

University of Veterinary Science
Department of Pharmacology and Toxicology
H-1078 Budapest, István u. 2.

FINAL REPORT

**ACUTE ORAL TOXICITY STUDY
OF AVEMAR IN RATS**

Code No of test: 9902

Budapest, 1999

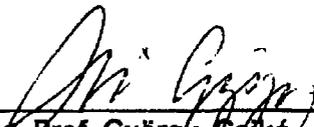
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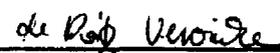
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RESPONSIBLE PERSONS

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date Ass. Prof. György Csikó
Ph.D., D.V.M.

Head of Department: 03.06. 1999 
date Prof. Gábor Semjén
Ph.D., D.V.M.

Quality-Assurance: 04.06. 
date Veronika Rátz
D.V.M.

QUALITY-ASSURANCE STATEMENT

I declare, that the final report of the "Acute oral toxicity study of AVEMAR in rats" (Code No of test: 9902) is based on correct experimental data, the written material is in conformity with from the study obtained data

Checking times	Report to	
	study director	head of department
26. 03. 1999	26. 03. 1999	26. 03. 1999
11. 05. 1999	11. 05. 1999	11. 05. 1999
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26. 05. 1999	26. 05. 1999	26. 05. 1999
03. 06. 1999	03. 06. 1999	-

Budapest, 03. 06. 1999

du Rát Veronika

Veronika Rátz

D.V.M. , Quality-Assurance

SUMMARY OF STUDY

TITLE OF STUDY: Acute oral toxicity study of AVEMAR in rats

NAME OF TEST COMPOUND: AVEMAR

SPECIES/STRAIN: rat /Wistar

GENDER: Male and female

NUMBER OF TEST ANIMALS: 40

MODE OF APPLICATION: oral

DURATION AND FREQUENCY OF TREATMENT: single dose

DOSAGE LEVEL: 2000 mg/kg b.w. (200 mg/100 g)

APPLIED VOLUME: 1 mL/100 g

VEHICLE: distilled water

POST TREATMENT EXAMINATION PERIOD: 14 days

TYPE OF EXAMINATIONS: Clinical symptoms
Mortality
Body weight
Pathological examination

RESULTS OF STUDY: The application of 2000 mg/kg Avemar caused no clinical symptoms or mortality during the test

The LD50 value of AVEMAR in male and female rats:
LD50 > 2000 mg/kg

1. GENERAL INFORMATION

1.1. Title of study

Acute oral toxicity study of AVEMAR in rats

1.2. Aim of study

Determine the acute oral LD₅₀ value of Avemar in rats. Collection of data about toxic properties of substance before introducing the subacute toxicity studies.

1.3. Type of study

The acute toxicity test was performed according to the GLP as described by regulation No P-44-1992 of the National Institute of Pharmacy (OGYI) and complying with the Good Laboratory Practice for Testing of Chemicals ENV/MC/CHEM (98)17. The test was carried out - with the aid of "Limit test" - according to the requirements of OECD Guidelines " Guidelines for testing of chemicals 401" (24 February 1987)

1.4. Place of study

University of Veterinary Science, Department of Pharmacology and Toxicology, H-1078 Budapest, István u. 2.

1.5. Data of Sponsor

BIROMEDICINA Research, Development and Commercial CO.
H-1088 Budapest Puskin u. 4.

2. TEST AND CONTROL SUBSTANCES

2.1. Test product

Name of product: Avemar

Manufacturer of product: BIROMEDICINA Research, Development
and Commercial CO., Budapest

Lot No: 00799115

Analytical test: Released on 15. 02.1999

Physical properties: brown granules

Storing of product: To be stored between 0-20 °C

Safety requirements: No special safety requirements are known

Main pharmacological effect: Stimulation of immune system

Expire date: February 2001

2.2. Control substance

Name of product: Distilled water

Manufacturer of product: PHARMAFONTANA G. L.

Charge No: 5022-9090

Analytical test No: OGYII/ 3035/37/99

Storing of product: To be stored at room temperature

Safety requirements: No special safety requirements are known

Expire date: 05.18.1999.

