

Pharmaceutical Control and Developing Laboratory Co. Ltd.

Mezőkövi út 9. Budapest, H-1149

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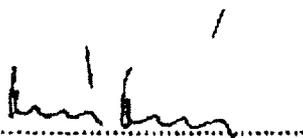
FINAL REPORT

ORAL ACUTE TOXICITY STUDY OF SUPPLEMENTED HUMIC ACID (DHS) IN MICE WITH "LIMIT TEST" METHOD

Study code: 9614

1996

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PC & DL

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study code: 9614

Staff in Charge

Director of the Laboratory:

Gyula Sebestyén
M.V.D., Ph.D.

Study Director:

Márta Kovács, dr.
toxicologist, pharmacist

Quality Assurance Unit:

Márta Szilli, dr.
chemical engineer

Study Director's Statement

I herewith declare, that the study titled Oral acute toxicity study of Supplemented Humic Acid (DHS) in mice with "limit test" method (study code: 9614) performed in Toxicological Department of PC & DL was set-up according to the regulation of GLP (OECD) and the valid SOP's. To the best of my knowledge, there were no deviations from the Good Laboratory Practice Regulations. Raw data obtained during the performance of the study are accurately reflected in the reported result.

19th November, 1996

Márta Kovács, dr.
Study Director

S U M M A R Y

General information: Oral acute toxicity study of Supplemented Humic Acid (DHS) was performed in male and female CFLP mice with "limit test" method, under GLP condition, with 14-day posttreatment observation period.

Lethality: No lethality was observed.

Oral LD₅₀ was found in male and female rats:

LD₅₀ > 40 ml/kg

Calculated to Humic Acid:

LD₅₀ > 600 mg/kg

Clinical symptom: No pathological symptom was observed either in male or in female mice during the study.

Bodyweight: No deviation from the controls was observed in both sex.

Necropsy: No macroscopic findings were observed related to the test substance.

Evaluation of the results:

Oral administration of 20 ml/kg DHS twice in 24 hours (total dose: 40 ml / kg / day) caused no toxic symptom or lethality.

1. GENERAL INFORMATION

1.1. Title of the study

ORAL ACUTE TOXICITY STUDY OF SUPPLEMENTED HUMIC ACID (DHS) IN MICE WITH "LIMIT TEST" METHOD

1.2. Objective of the study

Determination of toxic effect of DHS after oral administration in acute toxicity study.

1.3. Type of the study

Preclinical toxicological study performed according to the GLP as described by regulation No.P-44-1990 of the National Institute of Pharmacy (OGYI) and complying with the Good Laboratory Practices for Testing of Chemicals (OECD, 1982). The study was set-up according to the OECD GUIDELINES FOR TESTING OF CHEMICALS (Guideline No. 401; Adopted: 24, February, 1987).

1.4. Institution performing the study

Pharmaceutical Control and Developing Laboratory Co. Ltd. (PC & DL)
Mexikói út 9., Budapest, H-1149

1.5. Sponsor

HORIZON-MULTIPLAN Research and Developing Ltd.
Konkoly Thege út 29-33., Budapest, H-1121

2. TEST AND CONTROL SUBSTANCES

2.1. Characteristics of the test substance

Name of the substance:	Supplemented Humic Acid (DHS)
Batch number:	3380896
Active ingredient content calculated for Humic Acid:	15g/l
Number of the analytical examination:	88/96
Expiry:	08.02.1997.
Identification number in PC & DL:	20015
Package:	300 ml flask
Main pharmacological effect:	supplement of microelements
Storage conditions:	in dark, cold place, 2-8 °C
Safety regulation:	no special safety regulation

2.1.1. Chemical analysis

Analytical examination of the test substance was performed prior to study by the Sponsor.

Number of analytical examination: 88/96

2.2. Characteristics of the control substance

Name of the substance: Physiological saline

Batch number: N-0010196

Manufacturer: PC & DL, Toxicological Department

Number of the analytical examination: 756

Active ingredient content: 0.923 g/ 100 ml

Storage conditions: at room temperature

2.2.1. Chemical analysis

Analytical examination was performed by the Analytical Laboratory of PC & DL.

Number of the analytical examination: 756

2.2.2. Microbiological control

Sterility test was performed by the Microbiological Department of PC & DL.

2.3. Preparation of the test substance for the treatment

The container of DHS was opened 30 minutes before the treatment and a steril magnetic mixer was put in it. The content of covered container was mixing for 30 minutes. Administration of the test substance was carried out directly from the glass container.

