hair regrowth-Focal	LIVER: Lymphocytic infiltration 1a SPLEEN: Increased hemosiderosis 2 SKIN: Tissue present no change
G4	Rf2389	20000	UTERUS:Dilatation-Multifocal	LIVER: Necrobiotic focus(i) 1 THYMUS: Hemorrhage 1a OVARIES: Luteal cyst(s) UTERUS: Dilatation 4 STERNUM WITH MARROW: Cartilage degeneration 1a
G4	Rf2390	20000	SKIN(Fore head region):Hair thinning with hair regrowth-Focal	LIVER: Necrobiotic focus(i) 1 LUNGS: Pneumonic foci 3 SKIN: Epidermal hyperplasia 1a

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

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APPENDIX 19

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

DSM Food Specialties B.V.
R&D/Analysis

DSM

F-12202 version 1
Page 1 of 1

CERTIFICATE OF ANALYSIS

Name of the product	Enzyme preparation from *Aspergillus niger* GEP44
Batch no.	JLL 03 006 IDF
Study no.	ANA/03/D68
GLP-archive no.	GLP-0302
Status	ISO 9002
Date of manufacture	March 2003
Date of expiration	March 2004 (provisional)
Active component	Endoprotease
Date of issue	17 June 2003

Analysis type	Method number	Dimension	Result
Endoprotease activity	62186	PPU/g	11.0
Dry matter	60485	% (w/w)	25.9
Ash	60326	% (w/w)	0.7
Total organic solids (TOS)	W-10850NLv2	% (w/w)	25.2
Proteins by Kjeldahl Nitrogen x 6.25	62186	% (w/w)	13.9
Stability in water 21°C, 100 mg/ml	62186	hours	48
Stability in water 21°C, 350 mg/ml	62186	hours	48
Stability in water 21°C, undiluted	62186	hours	48
Stability in water 4°C, 100 mg/ml	62186	days	7
Stability in water 4°C, 350 mg/ml	62186	days	7
Stability in water 4°C, undiluted	62186	days	7

Signature Study Director: R.P.J.M. Snuverink

Date:

Remarks (If any):

APPENDIX 20

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

TEST ITEM PREPARATION DATA

Date of test item preparation	Group No.	Dose (mg/kg Bwt/day)	Test Item (ml)	Total volume (ml) with double distilled water
01.09.2003	G1	0	-	400
	G2	2000	37.1	400
	G3	7000	129.8	400
	G4	20000	270	#
04.09.2003	G1	0	-	400
	G2	2000	37.1	400
	G3	7000	129.8	400
	G4	20000	325	#
08.09.2003 & 11.09.2003	G1	0	-	325
	G2	2000	30.1	325
	G3	7000	105.5	325
	G4	20000	340	#
15.09.2003	G1	0	-	325
	G2	2000	30.1	325
	G3	7000	105.5	325
	G4	20000	300	#
18.09.2003	G1	0	-	425
	G2	2000	39.4	425
	G3	7000	137.9	425
	G4	20000	400	#
22.09.2003	G1	0	-	375
	G2	2000	34.8	375
	G3	7000	121.7	375
	G4	20000	355.5	#
25.09.2003	G1	0	-	475
	G2	2000	44.0	475
	G3	7000	154.1	475
	G4	20000	475	#

Note: - Not applicable
#: For G4 group, undiluted test item was administered at a dose volume of 18.54 ml/kg Bwt/day.

contd.

APPENDIX 20 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

TEST ITEM PREPARATION DATA

Date of test item preparation	Group No.	Dose (mg/kg Bwt/day)	Test Item (ml)	Total volume (ml) with double distilled water
29.09.2003	G1	0	-	425
	G2	2000	39.4	425
	G3	7000	137.9	425
	G4	20000	375	#
02.10.2003	G1	0	-	575
	G2	2000	53.3	575
	G3	7000	186.6	575
	G4	20000	500	#
06.10.2003	G1	0	-	475
	G2	2000	44.0	475
	G3	7000	154.1	475
	G4	20000	400	#
09.10.2003	G1	0	-	575
	G2	2000	53.3	575
	G3	7000	186.6	575
	G4	20000	500	#
13.10.2003	G1	0	-	475
	G2	2000	44.0	475
	G3	7000	154.1	475
	G4	20000	420	#
16.10.2003	G1	0	-	650
	G2	2000	60.3	650
	G3	7000	210.9	650
	G4	20000	560	#
20.10.2003	G1	0	-	550
	G2	2000	51.0	550
	G3	7000	178.5	550
	G4	20000	465	#

Note: - Not applicable
#: For G4 group, undiluted test item was administered at a dose volume of 18.54 ml/kg Bwt/day.

contd.

APPENDIX 20 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

TEST ITEM PREPARATION DATA

Date of test item preparation	Group No.	Dose (mg/kg Bwt/day)	Test Item (ml)	Total volume (ml) with double distilled water
23.10.2003	G1	0	-	725
	G2	2000	67.2	725
	G3	7000	235.3	725
	G4	20000	620	#
27.10.2003	G1	0	-	600
	G2	2000	55.6	600
	G3	7000	194.7	600
	G4	20000	510	#
30.10.2003	G1	0	-	800
	G2	2000	74.2	800
	G3	7000	259.6	800
	G4	20000	680	#
03.11.2003	G1	0	-	450
	G2	2000	41.7	450
	G3	7000	146.0	450
	G4	20000	420	#
06.11.2003	G1	0	-	650
	G2	2000	60.3	650
	G3	7000	210.9	650
	G4	20000	580	#
10.11.2003	G1	0	-	480
	G2	2000	44.5	480
	G3	7000	155.8	480
	G4	20000	450	#
13.11.2003	G1	0	-	640
	G2	2000	59.3	640
	G3	7000	207.7	640
	G4	20000	600	#

Note: - Not applicable
#: For G4 group, undiluted test item was administered at a dose volume of 18.54 ml/kg Bwt/day.

contd.

APPENDIX 20 contd.

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

TEST ITEM PREPARATION DATA

Date of test item preparation	Group No.	Dose (mg/kg Bwt/day)	Test Item (ml)	Total volume (ml) with double distilled water
17.11.2003	G1	0	-	510
	G2	2000	47.3	510
	G3	7000	165.5	510
	G4	20000	480	#
20.11.2003	G1	0	-	680
	G2	2000	63.1	680
	G3	7000	220.7	680
	G4	20000	640	#
24.11.2003	G1	0	-	540
&	G2	2000	50.1	540
27.11.2003	G3	7000	175.2	540
	G4	20000	510	#

Note: - Not applicable
#: For G4 group, undiluted test item was administered at a dose volume of 18.54 ml/kg Bwt/day.

APPENDIX 21

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY BY GAVAGE WITH ENZYME PREPARATION OF *Aspergillus niger* (GEP44) IN WISTAR RATS

BATCH ANALYSIS DATA

Date	Mean protein content in the sample (mg/ml)				Test item concentration in the sample (mg/ml)			
	G1	G2	G3	G4	G1	G2	G3	G4
01.09.2003	-	13.96	48.51	150.31	-	100.43	348.99	1081.37
06.10.2003	-	13.82	48.58	149.94	-	99.42	349.50	1078.71
06.11.2003	-	13.91	48.86	149.86	-	100.1	351.5	1078.1
Mean ± SD	-	13.90 ± 0.07	48.65 ± 0.19	150.03 ± 0.36	-	99.98 ± 0.52	350.00 ± 1.33	1079.39 ± 1.74

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ANNEXURE 1

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/1344 Date: 24.09.2003

Sample Details: Name: Ssniff Rats/Mice (pellet) Feed Maintenance Sampling Date: 01.09.2003

Batch No. : 6273424

Supplier : Ssniff Spezialdiäten GmbH, D-59494, Soest Germany

Manufacturer: Ssniff Spezialdiäten GmbH, D-59494, Soest Germany

ANALYSIS RESULTS
(Analysis on "as is basis")

No.	PARAMETER	(%)
1.	Moisture	17.3
2.	Crude protein (Nx6.25)	19.0
3.	Crude fat (Ether extract)	2.6
4.	Crude fibre	4.7
5.	Total ash	6.1
6.	Acid insoluble ash	0.6
7.	Nitrogen free extract	50.3
8.	Calcium (Ca)	1.27
9.	Phosphorus (P)	0.59

24/9/2003
Residue/Analytical Dept.,

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Peenya, Bangalore - 560 058.