2.3. Preparation of test substance

The test substance was diluted in distilled water (10 g up to 50 mL).

The dilution was made right before the treatment

2.4. Stability test

The stability test was performed by the sponsor.

3. APPLIED TEST-SYSTEM

3.1. Animals dosed in study

Species/ strain : rat / Wistar BR

Age at beginning of test: 5 weeks

Mean body weights (at receiving): males: 87,25-111,34 g

females: 80,40-112,60 g

Total number of the rats: 60

Animals used for test (after randomization): male: 20

female: 20

3.1.1. Source of experimental animals

Charles River Magyarország Kft., Kereskedelmi Iroda, 1078
Budapest, István u. 11.

Receiving of the animals: 12. 04. 1999

3.1.2. Hygienic status

SPF

3.2. Justifying of species

The species selection is based on request of sponsor.

3.3. Identification of animals

We placed 5-5 rats into each box. The animals possessed their own identification number scored from 1 to 40. The identification was based on individual marking (from 1 to 5) and the serial number of boxes according to the formula $No = /5 \cdot (X-1) / + n$ (where No = identification number of the rat, X = serial number of box, n = individual marking). The code number of study, the date of treatment and the individual number of rats were written onto the boxes.

3.4. Keeping conditions of rats

Mode of keeping: Conventional

Type of rabbit boxes: Macrolon 2

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Size of boxes

height: 19.0 cm

length: 42.0 cm

width: 28.0 cm

Number of rabbits at each box: 5

Animal room: Rodent room

3.4.1. Environmental values

Air change rate: 15 times/hour

Temperature: 22 ± 3 C°

Relative humidity: 30-80 %

Lighting: artificial with 12 hour dark, 12 hour light period / day

The room temperature and air humidity were recorded by thermo-hygrograph.

3.4.2. Feeding conditions

- **Producer:** Altromin GmbH, 32791 Germany Lange Str. 42.
- **Identification No:** 1343
- **Analysis:** regularly controlled by the producer. No 30316/99-ALTR. (02.03.99), Z01315/99 (27.01.99)
- **Microbiological test:** regularly controlled by the producer

3.4.3. Water supply

Tape water, of drinking water quality. Annual chemical and microbiological analysis (ANTSZ) is subject.

3.4.4. Parameters of used litter

During the test the animals were kept on LIGNOCEL litter of low germ.

- **Producer:** JRS Faserstoff-Werke, 73494 Germany, Ellwangen-Holzmühle

- **Microbiological test:** regularly controlled by the producer

3.5. Acclimatization period

The acclimatization period was one week after receiving of the animals. During this period the rats were kept in quarantine room. Daily clinical examination was done. For the test only clinically healthy animals were used.

3.6. Randomization

Randomization was done 1 day before the treatment, based on body weights, with the help of computer program. Date: 10. 05. 1999

4. PERFORMING OF TEST

4.1. Dosage groups, applied doses

Group	Dose mg/kg	Number of animals		Identification No	
		male	female	male	female
Control (D ₀)	0	10	10	1-10	11-20
AVEMAR (D ₁)	2000	10	10	21-30	31-40

4.2. Justifying of dose selection

The dose selection was based on request of sponsor. As to the information of Sponsor the substance was non-toxic, therefore we applied a limit test (dose 2000 mg/kg). No pilot study was performed.

5. EXPERIMENTAL TREATMENTS

5.1. Mode of administration of substance

Per os, via gastric tube.

5.2. Justifying of administration method of substance

The administration method of substances was based on request of sponsor.

5.3. Duration and frequency of administration of substance

Single application.

5.4. Applied dose in trial

200 mg/1 mL /100 g b.w.

5.5. Method of treatment

Based on request of sponsor before the administration of test substances the rats were not starved.

The animals were appropriately fixed with hand. The rats were treated individually once (between 9 and 11 a.m.) with the given dose (section 4.1.) of preparation. The controls were treated with distilled water (1 mL/100g). The date of applications was 11.05.1999.

6. POST-TREATMENT EXAMINATION PERIOD

After administration of test substances a 14 day-observation period was applied.