3. TEST SYSTEM

3.1. Animals

Species / Strain: mice / CFLP

Age at arrival: 5-6 weeks

Bodyweight in the beginning of the study:

males: 19.9-22.5 g

females: 18.8-20.6 g

Hygienic class: SPF at arrival, kept in conventional environment during the study.

Number of animals ordered: 30 males and 30 females

3.1.1. Supplier

Laboratory for Animal Breeding and Feed Production Co.
(LATI Co. 2100 Gödöllő, Táncsics Mihály u.17.)

3.2. Reason for the selection of animals

The LATI CFLP mouse commonly used for acute toxicological studies. The strain is a wellknown laboratory model with sufficient historical control.

3.3. Keeping conditions

Mode of the keeping: conventional
Type of animal cages: II type macrolone
Size of cage: height: 12.5 cm
width: 43.0 cm
depth: 15.5 cm
Change of the cage: three times a week
Number of animals per cage: 5
Number of animal room: I.
Bedding: hardwood

3.3.1. Environmental conditions

Air exchange: 15-20 times/hour
Temperature: $20 \pm 3^{\circ}\text{C}$
Relative humidity: 50-70%
Lighting: artificial, 12 hour light-dark cycles.

The temperature was continuously recorded on a PCA type temperature recorder, whereas the relative humidity content by a TZ - 18 type thermohygrograph. The measured values did not exceed the prescribed limits.

3.4. Feeding

The animals were starved for 18 hours before the treatment.
During the posttreatment observation period the animals consumed their feed ad libitum.

3.4.1. Feed

The animals were fed with CRLT/N standard mouse and rat diet.

Supplier: FARMER PROMPT Ltd; Rákóczi u. 141. H - 3031 Zagyvaszántó.

The diet was identified by the manufacturing time. During the study the animals was fed with the diet manufactured in 03.08., 24.08. and 29.09. 1996.

3.4.1.1. Chemical analysis

Regularly controlled by the Manufacturer.

3.4.1.2. Microbiological analysis

Total germ count of every batch was controlled by the Microbiological Department of PC & DL.

3.5. Drinking

During the study, the animals consumed tap water ad libitum, filled daily, via drinking bottles.

3.5.1. Chemical analysis

Weekly controlled by the Analytical Laboratory of PC & DL.

3.5.2. Microbiological analysis

Weekly controlled by the Microbiological Department of PC & DL. The total germ count of drinking water was found as required.

3.6. Identification and housing of animals

The animals was identified by ear numbering technique.

3.7. Acclimatization period

The animals was kept for 3 days prior to the initiation of the study in the place of the study. Only healthy animals, free of clinical symptom was used in the study.

3.8. Randomization

Grouping of the animals was made on the basis of a random table prepared by a computer 3 days before the treatment. The animals was randomly assigned to the groups on the basis of their bodyweight, so that the distribution of the bodyweights in the individual groups was similar.

4. STUDY DESIGN

Group	Dose	MALES		FEMALES	
		Number of animals	Animal code	Number of animals	Animal code
1.	Control	10	621-630	10	641-650
2.	DHS 40 ml/kg	10	631-640	10	651-660

4.1. Reason for dose selection

The study was performed as „Emit test“ since the data of non-GLP studies handed over by HORIZON-MULTIPLAN Ltd. showed that neither lethality nor toxic symptom should be expected.

The daily dose was 600 mg/kg, calculated to the Humic Acid. Since the dry matter content of the test substance was 57,3 g/l, the daily dose was 2292 mg/kg within 24 hours, calculated to the dry matter content and for volume of 40 ml/kg.

5. TREATMENT

Duration of the treatment: twice a day (at 8 o'clock in the morning and at 15 o'clock). Treatment was done twice to reach a higher dose of the test substance.

Route of the administration: oral, via stomach tube.

5.1. Basis of route of administration

The route of the administration corresponds to the intended human therapeutic use.

6. VOLUME

The test substance was administered in volume of 20 ml/kg, twice a day. The control animals were treated with physiological saline in volume of 20 ml/kg respectively.

7. POSTTREATMENT OBSERVATION PERIOD

The animals were observed for 14 days after the treatment.

8. METHODS

8.1. Lethality

Observation was made twice daily.

8.2. Bodyweight

Time points of measurement: at the arrival into the laboratory, on the day of randomization, before the treatment (after the starvation), 24 hours after the treatment in the males, 24 and 48 hours after in the females and in the 7. and 14. days of the 14 day posttreatment observation period.

8.3. Clinical symptom

All animals were kept under continuous observation during the first six hours after the treatment, then they were controlled twice a day during the posttreatment observation period.