ANNEXURE 2

TOXICOLOGY DEPARTMENT
FEED CONTAMINANT ANALYSIS REPORT FOR SSNIFF RATS/MICE DIET - MAINTENANCE MEAL

ANALYSED BY: Landwirtschaftliche Untersuchungs - und Forschungsanstalt Institut für Tiergesundheit und Lebensmittelqualität GmbH KIEL, Germany

AGRICULTURAL EXPERIMENTAL RESEARCH STATION AND INSTITUTE FOR ANIMAL HEALTH AND FOOD STUFF QUALITY GmbH KIEL, GERMANY

REFERENCE: SSNIFF RATS/MICE DIET - MAINTENANCE MEAL
Date of Sampling : 06.09.2002
Batch No. : 5362331

ANALYSIS REPORT
Date of Analysis: 17.10.2002
Reference No. : AN-55494 Li

I. CHLORINATED HYDROCARBONS		(mg/kg)
a.	Aldrine	n.d. < 0.005
b.	α - Chlordane	n.d. < 0.005
c.	χ - Chlordane	n.d. < 0.005
d.	Oxy - Chlordane	n.d. < 0.005
e.	p,p-DDD	n.d. < 0.005
f.	p,p-DDE	n.d. < 0.005
g.	o,p-DDT	n.d. < 0.005
h.	p,p-DDT	n.d. < 0.005
i.	Dieldine	n.d. < 0.005
j.	α - Endosulfane	n.d. < 0.005
k.	β - Endosulfane	n.d. < 0.005
l.	Endosulfansulfate	n.d. < 0.005
m.	Endrine	n.d. < 0.005
n.	HCB (Hexachlorbenzole)	n.d. < 0.005
o.	α - HCH	n.d. < 0.005
p.	β - HCH	n.d. < 0.005
q.	δ - HCH	n.d. < 0.005
r.	Epsilon - HCH	n.d. < 0.005
s.	χ - HCB (Lindan)	n.d. < 0.005
t.	Heptachlor	n.d. < 0.005
u.	cis - Heptachlorepoxide	n.d. < 0.005
v.	trans - Heptachlorepoxide	n.d. < 0.005
w.	Methoxychlor	n.d. < 0.005
x.	Quintozene	n.d. < 0.005
y.	Tecnazen	n.d. < 0.005
z.	Tetradifon	n.d. < 0.005

II. PHOSPHORIC ACID ESTERS		(mg/kg)
a.	Bromophos (-ethyle)	n.d. < 0.010
b.	Bromophos (-methyle)	n.d. < 0.010
c.	Chlorfenvinphos	n.d. < 0.010
d.	Chlorpyriphos (-ethyle)	n.d. < 0.010
e.	Chlorpyriphos (-methyle)	n.d. < 0.010
f.	Chlorthione	n.d. < 0.010
g.	Diazinone	n.d. < 0.010
h.	Dichlorvos	n.d. < 0.010
i.	Dimethoate	n.d. < 0.010
j.	Ethione	n.d. < 0.010
k.	Fenithrothione	n.d. < 0.010
l.	Fenthione	n.d. < 0.010
m.	Malathione	0.037
n.	Mecarbame	n.d. < 0.010
o.	Methidathione	n.d. < 0.010
p.	Parathion (-ethyle)	n.d. < 0.010
q.	Parathion (-methyle)	n.d. < 0.010
r.	Pirimiphos (-ethyle)	n.d. < 0.010
s.	Pirimiphos (-methyle)	0.312
t.	Profenofos	n.d. < 0.010
u.	Sulfotep	n.d. < 0.010

III. POLYCHLORIERTE BIPHENYLS (PCB)		mg/kg
a.	PCB EK 28	n.d. < 0.005
b.	PCB EK 52	n.d. < 0.005
c.	PCB EK 101	n.d. < 0.005
d.	PCB EK 118	n.d. < 0.005
e.	PCB EK 138	n.d. < 0.005
f.	PCB EK 153	n.d. < 0.005
g.	PCB EK 180	n.d. < 0.005

IV. AFLATOXINS		µg/kg
a.	Aflatoxine B1	n.d. < 1µg/kg
b.	Aflatoxine B2	n.d. < 1µg/kg
c.	Aflatoxine G1	n.d. < 1µg/kg
d.	Aflatoxine G2	n.d. < 1µg/kg

n.d: Not detected

Sd/-
Dr. Wehage

RALLIS RESEARCH CENTRE
Peenya, Bangalore - 560 058.

ANNEXURE 3

RALLIS RESEARCH CENTRE, 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/159

Date: 01.10.2003

Sample Details : Source of Collection : Outlet of the Aquaguard (At use point)

Date of Collection : 01.09.2003

ANALYSIS RESULTS

Sl. No.	Parameter	Content
1.	Colour	Colourless
2.	Odour	Odourless
3.	Turbidity	Clear
4.	PH	7.48
5.	Electrical Conductivity, dSm^{-1}	1.463
6.	Total solids, (ppm)	963
7.	Suspended solids, (ppm)	15
8.	Dissolved solids, (ppm)	948
9.	Dissolved oxygen, (ppm)	5.7
10.	Biochemical Oxygen Demand 5 days at 20°C, (ppm)	3.6
11.	Chemical Oxygen Demand (ppm)	8.1

Sl. No.	Parameter	Content (ppm)
12.	Total hardness as $CaCo_3$	444
13.	Calcium as Ca^{2+}	89
14.	Magnesium as Mg^{2+}	54
15.	Chlorides as Cl^-	271
16.	Sulphates as SO_4^{2-}	72
17.	Carbonates as CO_3^{2-}	--
18.	Bicarbonates as HCO_3^-	403
19.	Sodium as Na	89
20.	Potassium as K	9

01/10/2003

Residue/Analytical Dept.,

RALLIS RESEARCH CENTRE
Peenya, Bangalore - 560 058.

ANNEXURE 4

TOXICOLOGY DEPARTMENT
CONTAMINANT ANALYSIS REPORT FOR WATER SAMPLE

ANALYSED BY: **UMWELT CONTROL LABOR GmbH**
EUPENER STRASSE, 150
D-50933 KÖLN, GERMANY

REFERENCE : **WATER SAMPLE - FROM OUTLET OF AQUAGUARD WATER FILTER**

Sample No. : WATER; W-13
Date of Sampling : 06.09.2002
Date of receipt : 16.10.2002

Sl. No.	PARAMETERS	VALUES µg/l	Sl. No.	PARAMETERS	VALUES µg/l
ORGANOCHLORPESTICIDES					
1.	Hexachlorbenzol (HCB)	< 0.001	12.	Endrine	< 0.001
2.	Aldrine	< 0.001	13.	α - HCH	< 0.001
3.	o.p-DDD	< 0.001	14.	β - HCH	< 0.001
4.	p.p-DDD	< 0.001	15.	δ - HCH	< 0.001
5.	o.p-DDE	< 0.001	16.	χ - HCB (Lindan)	< 0.001
6.	p.p-DDE	< 0.001	17.	Heptachlor	< 0.001
7.	o.p-DDT	< 0.001	18.	cis - Heptachlorepoxide	< 0.001
8.	p.p-DDT	< 0.001	19.	trans - Heptachlorepoxide	< 0.001
9.	Dieldrin	< 0.001	20.	Methoxychlor	< 0.001
10.	α - Endosulfane	< 0.001	21.	Quintozene	< 0.001
11.	β - Endosulfane	< 0.001			< 0.001
III. POLYCHLORIERTE BIPHENYLS (PCB) µg/l					
22..	PCB EK 28	< 0.02			
23.	PCB EK 52	< 0.02			
24.	PCB EK 101	< 0.02			
25.	PCB EK 118	< 0.02			
26.	PCB EK 138	< 0.02			
27.	PCB EK 153	< 0.02			
28.	PCB EK 180	< 0.02			

Sd/-
Head of Laboratory
Cologne

ANNEXURE 5

GLP CERTIFICATE - GERMANY

Bundesinstitut
für gesundheitlichen Verbraucherschutz und Veterinärmedizin

bgvv

GUTE LABORPRAXIS / GOOD LABORATORY PRACTICE

GLP-Bestätigung / GLP Certificate

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

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

Prüfeinrichtung / Test facility

Rallis India, Ltd.
Rallis Research Centre
Peenya Industrial Area
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; Prüfungen zur Bioakkumulation und zur Metabolisierung / Studies on behaviour in water, soil and air, bioaccumulation
Prüfungen zur Bestimmung von Rückständen / Residue studies

Datum der Inspektion / Date of Inspection

13. - 20. December 2000

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.)

20. November 2001
Im Auftrag / For the Director

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

contd.

ANNEXURE 5 contd.

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.

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

ANNEXURE 6

HISTORICAL DATA - 33

SUBCHRONIC (90 DAY) ORAL TOXICITY STUDY IN WISTAR RATS

contd.

HISTORICAL CONTROL DATA - 33

SUBCHRONIC (90 DAY) ORAL TOXICITY STUDY IN WISTAR RATS

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

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV G/l	MCH pg	MCHC g/l	PLAT G/l	P.T. S	Retic %	Neut %	Lymp %	Eosi %	Mono %	Baso %
2632/99	Mean	7.1	8.69	148	0.461	53.2	17.1	321	583	18.3	@	20.8	75.6	1.6	2.0	0.0
	SD	1.94	0.61	6.94	0.03	1.81	0.67	6.38	65.24	2.15		4.44	4.77	0.97	1.33	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
2959/00	Mean	6.9	8.49	159	0.425	50.1	18.8	375	955	13.4	@	13.1	83.1	2.3	1.5	0.0
	SD	1.94	0.39	5.91	0.022	1.66	0.59	7.12	173.11	0.97		3.28	4.38	0.95	1.18	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3282/01	Mean	8.1	8.77	157	0.449	51.2	18.0	350	1084	15.2	@	14.7	82.6	2.3	0.4	0.0
	SD	1.90	0.46	7.54	0.024	0.75	0.4	6.88	98.51	1.07		4.24	4.50	1.70	0.70	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3270/01	Mean	5.7	8.76	162	0.432	49.4	18.5	375	957	18.4	@	14.6	82.2	2.4	0.8	0.0
	SD	1.76	0.31	3.88	0.016	1.46	0.44	9.25	139.14	1.34		5.5	5.71	2.27	1.03	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3219/01	Mean	6.8	8.57	152	0.473	55.3	17.7	321	757	15.56	@	12.3	86.6	1.1	0.0	0.0
	SD	1.51	0.31	4.45	0.014	1.47	0.49	3.41	55.07	0.79		4.5	4.97	0.88	0.00	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3302/01	Mean	7.1	9.17	161	0.465	50.7	17.6	347	1119	17.0	@	11.6	85.6	1.8	1.0	0.0
	SD	1.2	0.23	6.15	0.018	1.57	0.49	4.03	113.25	1.75		4.62	4.58	1.03	1.05	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3267/01	Mean	7.1	7.99	149	0.389	48.6	18.6	383	900	15.61	@	25.3	73.1	1.5	0.1	0.0
	SD	1.97	0.67	12.34	0.04	1.33	0.42	7.12	301.48	1.53		9.29	10.55	1.51	0.32	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10