The date of post-treatment examination was: 11.05.-25.05. 1999

7. OBSERVED PARAMETERS

7.1. Measuring of body weights

The weights of the rats were measured at receiving and at randomization of animals, as well as before and after (24 hour) treatment. On the first day after treatment a slight decrease in the body weight of some rats was recorded, therefore an additional measuring was done on the second day after administration of test substances. At this time each rat showed increase in body weight.

On days 7 and 14 of the study and just before the pathological examination the body weights of animals were also recorded.

7.2. General status, behavior, clinical symptoms

During the first 6 hours following the treatment each rat was clinically examined. During this period the animals were starved. In the post-treatment examination period the clinical symptoms were checked twice daily. Special attention was paid - besides of the general status, and behavior - on alterations of skin and fur, mucous membranes, eyes, circulation, breath, functions of vegetative nervous system, salivation, diarrhea, convulsions. The type and intensity of symptoms and local lesions were recorded individually.

7.3. Mortality

The mortality was recorded during the first 6 hours and thereafter twice a day for 14 days.

7.4. Pathological examination

At the end of the test - after post-treatment examination period - the euthanised animals (Nembutal injection 0,4 mL/200 g intra peritoneally) were examined pathologically. The macroscopic lesions were recorded. The date of pathological examination 26. 05. 1999.

8. STATISTICAL ANALYSIS

For statistical analysis of body weights T-probe was applied. As the result of statistical analysis revealed no significant difference (at level $P < 0,05$) between the groups no other test was done. The mean values and standard deviations (SD) of body weight was calculated with Pentium-100MHz-640KB PC. For statistical analysis we have used GraphPAD InStat software. The alterations between groups was tested with the use of "Paired two-tailed t-test".

9. EXPERIMENTAL PROCEDURE

The examination was performed according to the prescriptions of the Standard Operation Procedures of the Department of Pharmacology and Toxicology of University of Veterinary Science, Budapest.

10. ARCHIVATION OF DATA

The protocol, the raw data and the final report will be preserved for 10 years at the Archives Unit of the Department. The test compounds will be stored plus 1 year after their expire date. After this period the materials will be send back to the sponsor.

11. DEVIATIONS FROM THE PROTOCOL

- Because of body weights of rats we dissolved 10 g of Avemar in 50 mL distilled water instead of 5 g in 25 mL (which amount was given in protocol part 2.3.1)

- Based on the section 3.3. of protocol the individual marking of the test animals was based on mutilation of external ears. To avoid of negative influence of physical stress on the result of current study the marking was done as it is introduced at section 3.3.

- The amount of Nembutal injection (0,2 mL/200 g) given in the SOP "TOX-ÁLT-011" caused only deep anaesthesia instead of euthanasia, therefore a double dose of this preparation was applied.

12. RESULTS

12.1. Clinical symptoms

The control group and the AVEMAR treated (2000 mg/kg) group did not show clinical symptoms after single oral treatment during the whole (14 days post-treatment period) experiment (Table 1-2).

12.2. Mortality

The control group and the AVEMAR treated (2000 mg/kg) group did not show death after single oral treatment during the whole (14 days post-treatment period) experiment (Table 1-2).

12.3. Body weight

24 hours after administration of substances the individual body weights of the animals were measured. Some rats in the control group (No 7 male, No 13 and 15 female), as well as in AVEMAR treated group (No 25 and 28 male and 40 female) showed loss of body weight, therefore the measuring was continued until the normalization of body weights. The weights of the mentioned animals returned to the normal values after two day. In the other animals loss of weight was not observed during the whole study.

On days 7 and 14 of the post-treatment examination period we measured also the body weights. Table 3-6 show the results of measuring.

Based on the measured body weights, there was no significant difference between groups.

12.4. Pathological examination

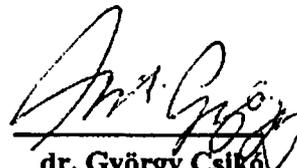
After 14 days post-treatment period the test animals did not show macroscopic alterations according to the pathological examination. (Table 7-8).