N: No. of rats @: Not evaluated

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

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV G/l	MCH pg	MCHC g/l	PLAT G/l	P.T. S	Retic %	Neut %	Lymp %	Eosi %	Mono %	Baso %
3343/02	Mean	8.4	8.27	150	0.410	49.5	18.9	381	1014	16.2	@	19.9	79.5	0.6	0.0	0.0
	SD	2.09	0.39	8.49	0.018	1.33	0.72	18.05	109.53	1.05		7.85	7.91	0.84	0.00	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3295/01	Mean	6.1	8.61	161	0.440	51.1	18.7	367	1103	15.7	@	17.2	79.5	2.8	0.5	0.0
	SD	1.18	0.32	6.91	0.023	1.19	0.47	11.12	93.14	1.60		7.25	7.81	1.81	0.85	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3287/01	Mean	9.0	9.10	159	0.462	50.7	17.5	344	1132	19.2	@	11.4	86.3	1.5	0.8	0.0
	SD	1.67	0.27	2.57	0.012	1.26	0.46	8.59	73.37	4.03		4.17	3.74	1.08	0.79	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
2933/00	Mean	7.2	8.67	158	0.429	49.5	18.3	369	865	18.6	@	14.3	81.4	3.4	0.9	0.0
	SD	0.94	0.37	4.89	0.020	1.48	0.62	8.08	71.34	2.05		5.31	5.44	1.35	0.57	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3383/02	Mean	5.6	8.74	157	0.485	55.5	18.0	324	419	16.0	@	21.6	75.5	2.0	0.9	0.0
	SD	1.21	0.25	5.49	0.024	1.98	0.56	8.56	17.54	1.32		5.44	5.30	1.33	0.88	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3402/02	Mean	5.8	8.72	151	0.421	48.3	17.4	360	850	21.0	@	15.9	79.7	3.8	0.6	0.0
	SD	1.56	0.33	6.22	0.021	1.69	0.46	10.26	93.50	1.15		8.14	8.26	1.32	0.84	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3361/02	Mean	7.5	7.40	149	0.347	47.0	20.2	429	766	14.9	0.4	16.3	77.9	2.3	3.5	0.0
	SD	1.65	0.60	10.98	0.028	1.90	0.91	18.03	188.46	0.90	0.20	5.93	7.29	1.49	2.17	0.00
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

N: No. of rats @: Not evaluated

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

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV G/l	MCH pg	MCHC g/l	PLAT G/l	P.T. S	Retic %	Neut %	Lymp %	Eosi %	Mono %	Baso %
3448/02	Mean	9.2	8.20	152	0.422	51.4	18.6	361	967	19.4	@	12.0	84.1	2.4	1.5	0.0
	SD	1.90	0.27	4.24	0.016	1.09	0.44	6.56	99.58	1.62		3.65	4.25	1.58	1.08	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3446/02	Mean	6.9	8.55	157	0.428	50.0	18.4	368	934	14.8	@	21.8	75.1	2.2	0.9	0.0
	SD	1.89	0.39	5.13	0.019	1.40	0.59	11.06	65.25	0.79		15.41	15.75	1.62	1.45	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3351/02	Mean	10.6	8.50	159	0.416	49.0	18.7	381	886	16.1	@	18.8	75.5	4.2	1.5	0.0
	SD	2.54	0.41	4.40	0.017	1.07	0.50	8.36	67.17	1.49		4.13	4.48	1.69	1.43	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3345/01	Mean	7.2	7.91	151	0.390	49.3	19.0	386	1011	14.5	@	11.7	85.1	1.5	1.7	0.0
	SD	1.59	0.41	5.58	0.015	1.24	0.41	6.05	67.79	1.48		3.95	5.11	0.85	1.95	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
Mean		7.4	8.51	155	0.430	50.5	18.3	363	906	16.7	0.4	16.3	80.5	2.2	1	0
SD		1.73	0.41	6.66	0.022	1.46	0.55	9.62	122.25	1.67	0.20	6.59	6.99	1.4	1.13	0.0
1 SD: Range - Low		5.7	8.10	148	0.408	49.0	17.8	353	784	15	0.2	9.7	73.5	0.8	-0.1	0
1 SD: Range - High		9.1	8.92	162	0.452	52.0	18.9	373	1028	18.4	0.6	22.9	87.5	3.6	2.1	0
2 SD: Range - Low		3.9	7.69	142	0.386	47.6	17.2	344	662	13.4	0	3.1	66.5	-0.6	-1.3	0
2 SD: Range - High		10.9	9.33	168	0.474	53.4	19.4	382	1151	20	0.8	29.5	94.5	5	3.3	0

N: No. of rats @: Not evaluated
Note: The negative value of 1SD and 2 SD should be considered as "zero"

HISTORICAL CONTROL DATA - 33

SUBCHRONIC (90 DAY) ORAL TOXICITY STUDY IN WISTAR RATS

33.5 : HAEMATOLOGICAL VALUES - MALES (CONTROL RECOVERY GROUP - G1R)

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV G/l	MCH pg	MCHC g/l	PLAT G/l	P.T. S	Retic %	Neut %	Lymp %	Eosi %	Mono %	Baso %
2632/99	Mean	6.9	9.55	159	0.473	49.5	16.7	337	691	20.2	@	14.6	81.9	1.5	20.0	0.0
	SD	1.62	0.23	4.66	0.02	1.50	0.33	8.16	61.51	2.33		1.71	2.69	0.85	1.25	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
2959/00	Mean	7.7	8.93	160	0.435	48.7	18.0	369	1057	17.2	@	12.7	84.5	2.0	0.8	0.0
	SD	2.08	0.31	4.67	0.017	1.39	0.41	6.53	104.83	1.34		6.13	6.54	1.15	1.03	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3282/01	Mean	5.8	8.75	158	0.447	51.1	18.1	355	1029	16.2	@	11.4	85.6	1.9	1.1	0.0
	SD	1.20	0.34	5.81	0.017	1.22	0.34	9.88	84.38	1.90		4.09	4.58	1.29	0.99	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3270/01	Mean	@														
	SD															
	N															
3219/01	Mean	5.7	8.55	158	0.423	49.4	18.5	375	977	16.85	@	11.8	87.2	0.9	0.1	0.0
	SD	1.98	0.47	7.73	0.024	0.99	0.54	10.01	77.58	1.17		4.96	5.71	1.37	0.32	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3302/01	Mean	@														
	SD															
	N															
3267/01	Mean	5.2	8.84	160	0.449	50.9	18.1	356	999	15.82	@	13.5	85.5	0.8	0.2	0.0
	SD	2.30	0.40	6.73	0.03	1.56	0.41	9.31	135.84	1.31		6.35	5.80	1.14	0.42	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10

N: No. of rats @: Not evaluated

33.5 : HAEMATOLOGICAL VALUES - MALES (CONTROL RECOVERY GROUP - G1R)

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV G/l	MCH pg	MCHC g/l	PLAT G/l	P.T. S	Retic %	Neut %	Lymp %	Eosi %	Mono %	Baso %
3343/02	Mean	7.5	8.11	149	0.391	48.3	18.4	382	955	20.1	@	13.0	86.0	1.0	0.0	0.0
	SD	1.88	0.86	15.64	0.043	1.99	0.49	18.08	91.76	1.93		1.83	1.94	1.15	0.00	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3295/01	Mean	6.3	9.14	166	0.462	50.6	18.2	360	976	18.1	@	14.3	83.4	2.0	0.3	0.0
	SD	1.46	0.19	5.20	0.015	0.98	0.32	7.06	69.55	2.35		5.96	6.87	1.41	0.67	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3287/01	Mean	8.0	8.90	162	0.467	52.5	18.2	347	880	18.9	@	8.2	88.7	2.2	0.9	0.0
	SD	1.50	0.32	4.88	0.017	1.29	0.63	15.50	208.32	1.17		3.29	3.89	1.14	0.99	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
2933/00	Mean	6.9	8.78	152	0.505	57.6	17.3	301	830	18.7	@	13.3	82.3	3.7	0.7	0.0
	SD	1.45	0.24	4.42	0.018	1.74	0.39	5.12	125.76	1.07		4.67	4.85	1.34	0.67	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3383/02	Mean	5.4	8.74	146	0.420	48.1	16.7	347	797	19.5	@	10.2	85.8	3.6	0.4	0.0
	SD	1.94	0.42	7.32	0.019	1.46	0.79	7.83	84.49	2.30		3.05	4.52	2.22	0.70	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3402/02	Mean	7.1	8.95	158	0.410	45.8	17.6	385	648	20.1	@	16.2	80.0	2.7	1.1	0.0
	SD	1.30	0.25	4.74	0.011	0.77	0.39	7.61	55.02	0.90		7.18	7.56	2.06	0.99	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3361/02	Mean	9.0	8.76	161	0.424	48.4	18.4	380	745	14.6	0.6	9.7	88.5	1.0	0.8	0.0
	SD	1.25	0.41	4.22	0.022	1.22	0.80	16.92	92.82	0.95	0.36	2.87	3.44	0.94	0.92	0.00
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

N: No. of rats @: Not evaluated

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33.5 : HAEMATOLOGICAL VALUES - MALES (CONTROL RECOVERY GROUP - G1R)

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV G/l	MCH pg	MCHC g/l	PLAT G/l	P.T. S	Retic %	Neut %	Lymp %	Eosi %	Mono %	Baso %
3448/02	Mean	8.4	8.38	155	0.408	48.7	18.5	381	797	15.4	@	18.3	77.0	3.7	1.0	0.0
	SD	1.57	0.36	5.67	0.018	1.54	0.57	6.87	59.53	1.04		5.48	6.09	1.57	0.82	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3446/02	Mean	7.0	8.59	161	0.418	48.7	18.7	384	958	10.5	@	15.4	80.8	3.3	0.5	0.0
	SD	1.59	0.39	8.22	0.020	1.07	0.60	10.98	118.99	0.81		6.98	8.74	2.63	0.71	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3351/02	Mean	9.9	8.10	154	0.393	48.5	19.0	392	818	15.2	@	13.7	81.8	3.6	0.9	0.0
	SD	2.20	0.32	4.93	0.018	1.87	0.58	8.26	105.87	2.38		4.35	5.98	1.84	0.99	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3345/01	Mean	8.3	8.21	151	0.400	48.7	18.4	378	916	14.8	@	7.6	90.5	1.4	0.5	0.0
	SD	1.04	0.63	9.09	0.032	0.90	0.59	14.04	89.58	1.06		2.27	3.27	1.17	0.71	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
Mean		7.2	8.71	157	0.433	49.7	18.1	364	880	17	0.6	12.7	84.3	2 2	1.8	0
SD		1.69	0.42	7.06	0.023	1.39	0.53	10.83	104.45	1.60	0.36	4.78	5.46	1.53	0.82	0.0
1 SD: Range - Low		5.5	8.29	150	0.410	48.3	17.6	353	776	15.4	0.2	7.9	78.8	0.7	1.0	0
1 SD: Range - High		8.9	9.13	164	0.456	51.1	18.6	375	984	18.6	1.0	17.5	89.8	3.7	2.6	0
2 SD: Range - Low		3.8	7.87	143	0.387	46.9	17.0	342	671	13.8	-0.1	3.1	73.4	-0.9	0.2	0
2 SD: Range - High		10.6	9.55	171	0.479	52.5	19.2	386	1089	20.2	1.3	22.3	95.2	5.3	3.4	0

N: No. of rats @: Not evaluated
Note: The negative value of 1 SD and 2 SD should be considered as "zero"

HISTORICAL CONTROL DATA - 33

SUBCHRONIC (90 DAY) ORAL TOXICITY STUDY IN WISTAR RATS

33.5: HAEMATOLOGICAL VALUES - FEMALES (CONTROL GROUP - G1)

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV G/l	MCH pg	MCHC g/l	PLAT G/l	P.T. S	Retic %	Neut %	Lymp %	Eosi %	Mono %	Baso %
2632/99	Mean	5.5	8.28	153	0.467	56.4	18.5	327	499	17.3	@	16.6	80.2	1.5	1.7	0.0
	SD	1.56	0.26	4.61	0.02	1.46	0.49	5.37	47.17	2.42		2.55	2.39	0.71	0.95	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
2959/00	Mean	5.3	8.26	155	0.409	49.5	18.7	378	928	13.3	@	13.1	83.2	2.4	1.3	0.0
	SD	1.42	0.29	5.25	0.015	1.10	0.46	5.45	226.80	0.96		10.84	10.48	1.43	0.95	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3282/01	Mean	5.2	8.17	153	0.427	52.3	18.7	359	951	15.8	@	14.5	80.9	2.6	2.0	0.0
	SD	1.63	0.29	4.06	0.021	1.90	0.57	14.10	78.43	0.91		4.58	6.72	2.01	1.83	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3270/01	Mean	4.9	7.91	159	0.397	50.2	20.1	400	1034	15.9	@	11.3	85.8	1.8	1.1	0.0
	SD	1.03	0.29	4.57	0.014	1.11	0.65	9.60	82.49	1.60		6.04	7.13	1.62	1.45	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3219/01	Mean	4.8	8.16	158	0.419	51.3	19.4	378	1002	14.61	@	15.0	83.9	1.1	0.0	0.0
	SD	1.44	0.36	4.86	0.020	1.82	0.34	10.50	110.77	0.79		6.06	5.38	1.29	0.00	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3302/01	Mean	5.3	8.33	152	0.441	53.0	18.3	346	993	15.7	@	16.1	81.2	1.7	1.0	0.0
	SD	1.61	0.23	5.13	0.013	1.46	0.51	7.28	123.85	1.01		6.30	5.65	0.95	1.05	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3267/01	Mean	5.5	8.18	162	0.430	52.5	19.8	376	955	15.23	@	14.6	83.7	1.6	0.1	0.0
	SD	1.98	0.46	7.23	0.03	1.83	0.73	11.65	132.72	1.26		6.31	6.93	1.96	0.32	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10

N: No. of rats @: Not evaluated

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33.5: HAEMATOLOGICAL VALUES - FEMALES (CONTROL GROUP - G1)

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV G/l	MCH pg	MCHC g/l	PLAT G/l	P.T. S	Retic %	Neut %	Lymp %	Eosi %	Mono %	Baso %
3343/02	Mean	7.4	7.82	151	0.401	51.3	19.3	370	1079	14.6	@	13.3	85.9	0.8	0.0	0.0
	SD	1.88	0.29	4.62	0.012	0.90	0.60	9.29	146.00	0.60		4.00	4.12	1.14	0.00	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3295/01	Mean	6.2	9.01	162	0.465	51.7	18.0	348	1009	15.0	@	14.1	83.5	2.1	0.3	0.0
	SD	2.06	0.35	4.92	0.013	1.36	0.54	11.59	80.95	1.57		8.52	9.22	1.97	0.67	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3287/01	Mean	6.0	8.24	151	0.436	53.0	18.3	346	944	17.8	@	12.5	85.7	1.1	0.7	0.0
	SD	3.33	0.27	5.99	0.016	1.93	0.55	11.35	167.40	0.96		15.40	15.30	0.99	0.95	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
2933/00	Mean	4.6	8.08	153	0.405	50.1	18.9	377	848	20.7	@	9.7	87.9	1.8	0.6	0.0
	SD	1.04	0.17	2.42	0.011	0.76	0.43	11.54	170.89	1.22		4.30	3.78	0.79	0.97	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3383/02	Mean	5.4	8.36	159	0.483	57.9	19.0	329	425	15.3	@	14.3	82.2	2.8	0.7	0.0
	SD	1.89	0.51	6.72	0.022	2.85	0.54	10.65	32.67	0.80		6.50	6.14	0.92	0.67	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3402/02	Mean	5.6	8.17	154	0.409	50.1	18.8	375	761	19.2	@	11.6	85.1	2.8	0.5	0.0
	SD	2.11	0.34	6.38	0.020	1.61	0.61	12.64	61.66	2.13		3.53	4.65	1.69	0.71	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3361/02	Mean	5.8	7.47	150	0.375	50.2	20.0	399	826	18.0	0.6	16.3	80.3	2.0	1.4	0.0
	SD	1.94	0.45	8.38	0.021	1.39	0.42	14.39	76.85	3.05	0.29	5.52	6.24	1.63	1.07	0.00
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

N: No. of rats @: Not evaluated

RALLIS RESEARCH CENTRE
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33.5: HAEMATOLOGICAL VALUES - FEMALES (CONTROL GROUP - G1)

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV G/l	MCH pg	MCHC g/l	PLAT G/l	P.T. S	Retic %	Neut %	Lymp %	Eosi %	Mono %	Baso %
3448/02	Mean	5.7	8.25	159	0.433	52.5	19.3	367	866	19.9		11.5	85.6	1.6	1.3	0.0
	SD	2.51	0.67	9.87	0.036	0.79	0.71	10.94	216.48	1.59	@	3.57	3.06	0.84	0.82	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3446/02	Mean	8.6	7.66	151	0.401	52.3	19.7	378	889	16.9		13.9	84.2	1.2	0.7	0.0
	SD	2.91	0.56	6.98	0.033	1.21	0.67	15.56	77.94	1.66	@	6.74	7.90	0.63	1.06	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3351/02	Mean	4.8	8.53	160	0.439	51.4	18.8	365	731	16.7		13.6	82.0	2.7	1.7	0.0
	SD	1.41	0.33	4.42	0.020	1.64	0.44	11.98	46.63	2.15	@	7.03	6.22	1.64	1.77	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3345/01	Mean	6.3	7.45	152	0.393	52.8	20.4	386	964	14.2		12.9	84.1	1.7	1.3	0.0
	SD	1.88	0.68	12.15	0.036	1.41	0.78	11.92	151.01	1.23	@	4.07	5.47	1.57	1.34	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
Mean		5.7	8.13	155	0.424	52.1	19.1	367	872	16.5	0.6	13.6	83.6	1.9	0.9	0
SD		1.95	0.40	6.43	0.022	1.55	0.57	11.2	125.97	1.57	0.29	6.88	7.11	1.39	1.04	0.0
1 SD: Range - Low		3.8	7.73	149	0.402	50.6	18.5	356	746	14.9	0.3	6.7	76.5	0.5	-0.1	0
1 SD: Range - High		7.7	8.53	161	0.446	53.7	19.7	378	998	18.1	0.9	20.5	90.7	3.3	1.9	0
2 SD: Range - Low		1.8	7.33	142	0.380	49.0	18.0	345	620	13.4	0.0	-0.2	69.4	-0.9	-1.2	0
2 SD: Range - High		9.6	8.93	168	0.468	55.2	20.2	389	1124	19.6	1.2	27.4	97.8	4.7	3.0	0

N: No. of rats @: Not evaluated
Note: The negative value of 1 SD and 2 SD should be considered as "zero"

RALLIS RESEARCH CENTRE
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HISTORICAL CONTROL DATA - 33

SUBCHRONIC (90 DAY) ORAL TOXICITY STUDY IN WISTAR RATS

33.5 : HAEMATOLOGICAL VALUES - FEMALES (CONTROL RECOVERY GROUP - G1R)

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV G/l	MCH pg	MCHC g/l	PLAT G/l	P.T. S	Retic %	Neut %	Lymp %	Eosi %	Mono %	Baso %
2632/99	Mean	5.6	8.52	156	0.451	52.9	18.3	347	810	17.3	@	16.5	79.6	1.9	20.0	0.0
	SD	1.83	0.51	6.88	0.03	1.23	0.58	15.97	75.02	1.47		3.17	2.67	1.52	1.15	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
2959/00	Mean	4.2	8.08	153	0.453	56.2	19.0	340	1577	16.1	@	13.3	83.9	1.2	1.6	0.0
	SD	0.99	0.26	4.90	0.023	4.01	0.29	24.26	295.52	0.83		5.19	5.17	1.14	1.08	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3282/01	Mean	4.6	8.13	157	0.425	52.3	19.4	370	979	16.2	@	14.7	83.6	1.0	0.7	0.0
	SD	1.19	0.31	8.07	0.020	1.51	1.04	13.91	48.99	1.47		4.22	3.92	1.05	0.95	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3270/01	Mean	@														
	SD															
	N															
3219/01	Mean	5.0	7.91	158	0.415	52.5	20.0	381	918	15.75	@	12.4	86.7	0.9	0.0	0.0
	SD	1.30	0.32	6.96	0.022	1.15	0.88	17.01	84.83	1.01		5.83	6.09	1.29	0.00	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3302/01	Mean	@														
	SD															
	N															
3267/01	Mean	4.6	8.22	159	0.435	53.0	19.3	365	917	14.93	@	13.2	85.2	1.5	0.1	0.0
	SD	1.12	0.35	5.13	0.02	1.84	0.70	8.66	189.15	0.82		6.25	5.92	1.65	0.32	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10

N: No. of rats @: Not evaluated

RALLIS RESEARCH CENTRE
Peenya, Bangalore - 560 058.