12.5. Evaluation of results

The AVEMAR at a single oral dose of 2000 mg/kg did not cause death, or clinical symptoms in male or female rats. The decrease in body weight in certain animals occurred both in control and treated groups to, therefore it can not be taken as an effect of test compound. The LD50 value of AVEMAR test substance in male and female rats, after single oral treatment is:

LD50 > 2000 mg/kg

Budapest, 03. 06. 1999.


dr. György Csikó
study director

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Table 1

CLINICAL SYMPTOMS AND MORTALITY DURING THE STUDY IN MALE RATS

Identifi- cation number	Dose	After treat- ment*	Days of post treatment examination													
			1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	Control	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
2		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
3		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
4		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
5		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
6	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
7	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
8	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
9	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
10	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
21	2000 mg/kg	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
22		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
23		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
24		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
25		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
26	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø		
27	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø		
28	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø		
29	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø		
30	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø		

* = during first 6 hours after treatment

NS= No symptoms Ø= No death

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Table 2

CLINICAL SYMPTOMS AND MORTALITY DURING THE STUDY IN FEMALE RATS

Identification number	Dose	After treatment*	Days of post treatment examination													
			1	2	3	4	5	6	7	8	9	10	11	12	13	14
11	Control	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
12		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
13		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
14		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
15		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø
16	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
17	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
18	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
19	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
20	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
31	2000 mg/kg	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
32		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
33		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
34		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
35		NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	
		Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	
36	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø		
37	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø		
38	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø		
39	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø		
40	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		
	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø		

* = during first 6 hours after treatment

NS= No symptoms Ø= No death

Table 3

INDIVIDUAL BODY WEIGHTS OF MALE RATS DURING THE STUDY

Identification number	Dose	TREATMENT						
		BEFORE		AFTER				
		Day 1	Day 2	Day 1	Day 2	Day 7	Day 14	Day 15
1	Control	132.17	149.18	156.79	158.20	184.45	245.28	245.71
2		138.95	144.17	144.80	146.74	169.05	216.92	217.61
3		141.87	151.05	151.30	152.89	181.17	244.97	246.48
4		132.87	139.10	147.61	148.76	183.97	233.32	234.58
5		129.44	139.40	143.39	147.01	183.85	229.18	230.93
6		144.11	159.02	159.10	159.97	186.03	242.81	244.40
7		139.26	146.64	136.52	147.15	174.10	233.01	233.10
8		132.28	149.00	154.70	161.43	188.93	252.18	256.05
9		131.27	146.78	156.33	161.48	191.60	248.11	249.62
10		130.69	150.04	157.35	162.41	190.48	254.27	256.32
21	2000 mg/kg	137.55	146.10	151.69	154.59	180.60	230.18	231.21
22		131.20	136.80	140.82	143.58	166.31	226.91	229.30
23		142.25	149.90	160.36	165.57	196.16	259.18	260.32
24		139.85	155.91	162.10	165.32	194.92	256.24	257.43
25		129.41	135.74	127.57	135.89	163.32	218.33	219.60
26		138.36	139.00	146.82	149.96	185.82	246.83	248.21
27		128.61	131.72	143.18	146.72	179.72	232.25	234.50
28		130.52	136.22	135.16	141.21	177.84	229.17	230.72
29		138.90	140.92	153.07	157.81	195.53	258.41	259.80
30		136.30	136.59	152.08	160.89	200.11	251.52	252.25