33.5 : HAEMATOLOGICAL VALUES - FEMALES (CONTROL RECOVERY GROUP - G1R)

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV G/l	MCH pg	MCHC g/l	PLAT G/l	P.T. S	Retic %	Neut %	Lymp %	Eosi %	Mono %	Baso %
3343/02	Mean	4.1	7.54	150	0.388	51.4	19.8	386	972	20.0	@	12.1	87.2	0.7	0.0	0.0
	SD	0.90	0.42	4.55	0.019	1.29	0.75	10.50	83.37	1.16		1.73	2.10	0.82	0.00	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3295/01	Mean	4.5	8.85	171	0.457	51.7	19.4	374	957	16.7	@	15.9	82.9	1.1	0.1	0.0
	SD	1.73	0.43	6.09	0.018	1.39	0.44	9.65	77.91	1.18		8.71	10.29	1.52	0.32	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3287/01	Mean	10.8	9.23	165	0.466	50.5	17.9	354	1025	18.3	@	8.6	88.9	1.8	0.7	0.0
	SD	2.70	0.50	7.08	0.025	1.70	0.37	7.09	112.82	2.07		3.24	3.51	1.14	0.67	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
2933/00	Mean	5.1	8.17	157	0.502	61.5	19.3	313	808	17.8	@	13.3	83.3	2.9	0.5	0.0
	SD	1.07	0.37	8.99	0.023	1.45	0.70	6.90	40.48	1.42		5.40	5.40	1.37	0.53	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3383/02	Mean	4.9	7.92	155	0.402	50.8	19.5	385	681	17.9	@	8.6	88.3	2.6	0.5	0.0
	SD	1.30	0.43	5.15	0.018	1.40	0.54	6.92	66.40	1.69		3.63	4.06	0.70	0.53	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3402/02	Mean	4.3	8.26	156	0.399	48.2	18.9	393	715	18.7	@	10.9	85.3	2.5	1.3	0.0
	SD	1.01	0.42	7.23	0.025	1.12	0.39	9.27	60.39	0.84		3.87	4.57	0.85	1.34	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3361/02	Mean	6.6	7.21	154	0.368	51.1	21.4	418	573	16.2	0.7	8.6	89.2	1.5	0.7	0.0
	SD	1.87	0.18	4.52	0.010	1.70	0.42	11.02	51.32	0.69	0.25	2.41	3.33	1.35	0.82	0.00
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

N: No. of rats @: Not evaluated

RALLIS RESEARCH CENTRE
Peenya, Bangalore - 560 058.

33.5 : HAEMATOLOGICAL VALUES - FEMALES (CONTROL RECOVERY GROUP - G1R)

Study No.		WBC G/l	RBC T/l	Hb g/l	Hct l/l	MCV G/l	MCH pg	MCHC g/l	PLAT G/l	P.T. S	Retic %	Neut %	Lymp %	Eosi %	Mono %	Baso %
3448/02	Mean	6.5	7.80	153	0.394	50.5	19.6	388	716	15.5		17.0	78.4	3.8	0.8	0.0
	SD	1.94	0.20	3.68	0.010	1.25	0.48	5.48	75.09	0.85	@	7.85	8.04	2.04	0.92	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3446/02	Mean	5.3	7.59	156	0.388	51.1	20.5	401	726	12.8		14.1	83.6	1.5	0.8	0.0
	SD	1.84	0.43	10.47	0.025	1.57	0.71	7.87	225.71	1.59	@	6.95	7.86	1.90	0.79	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3351/02	Mean	6.2	7.65	156	0.388	50.7	20.4	402	806	15.2		17.2	78.8	2.7	1.3	0.0
	SD	1.23	0.20	4.71	0.013	1.81	0.75	9.70	60.21	2.01	@	6.63	6.89	0.67	0.95	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
3345/01	Mean	6.1	7.58	150	0.385	50.8	19.9	391	868	14.3		8.6	89.0	1.7	0.7	0.0
	SD	1.21	0.63	8.12	0.022	1.85	1.30	16.15	95.12	0.59	@	2.50	3.37	1.25	0.95	0.00
	N	10	10	10	10	10	10	10	10	10		10	10	10	10	10
Mean		5.5	8.04	157	0.420	52.2	19.5	376	878	16.5	0.7	12.8	84.6	1.8	1.9	0
SD		1.53	0.39	6.66	0.021	1.77	0.70	12.26	123.91	1.31	0.25	5.25	5.63	1.32	0.80	0.0
1 SD: Range - Low		4.0	7.65	150	0.399	50.4	18.8	364	754	15.2	0.5	7.6	79.0	0.5	1.1	0
1 SD: Range - High		7.0	8.43	164	0.441	54.0	20.2	388	1002	17.8	1.0	18.1	90.2	3.1	2.7	0
2 SD: Range - Low		2.4	7.26	144	0.378	48.7	18.1	351	630	13.9	0.2	2.3	73.3	-0.8	0.3	0
2 SD: Range - High		8.6	8.82	170	0.462	55.7	20.9	401	1126	19.1	1.2	23.3	95.9	4.4	3.5	0

N: No. of rats @: Not evaluated
Note: The negative value of 1 SD and 2 SD should be considered as "zero"

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HISTORICAL CONTROL DATA - 33

SUBCHRONIC (90 DAY) ORAL TOXICITY STUDY IN WISTAR RATS

33.6: 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	Che_pl U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
2632/99	Mean	9.00	2.88	6.16	61.9	104	58	89	7	@	3.30	28	29.4	1.85	2.67	2.00	104	142.2	4.30
	SD	0.63	0.24	0.51	2.47	27.35	11.61	13.99	1.58		0.72	2.97	1.24	0.18	0.06	0.22	1.97	1.22	0.54
	N	10	10	10	10	10	10	10	10		10	10	10	10	10	10	10	10	10
2959/00	Mean	8.79	2.52	5.40	68.0	69	48		1			26	36.1	1.75	2.70	2.27		143.7	4.13
	SD	0.80	0.18	0.38	2.14	16.22	8.39	@	1.48	@	@	4.62	1.42	0.25	0.10	0.37	@	1.82	0.26
	N	10	10	10	10	10	10		10			10	10	10	10	10		10	10
3282/01	Mean	9.52	3.42	7.32	62.4	75	32		3			77	31.5	1.96		2.18		141.3	3.84
	SD	0.93	0.36	0.78	1.40	6.02	7.35	@	1.45	@	@	5.25	1.52	0.13	@	0.49	@	1.11	0.29
	N	10	10	10	10	10	10		10			10	10	10		10		10	10
3270/01	Mean	8.28	2.45	5.25	58.4	81	38		3		3.60	77	32.4	1.97	2.67	2.23	108	143.2	4.12
	SD	0.72	0.20	0.42	1.62	11.83	4.88	@	2.07	@	0.62	3.74	1.05	0.17	0.05	0.42	0.92	1.64	0.24
	N	10	10	10	10	10	10		10		10	10	10	10	10	10	10	10	10
3219/01	Mean	8.96	2.67	5.71	62.0	89	49		4			78	30.7	2.57	2.87	2.41		142.6	4.94
	SD	0.96	0.37	0.80	1.90	13.00	9.59	@	1.83	@	@	10.12	0.92	0.20	0.07	0.55	@	1.67	0.64
	N	10	10	10	10	10	10		10			10	10	10	10	10		10	10
3302/01	Mean	9.57	2.76	5.91	65.6	92	52		10		3.75	56	31.6	1.79	2.71	2.28	100	139.3	4.47
	SD	0.76	0.33	0.72	1.58	12.58	12.38	@	7.34	@	1.56	7.15	1.12	0.18	0.07	0.30	1.35	2.35	0.43
	N	10	10	10	10	10	10		10		10	10	10	10	10	10	10	10	10
3267/01	Mean	8.97	2.26	4.85	63.8	88	45		13			59	32.1			2.40		144.0	4.20
	SD	0.48	0.24	0.50	1.66	7.60	7.14	@	5.96	@	@	3.92	1.69	@	@	0.56	@	1.41	0.42
	N	10	10	10	10	10	10		10			10	10			10		10	10

N: No. of rats @: Not evaluated

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ANNEXURE 6 contd.

33.6: 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	Che_pl U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
3343/02	Mean	8.54	2.49	5.33	62.2	111	38	@	10	@	@	45	31.3	1.83	@	2.25	@	141.9	4.12
	SD	0.69	0.42	0.91	1.76	20.96	12.07		4.61			5.33	1.64	0.20		0.23		2.53	0.31
	N	10	10	10	10	10	10		10			10	10	10		10		10	10
3295/01	Mean	9.32	3.14	6.73	65.4	96	45	@	2	149	@	64	33.9	@	@	2.29	@	143.3	4.57
	SD	0.81	0.29	0.62	2.81	15.03	11.87		1.49	36.86		9.64	1.47			0.24		1.79	0.60
	N	10	10	10	10	10	10		10	10		10	10			10		10	10
3287/01	Mean	8.56	3.07	6.58	70.1	85	42	69	8	@	@	66	32.3	1.54	@	2.58	@	139.9	3.72
	SD	1.09	0.20	0.44	3.58	17.27	7.95	9.78	3.89			8.92	2.73	0.11		0.37		2.96	0.26
	N	10	10	10	10	10	10	10	10			10	10	10		10		10	10
2933/00	Mean	8.53	2.81	6.01	65.2	67	48	@	7	@	@	68	30.5	@	@	2.24	@	138.0	3.87
	SD	0.55	0.44	0.93	1.88	15.05	5.50		2.27			3.09	1.63			0.38		2.64	0.20
	N	10	10	10	10	10	10		10			10	10			10		10	10
3383/02	Mean	9.54	3.12	6.68	65.1	63	48	@	0	@	@	56	32.7	@	@	2.46	@	139.4	4.26
	SD	1.42	0.40	0.87	2.14	8.44	6.50		0.32			9.32	1.52			0.61		1.75	0.36
	N	10	10	10	10	10	10		10			10	10			10		10	10
3402/02	Mean	9.82	2.89	6.19	65.7	69	42	@	8	@	@	62	32.6	@	@	2.50	@	143.7	4.14
	SD	1.02	0.26	0.55	2.76	11.21	8.81		7.38			12.45	2.37			0.40		4.33	0.18
	N	10	10	10	10	10	10		10			10	10			10		10	10
3361/02	Mean	9.85	3.15	6.75	63.8	70	55	@	8	@	@	61	30.2	@	@	2.42	@	138.7	4.31
	SD	0.76	0.56	1.21	1.37	10.67	12.92		2.33			5.74	1.07			0.49		4.37	0.28
	N	10	10	10	10	10	10		10			10	10			10		10	10

N: No. of rats @: Not evaluated

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33.6: 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	Che_pl U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
3448/02	Mean	9.45	2.77	5.94	59.1	50	31	@	5	@	@	51	30.9	@	@	2.17	@	146.0	4.27
	SD	0.79	0.43	0.93	1.53	9.12	5.85		1.20			7.95	1.22			0.39		1.48	0.29
	N	10	10	10	10	10	10		10			10	10			10		10	10
3446/02	Mean	8.83	2.39	5.12	65.5	58	29	@	1	@	@	45	33.0	@	@	2.65	@	148.8	3.82
	SD	0.67	0.36	0.77	2.79	7.87	3.52		1.14			7.44	2.02			0.64		3.04	0.23
	N	10	10	10	10	10	10		10			10	10			10		10	10
3351/02	Mean	8.79	2.55	5.46	65.6	39	35	@	8	@	@	52	33.1	@	@	2.32	@	145.7	4.15
	SD	0.88	0.32	0.68	1.64	9.35	5.98		4.27			7.29	0.94			0.18		3.10	0.17
	N	10	10	10	10	10	10		10			10	10			10		10	10
3345/01	Mean	9.34	2.36	5.04	60.7	63	63	@	0	@	@	74	35.2	@	@	2.56	@	144.5	4.11
	SD	1.01	0.34	0.72	1.73	7.37	10.40		0.32			6.13	1.58			0.43		3.93	0.34
	N	10	10	10	10	10	10		10			10	10			10		10	10
Mean		9.09	2.76	5.91	63.9	76	44	79	5	149	3.55	58	32.20	1.91	2.72	2.35	104	142.6	4.19
SD		0.86	0.34	0.74	2.13	13.66	8.93	12.07	3.56	36.86	1.05	7.21	1.58	0.18	0.07	0.42	1.48	2.60	0.36
1 SD: Range - Low		8.23	2.42	5.17	61.8	62	35	67	1	112	2.50	51	30.62	1.73	2.65	1.93	103	140.0	3.83
1 SD: Range - High		9.95	3.10	6.65	66.0	90	53	91	9	186	4.60	65	33.78	2.09	2.79	2.77	105	145.2	4.55
2 SD: Range - Low		7.37	2.08	4.43	59.6	49	26	55	-2	75	1.45	44	29.04	1.55	2.58	1.51	101	137.4	3.47
2 SD: Range - High		10.81	3.44	7.39	68.2	103	62	103	12	223	5.65	72	35.36	2.27	2.86	3.19	107	147.8	4.91

N: No. of rats @: Not evaluated
Note: The negative value of 1 SD and 2 SD should be considered as "zero"

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HISTORICAL CONTROL DATA - 33

SUBCHRONIC (90 DAY) ORAL TOXICITY STUDY IN WISTAR RATS

33.6: 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	Che_pl U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
2632/99	Mean	7.52	2.57	5.51	62.0	74	50	65	1	@	3.57	35	34.6	2.03	2.74	1.78	107	143.2	3.97
	SD	0.58	0.27	0.58	1.62	9.11	8.20	9.98	0.63		0.47	5.25	1.16	0.19	0.05	0.26	1.89	0.88	0.37
	N	10	10	10	10	10	10	10	10		10	10	10	10	10	10	10	10	10
2959/00	Mean	8.83	2.76	5.92	71.5	77	48	@	0	@	@	28	36.3	1.96	2.65	2.16	@	141.6	4.23
	SD	0.78	0.27	0.58	2.71	14.34	8.06		0.32			3.50	1.48	0.20	0.21	0.22		1.87	0.41
	N	10	10	10	10	10	10		10			10	10	10	10	10		10	10
3282/01	Mean	9.21	3.28	7.03	63.9	98	47	@	7	@	@	84	32.1	1.95	@	2.98	@	143.1	4.29
	SD	0.48	0.40	0.85	2.04	18.08	13.00		1.26			7.48	2.67	0.11		0.75		1.72	0.33
	N	10	10	10	10	10	10		10			10	10	10		10		10	10
3270/01	Mean	@																	
	SD																		
	N																		
3219/01	Mean	8.77	2.63	5.63	62.6	78	42	@	1	@	@	63	31.0	1.86	2.78	2.20	@	146.0	4.20
	SD	0.59	0.26	0.55	1.51	6.47	5.14		0.97			11.95	2.58	0.23	0.06	0.43		1.79	0.31
	N	10	10	10	10	10	10		10			10	10	10	10	10		10	10
3302/01	Mean	@																	
	SD																		
	N																		
3267/01	Mean	8.77	2.62	5.61	59.0	71	50	@	2	@	@	51	30.4	@	@	2.29	@	142.0	4.60
	SD	0.72	0.44	0.95	1.67	15.33	18.59		1.90			8.38	1.26			0.33		1.24	0.35
	N	10	10	10	10	10	10		10			10	10			10		10	10

N: No. of rats @: Not evaluated

33.6: 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	Che_pl U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
3343/02	Mean	10.02	3.15	6.74	64.3	58	38	@	6	@	@	99	31.4	1.87	@	2.47	@	142.4	4.57
	SD	0.64	0.35	0.74	2.32	7.24	8.73		2.85			8.39	1.75	0.19		0.33		4.27	0.45
	N	10	10	10	10	10	10		10			10	10	10		10		10	10
3295/01	Mean	8.75	2.93	6.27	61.1	76	43	@	7	153	@	74	31.7	@	@	2.24	@	142.9	4.02
	SD	0.84	0.45	0.96	1.84	14.73	3.47		1.20	33.14		4.74	1.84			0.21		2.21	0.29
	N	10	10	10	10	10	10		10	10		10	10			10		10	10
3287/01	Mean	7.70	2.97	6.37	66.8	108	45	47	1	@	@	76	37.5	1.14	@	2.04	@	137.1	4.00
	SD	0.67	0.23	0.48	2.85	16.40	8.49	8.64	2.10			7.37	2.52	0.20		0.38		4.08	0.19
	N	10	10	10	10	10	10	10	10			10	10	10		10		10	10
2933/00	Mean	9.81	2.53	5.43	67.1	59	57	@	3	@	@	57	31.1	©	@	2.75	@	136.7	4.04
	SD	1.15	0.46	0.98	1.74	16.29	13.98		3.74			6.22	2.54			0.49		4.18	0.42
	N	10	10	10	10	10	10		10			10	10			10		10	10
3383/02	Mean	9.03	3.41	7.29	63.4	49	42	@	2	@	@	51	31.8	@	@	3.09	@	140.1	4.09
	SD	1.08	0.35	0.75	2.00	3.99	13.93		1.87			8.75	2.59			1.23		2.03	0.25
	N	10	10	10	10	10	10		10			10	10			10		10	10
3402/02	Mean	9.24	2.70	5.79	65.1	56	56	@	9	@	@	75	32.8	@	@	2.30	@	143.5	4.21
	SD	0.65	0.53	1.14	2.43	9.16	14.83		2.76			5.92	1.62			0.22		4.58	0.22
	N	10	10	10	10	10	10		10			10	10			10		10	10
3361/02	Mean	7.54	2.90	6.20	66.6	90	73	@	2	@	@	71	30.8	@	@	2.59	@	135.3	3.86
	SD	0.29	0.38	0.82	2.88	47.53	51.25		2.31			7.59	1.53			0.50		4.12	0.22
	N	10	10	10	10	10	10		10			10	10			10		10	10