Table 4

INDIVIDUAL BODY WEIGHTS OF FEMALE RATS DURING THE STUDY

Identification number	Dose	TREATMENT						
		BEFORE		AFTER				
		Day 1	Day 2	Day 1	Day 2	Day 7	Day 14	Day 15
11	Control	111.05	123.96	129.53	130.68	140.90	177.18	179.80
12		119.54	137.10	142.21	149.01	153.94	187.18	189.16
13		116.40	130.60	123.33	131.75	139.72	170.01	170.75
14		104.55	115.80	120.95	123.20	162.60	201.12	203.35
15		110.32	124.40	122.54	129.01	148.24	183.91	185.30
16		111.22	122.20	129.23	132.63	147.46	175.71	177.69
17		107.75	114.03	114.01	117.66	141.47	168.21	170.54
18		110.63	120.84	125.70	127.84	138.84	169.03	170.22
19		109.27	124.52	128.82	131.25	150.58	184.19	186.80
20		108.11	116.64	117.27	119.52	135.55	154.19	156.80
31	2000 mg/kg	118.41	132.31	134.15	136.68	151.16	181.91	183.80
32		112.73	127.74	132.17	132.69	150.24	174.12	175.26
33		117.98	131.41	134.59	138.22	160.42	190.18	191.02
34		108.17	117.64	120.05	122.53	143.19	166.98	169.70
35		118.22	132.34	135.41	140.69	155.79	188.22	189.42
36		114.79	122.61	124.52	128.91	142.72	167.71	169.15
37		116.32	127.19	131.41	132.30	151.01	180.10	181.05
38		109.75	121.88	126.15	127.03	143.84	166.61	169.85
39		105.47	116.43	121.46	123.60	144.13	188.03	189.20
40		110.63	122.47	120.98	124.49	144.83	171.81	173.79

Table 5

THE MEAN BODY WEIGHTS OF MALE RATS

Dose	Treatment						
	Before		After				
	Day 1	Day 0	Day 1	Day 2	Day 7	Day 14	Day 15
CONTROL							
X	135.29	147.44	150.79	154.60	183.36	240.01	241.48
± SD	5.23	5.82	7.44	6.74	7.10	11.65	12.24
2000 mg/kg							
X	135.30	140.89	147.29	152.15	184.03	240.90	242.33
± SD	4.90	7.49	10.86	10.33	12.79	15.12	14.89

There is no significant difference between groups.

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Table 6

THE MEAN BODY WEIGHTS OF FEMALE RATS

Dose	Before		Treatment				
	Day 1	Day 0	Day 1	Day 2	After Day 7	Day 14	Day 15
CONTROL							
X	110.88	123.01	125.36	192.26	145.93	177.07	179.04
± SD	4.30	6.95	7.85	8.70	8.25	12.89	12.95
2000 mg/kg							
X	113.25	152.20	128.10	130.71	148.73	177.57	178.92
± SD	4.61	5.87	6.11	6.42	6.03	9.32	8.44

There is no significant difference between groups.

Table 7

THE RESULTS OF PATHOLOGICAL EXAMINATIONS OF MALES

Identification number	Dose	Macroscopic lesions
1	Control	no macroscopic alteration occurred
2		no macroscopic alteration occurred
3		no macroscopic alteration occurred
4		no macroscopic alteration occurred
5		no macroscopic alteration occurred
6		no macroscopic alteration occurred
7		no macroscopic alteration occurred
8		no macroscopic alteration occurred
9		no macroscopic alteration occurred
10		no macroscopic alteration occurred
21	2000 mg/kg	no macroscopic alteration occurred
22		no macroscopic alteration occurred
23		no macroscopic alteration occurred
24		no macroscopic alteration occurred
25		no macroscopic alteration occurred
26		no macroscopic alteration occurred
27		no macroscopic alteration occurred
28		no macroscopic alteration occurred
29		no macroscopic alteration occurred
30		no macroscopic alteration occurred

Table 8

THE RESULTS OF PATHOLOGICAL EXAMINATIONS OF FEMALES

Identification number	Dose	Macroscopic lesions
11	Control	no macroscopic alteration occurred
12		no macroscopic alteration occurred
13		no macroscopic alteration occurred
14		no macroscopic alteration occurred
15		no macroscopic alteration occurred
16		no macroscopic alteration occurred
17		no macroscopic alteration occurred
18		no macroscopic alteration occurred
19		no macroscopic alteration occurred
20		no macroscopic alteration occurred
31	2000 mg/kg	no macroscopic alteration occurred
32		no macroscopic alteration occurred
33		no macroscopic alteration occurred
34		no macroscopic alteration occurred
35		no macroscopic alteration occurred
36		no macroscopic alteration occurred
37		no macroscopic alteration occurred
38		no macroscopic alteration occurred
39		no macroscopic alteration occurred
40		no macroscopic alteration occurred