N: No. of rats @: Not evaluated

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33.6: 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	Che_pl U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
3448/02	Mean	8.63	2.87	6.14	59.9	53	36	@	6	@	@	43	32.0	@	@	2.30	@	145.9	4.30
	SD	0.93	0.41	0.88	2.30	12.35	9.44		25.00			6.25	2.17			0.55		4.05	0.29
	N	10	10	10	10	10	10		10			10	10			10		10	10
3446/02	Mean	8.60	2.67	5.71	64.2	59	48	@	1	@	@	57	31.5	@	@	2.61	@	144.6	3.72
	SD	1.61	0.38	0.81	1.96	7.65	17.09		0.48			5.00	1.38			0.49		1.33	0.21
	N	10	10	10	10	10	10		10			10	10			10		10	10
3351/02	Mean	8.48	2.70	5.78	63.5	50	41	@	3	@	@	46	31.7	@	@	2.31	@	145.0	4.21
	SD	0.65	0.44	0.93	2.71	7.62	8.97		2.85			10.05	1.45			0.26		3.32	0.13
	N	10	10	10	10	10	10		10			10	10			10		10	10
3345/01	Mean	9.49	2.69	5.76	61.1	47	43	@	2	@	@	54	31.0	@	@	2.48	@	147.1	4.15
	SD	0.55	0.29	0.62	2.72	7.20	6.49		1.58			2.53	1.06			0.42		1.31	0.33
	N	10	10	10	10	10	10		10			10	10			10		10	10
Mean		8.77	2.64	6.07	63.9	69	47	56	3	153	3.57	60	32.36	1.80	2.72	2.41	107	142.3	4.15
SD		0.82	0.38	0.81	2.25	13.54	16.91	9.33	6.55	33.14	0.47	7.23	1.93	0.19	0.13	0.51	1.89	2.98	0.31
1 SD: Range - Low		7.95	2.46	5.26	61.7	52	30	47	-4	120	3.10	53	30.43	1.61	2.59	1.90	105	139.3	3.84
1 SD: Range - High		9.59	3.22	6.88	66.2	86	64	65	10	186	4.04	67	34.29	1.99	2.85	2.92	109	145.3	4.46
2 SD: Range - Low		7.13	2.08	4.45	59.4	36	13	37	-10	87	2.63	46	28.50	1.42	2.46	1.39	103	136.3	3.53
2 SD: Range - High		10.41	3.6	7.69	68.4	102	81	75	16	219	4.51	74	36.22	2.18	2.98	3.43	111	148.3	4.77

N: No. of rats @: Not evaluated

Note: The negative value of 1 SD and 2 SDshould be considered as "zero"

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HISTORICAL CONTROL DATA - 33

SUBCHRONIC (90 DAY) ORAL TOXICITY STUDY IN WISTAR RATS

33.6: 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	Che_pl U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
2632/99	Mean	7.47	3.46	7.41	62.3	106	45	58	5	@	2.92	32	30.5	1.43	2.60	1.73	106	140.0	3.98
	SD	0.56	0.70	1.49	2.34	31.63	13.05	15.15	1.32		0.55	4.86	1.18	0.27	0.13	0.23	2.78	0.97	0.48
	N	10	10	10	10	10	10	10	10		10	10	10	10	10	10	10	10	10
2959/00	Mean	6.17	2.79	5.96	64.0	69	33		0			22	36.5	1.53	2.42	2.22	@	139.4	3.90
	SD	0.71	0.29	0.63	2.55	4.88	5.07	@	0.00	@	@	6.11	2.36	0.40	0.09	0.30		1.27	0.46
	N	10	10	10	10	10	10		10			10	10	10	10	10		10	10
3282/01	Mean	8.47	2.66	5.70	61.3	93	32		4			72	34.5	1.59	@	1.88	@	141.9	3.81
	SD	0.64	0.38	0.82	3.24	22.36	11.15	@	2.28	@	@	7.79	2.64	0.29		0.28		1.57	0.61
	N	10	10	10	10	10	10		10			10	10	10		10		10	10
3270/01	Mean	6.99	2.64	5.64	61.7	93	35		3		4.08	75	34.2	1.79	2.68	1.92	108	144.1	4.04
	SD	0.42	0.26	0.56	2.87	15.77	8.71	@	2.13	@	0.82	6.00	2.15	0.32	0.06	0.22	2.01	2.73	0.37
	N	10	10	10	10	10	10		10		10	10	10	10	10	10	10	10	10
3219/01	Mean	7.12	2.82	6.03	62.9	90	42		4			81	36.1	1.99	2.74	2.07	@	142.9	4.05
	SD	0.81	0.31	0.66	3.05	22.76	7.29	@	1.35	@	@	12.36	1.84	0.18	0.09	0.24		1.57	0.35
	N	10	10	10	10	10	10		10			10	10	10	10	10		10	10
3302/01	Mean	8.92	2.37	5.06	68.7	82	41		1		2.58	41	37.2	1.56	2.71	1.94	100	140.0	4.20
	SD	0.68	0.48	1.03	3.82	7.86	10.44	@	2.85	@	0.40	6.56	2.54	0.31	0.07	0.31	2.05	2.11	0.54
	N	10	10	10	10	10	10		10		10	10	10	10	10	10	10	10	10
3267/01	Mean	8.07	2.63	5.64	63.1	90	32		4			55	35.5			2.05		145.0	4.10
	SD	0.45	0.55	1.18	1.87	10.19	9.38	@	3.71	@	@	7.17	1.19	@	@	0.32	@	1.58	0.29
	N	10	10	10	10	10	10		10			10	10			10		10	10

N: No. of rats @: Not evaluated

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ANNEXURE 6 contd.

33.6: 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	Che_pl U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
3343/02	Mean	8.36	2.90	6.21	64.3	108	41	@	7	@	@	82	36.2	1.11	@	2.05	@	139.7	3.45
	SD	0.81	0.36	0.76	2.65	20.67	7.31		3.43			5.72	2.02	0.25		0.24		2.71	0.24
	N	10	10	10	10	10	10		10			10	10	10		10		10	10
3295/01	Mean	8.09	3.46	7.40	65.2	83	37		2	1178		63	37.5			1.91		143.0	4.02
	SD	1.10	0.29	0.63	2.72	8.44	6.00	@	2.71	355.27	@	11.34	1.46	@	@	0.35	@	1.16	0.20
	N	10	10	10	10	10	10		10	10		10	10			10		10	10
3287/01	Mean	7.50	2.84	6.07	69.4	88	36	47	4			61	37.5	1.46		2.20		141.8	3.70
	SD	0.55	0.40	0.85	3.94	13.33	10.33	9.64	2.42	@	@	6.61	3.55	0.26	@	0.19	@	2.64	0.18
	N	10	10	10	10	10	10	10	10			10	10	10		10		10	10
2933/00	Mean	8.60	2.85	6.09	66.5	68	47		0			75	34.5			2.04		139.9	3.77
	SD	0.71	0.44	0.95	2.45	5.52	5.84	@	0.95	@	@	4.50	1.98	@	@	0.39	@	1.66	0.20
	N	10	10	10	10	10	10		10			10	10			10		10	10
3383/02	Mean	8.40	3.62	7.75	62.7	63	40		2			59	36.7			2.15		140.4	4.06
	SD	0.61	0.86	1.83	1.36	4.00	8.28	@	1.51	@	@	10.32	1.35	@	@	0.15	@	0.73	0.37
	N	10	10	10	10	10	10		10			10	10			10		10	10
3402/02	Mean	8.55	3.64	7.79	64.8	69	51		11			58	35.1			2.21		144.8	4.29
	SD	0.93	0.56	1.21	3.20	12.94	8.64	@	2.73	@	@	5.91	2.01	@	@	0.32	@	4.66	0.30
	N	10	10	10	10	10	10		10			10	10			10		10	10
3361/02	Mean	7.72	3.16	6.77	63.6	72	39		0			58	36.1			2.24		141.9	3.67
	SD	0.73	0.51	1.08	2.82	12.59	9.17	@	0.42	@	@	5.28	2.08	@	@	0.37	@	2.09	0.35
	N	10	10	10	10	10	10		10			10	10			10		10	10

N: No. of rats @: Not evaluated

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33.6: 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	Che_pl U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
3448/02	Mean	8.50	2.57	5.51	59.9	49	30		5			53	31.5			1.79		142.5	4.18
	SD	0.56	0.28	0.59	2.05	12.36	7.12	@	4.10	@	@	9.57	2.01	@	@	0.34	@	1.27	0.24
	N	10	10	10	10	10	10		10			10	10			10		10	10
3446/02	Mean	8.77	2.49	5.33	61.6	77	30		6			42	35.9			1.94		144.2	3.77
	SD	0.62	0.28	0.60	3.10	10.66	6.70	@	1.60	@	@	5.16	1.78	@	@	0.38	@	1.70	0.25
	N	10	10	10	10	10	10		10			10	10			10		10	10
3351/02	Mean	8.25	2.42	5.19	66.2	55	27		2			43	38.0			1.83		145.3	4.23
	SD	0.53	0.35	0.74	2.52	6.50	5.75	@	2.40	@	@	6.26	2.04	@	@	0.23	@	3.26	0.20
	N	10	10	10	10	10	10		10			10	10			10		10	10
3345/01	Mean	8.61	2.46	5.26	57.9	60	63		0			62	34.4			2.07		143.4	4.49
	SD	1.34	0.47	1.00	1.35	9.13	20.31	@	0.42	@	@	6.45	1.34	@	@	0.27	@	4.14	0.28
	N	10	10	10	10	10	10		10			10	10			10		10	10
Mean		8.03	2.88	6.16	63.7	79	39	53	3	1178	3.19	57	35.44	1.56	2.63	2.01	105	142.2	3.98
SD		0.74	0.46	0.98	2.75	14.71	9.56	12.70	2.31	355.27	0.62	7.45	2.05	0.29	0.09	0.29	2.31	2.35	0.35
1 SD: Range - Low		7.29	2.42	5.18	61.0	64	29	40	1	823	2.57	50	33.39	1.27	2.54	1.72	103	139.9	3.63
1 SD: Range - High		8.77	3.34	7.14	66.5	94	49	66	5	1533	3.81	64	37.49	1.85	2.72	2.30	107	144.6	4.33
2 SD: Range - Low		6.55	1.96	4.2	58.2	50	20	28	-2	467	1.95	42	31.34	0.98	2.45	1.43	100	137.5	3.28
2 SD: Range - High		9.51	3.8	8.12	69.2	108	58	78	8	1889	4.43	72	39.54	2.14	2.81	2.59	110	146.9	4.68

N: No. of rats @: Not evaluated
Note: The negative value of 1 SD and 2 SD should be considered as "zero"

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HISTORICAL CONTROL DATA - 33

SUBCHRONIC (90 DAY) ORAL TOXICITY STUDY IN WISTAR RATS

33.6: 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	Che_pl U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
2632/99	Mean	6.98	3.08	6.60	60.5	80	36	43	1	@	3.31	41	37.4	1.75	2.67	1.66	110	141.7	3.81
	SD	0.49	0.56	1.20	3.60	9.45	4.59	5.93	0.70		0.27	4.33	1.95	0.24	0.10	0.33	2.71	1.54	0.28
	N	10	10	10	10	10	10	10	10		10	10	10	10	10	10	10	10	10
2959/00	Mean	7.82	2.59	5.55	74.0	80	37		0			28	40.9	1.43	2.64	2.34		143.0	4.06
	SD	0.64	0.14	0.30	2.82	12.01	6.30	@	0.00	@	@	4.87	1.70	0.26	0.07	0.17	@	1.27	0.23
	N	10	10	10	10	10	10		10			10	10	10	10	10		10	10
3282/01	Mean	8.65	2.93	6.28	61.8	106	42		6			90	36.1	1.40		2.05		141.8	3.71
	SD	0.73	0.27	0.59	2.83	9.51	7.56	@	1.27	@	@	10.54	2.38	0.34	@	0.35	@	1.37	0.23
	N	10	10	10	10	10	10		10			10	10	10		10		10	10
3270/01	Mean	@																	
	SD																		
	N																		
3219/01	Mean	7.92	2.46	5.26	62.3	99	34		2			72	34.9	1.69	2.74	2.06		145.7	3.98
	SD	0.88	0.35	0.75	2.24	15.74	7.96	@	1.52	@	@	9.30	1.43	0.27	0.07	0.46	@	1.00	0.37
	N	10	10	10	10	10	10		10			10	10	10	10	10		10	10
3302/01	Mean	@																	
	SD																		
	N																		
3267/01	Mean	8.25	2.67	5.73	58.7	90	45		2			47	33.9			1.82		143.0	4.40
	SD	1.03	0.31	0.66	3.06	14.52	7.11	@	2.11	@	@	10.04	2.43	@	@	0.20	@	1.50	0.61
	N	10	10	10	10	10	10		10			10	10			10		10	10

N: No. of rats @: Not evaluated

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33.6: 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	Che_pl U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
3343/02	Mean	8.83	2.88	6.18	63.9	64	36		7			106	35.2	1.55		2.29		144.9	4.17
	SD	1.04	0.45	0.97	3.06	11.23	5.27	@	3.35	@	@	8.92	2.43	0.20	@	0.50	@	2.55	0.50
	N	10	10	10	10	10	10		10			10	10	10		10		10	10
3295/01	Mean	7.84	3.07	6.58	58.7	79	38		7	991		74	33.7			1.71		144.3	3.76
	SD	0.61	0.46	0.98	1.17	10.57	4.90	@	3.20	319.72	@	5.99	1.25	@	@	0.39	@	1.67	0.43
	N	10	10	10	10	10	10		10	10		10	10			10		10	10
3287/01	Mean	8.48	2.85	6.10	67.4	88	47	68	6			86	35.5	1.59		2.41		142.4	3.97
	SD	1.11	0.31	0.67	2.77	9.92	6.77	14.71	3.14	@	@	8.02	1.42	0.17	@	0.25	@	1.05	0.08
	N	10	10	10	10	10	10	10	10			10	10	10		10		10	10
2933/00	Mean	8.56	2.86	6.12	67.8	73	51		6			64	35.2			2.42		140.0	3.77
	SD	0.88	0.54	1.15	2.12	9.13	5.47	@	4.58	@	@	6.06	1.12	@	@	0.44	@	2.05	0.52
	N	10	10	10	10	10	10		10			10	10			10		10	10
3383/02	Mean	8.06	3.60	7.70	62.6	56	50		1			53	36.4			2.07		140.0	3.88
	SD	0.61	0.51	1.09	2.60	4.80	13.17	@	1.27	@	@	5.70	2.55	@	@	0.34	@	2.19	0.17
	N	10	10	10	10	10	10		10			10	10			10		10	10
3402/02	Mean	8.72	2.60	5.57	67.0	59	47		5			71	37.5			2.16		143.7	4.21
	SD	0.96	0.32	0.69	3.85	14.80	4.95	@	3.95	@	@	6.00	2.33	@	@	0.37	@	3.96	0.25
	N	10	10	10	10	10	10		10			10	10			10		10	10
3361/02	Mean	7.23	3.10	6.63	67.2	69	42		4			70	36.7			2.29		142.3	3.54
	SD	0.63	0.33	0.71	3.35	12.29	4.93	@	1.48	@	@	6.85	2.55	@	@	0.40	@	2.12	0.28
	N	10	10	10	10	10	10		10			10	10			10		10	10

N: No. of rats @: Not evaluated

33.6: 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	Che_pl U/l	Tot.Bil µmol/l	Creat µmol/l	Alb g/l	Pi mmol/l	Ca mmol/l	Chol mmol/l	Cl mEq/l	Na mEq/l	K mEq/l
3448/02	Mean	7.58	2.84	6.08	59.6	68	43		9			53	34.3			1.99		145.3	4.23
	SD	0.57	0.37	0.79	3.40	14.55	13.91	@	1.20	@	@	8.67	2.19	@	@	0.27	@	2.39	0.21
	N	10	10	10	10	10	10		10			10	10			10		10	10
3446/02	Mean	7.21	2.61	5.59	62.7	54	37		0			61	33.6			1.89		145.6	3.69
	SD	0.66	0.27	0.58	1.59	8.94	15.87	@	0.32	@	@	5.23	1.20	@	@	0.38	@	1.27	0.35
	N	10	10	10	10	10	10		10			10	10			10		10	10
3351/02	Mean	7.21	2.63	5.63	62.4	59	42		3			49	32.0			1.87		146.0	4.29
	SD	0.64	0.28	0.59	1.69	11.37	8.83	@	1.06	@	@	5.04	1.33	@	@	0.26	@	2.74	0.18
	N	10	10	10	10	10	10		10			10	10			10		10	10
3345/01	Mean	8.86	2.66	5.70	63.3	62	50		0			57	35.0			2.17		150.7	3.95
	SD	0.70	0.38	0.81	2.38	13.12	8.92	@	0.42	@	@	8.23	1.87	@	@	0.29	@	2.28	0.35
	N	10	10	10	10	10	10		10			10	10			10		10	10
Mean		8.01	2.84	6.08	63.7	74	42	56	4	991	3.31	64	35.52	1.57	2.68	2.08	110	143.8	3.96
SD		0.78	0.38	0.82	2.76	11.69	8.60	11.21	2.28	319.72	0.27	7.37	1.95	0.25	0.08	0.35	2.71	2.07	0.34
1 SD: Range - Low		7.23	2.46	5.26	60.9	62	33	45	2	671	3.04	57	33.57	1.32	2.60	1.73	107	141.7	3.62
1 SD: Range - High		8.79	3.22	6.90	66.5	86	51	67	6	1311	3.58	71	37.47	1.82	2.76	2.43	113	145.9	4.30
2 SD: Range - Low		6.45	2.08	4.44	58.2	51	25	34	-1	352	2.77	49	31.62	1.07	2.52	1.38	105	139.7	3.28
2 SD: Range - High		9.57	3.6	7.72	69.2	97	59	78	9	1630	3.85	79	39.42	2.07	2.84	2.78	115	147.9	4.64

N: No. of rats @: Not evaluated
Note: The negative value of 1 SD and 2 SD should be considered as "zero"

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ANNEXURE 7

ssniff R/M-H

Complete diet for rats/mice - maintenance

Constituents

Crude protein	19.00	%	Calcium	1.00	%
Crude fat	3.30	%	Phosphorus	0.70	%
Crude fiber	4.90	%	Sodium	0.25	%
Crude ash	6.70	%	Magnesium	0.20	%
			Potassium	0.90	%

Amino Acids			Vitamins (je kg)		
Lysine	1.00	%	A	15000	IE
Methionine	0.30	%	D3	1000	IE
Cystine	0.30	%	E	100	mg
Glycine	0.90	%	B1	10	mg
Leucine	1.30	%	B2	20	mg
Isoleucine	0.70	%	B6	12	mg
Arginine	1.20	%	B12	80	µg
Phenylalanine	0.90	%	Biotin	400	µg
Tryptophan	0.25	%	Pantothenic acid	30	mg
Histidine	0.50	%	Choline	1600	mg
Tyrosine	0.60	%	Folic acid	4	mg
Aspartic acid	1.70	%	Nicotinic acid	60	mg
Glutaminic acid	3.80	%	K3	5	mg
Valine	0.90	%	Inositol	50	mg
Threonine	0.70	%			

Trace elements (je kg)			ME (je kg)	12.2	MJ
Manganese	90	mg			
Copper	12	mg			
Zinc	75	mg			
Iodine	2	mg			
Iron	220	mg			
Selenium	0.2	mg			
Cobalt	2	mg			