The type, the intensity, the time of the appearance and the duration of the symptom was recorded.

The observation was included: the state of the skin, fur, eyes and mucous membranes; respiratory function, circulation, autonomic nervous function; somatomotor activity, trembling, convulsions, salivation, diarrhoea, somnolence.

8.4. Necropsy

The animals were autopsied at the end of the posttreatment observation period. Macroscopic alterations were recorded.

9. **STATISTICAL ANALYSIS**

Bartlett's test was used to compare the variances among the groups of data of bodyweights. Since the variances of the groups proved to be homogeneous, one-way variance analysis (ANOVA) was performed. No significant difference was found among the groups on the base of ANOVA.

10. **SCHEDULE OF THE STUDY**

Arrival of the animals:	16th September, 1996
Randomization:	19th September, 1996
The day of the treatment:	23rd September, 1996
Autopsy:	8th October, 1996
Draft Final Report:	25th October, 1996

11. **PROCEDURES**

The examinations were performed according to the prescriptions of the Standard Operation Procedures of Toxicological Department of the Pharmaceutical Control and Developing Laboratory Co. Ltd.

12. **DEVIATION FROM THE PROTOCOL**

The code of the diet was CRLT/N (3.4.1. point in the protocol)

13. **ARCHIVES**

The data obtained in the course of the study was recorded in the Study file. The study plan, the documents and any information in connection with the study will be stored for 10 years, the final report for 20 years, the control sample of the test substance until expiry in the Archives of the Toxicological Department of Pharmaceutical Control and Developing Laboratory Co. Ltd. (Mexikói út 9. Budapest, H-1149).

14. RESULTS

14.1. Lethality

(see Table 1. and Appendices 1.1-1.2.)

No lethality was found after the treatment or during the 14-day posttreatment observation period in male and female rats treated twice within 24 hours with 20 ml/kg DHS.

Oral LD₅₀ was found in male and female rats:

$$LD_{50} > 40 \text{ ml/kg}$$

Calculated to Humic Acid:

$$LD_{50} > 600 \text{ mg/kg}$$

14.2. Clinical symptom

(see Tables 2.1-2.2. and Appendices 2.1-2.2.)

No pathological symptom were observed in the control and DHS treated animals after the treatment or during the 14-day posttreatment observation period.

14.3. Bodyweight

(see Tables 3.1-3.2. and Appendices 3.1-3.2.)

The development of the animals during the study period corresponded to their age and species.

14.4. Autopsy

(see Tables 4.1-4.2. and Appendices 4.1-4.2.)

The observed haemorrhage and emphysema in the lung, haemorrhage in the thymus and hyperaemia of the spleen were related with the agony.

Hyperaemia and hydrometra of the uterus were connected with the neurohumoral regulation of sexual function or the cyclic physiological state of uterus.

Summarized the results, no macroscopic findings related to the treatment were found due to the oral administration of 20 ml/kg Supplemented Humic Acid (DHS) in rats twice within 24 hours after 14-day posttreatment observation period.

15. EVALUATION OF THE RESULTS

20 ml/kg DHS administered orally twice in 24 hours caused no toxic symptom or lethality.

Maximal tolerable dose (MTD): > 40 ml/kg, administered within 24 hours
(calculated to Humic Acid > 600 mg/kg)

ORAL ACUTE TOXICITY STUDY OF SUPPLEMENTED HUMIC ACID (DHS) IN MICE
WITH "LIMIT TEST" METHOD

Table 1.

LETHALITY DURING THE STUDY

Group	MALE lethality / number of animals	FEMALE lethality / number of animals
Control	0/10	0/10
Supplemented Humic Acid 40 ml/kg	0/10	0/10

ORAL ACUTE TOXICITY STUDY OF SUPPLEMENTED HUMIC ACID (DHS) IN MICE
WITH "LIMIT TEST" METHOD

Table 2.1.

CLINICAL SYMPTOM
during the first 6 hours after the treatment

Group	MALE	FEMALE
	clinical symptom / total number of observation	
	SF	SF
Control	10/10	10/10
Supplemented Humic Acid 40 ml/kg	10/10	10/10

Comment: SF = Symptom Free

ORAL ACUTE TOXICITY STUDY OF SUPPLEMENTED HUMIC ACID (DHS) IN MICE
WITH "LIMIT TEST" METHOD

Table 2.2.

INCIDENCE OF CLINICAL SYMPTOM
during the 14-day posttreatment observation period

Group	MALE	FEMALE
	clinical symptom / total number of observation	
	SF	SF
Control	280/280	280/280
Supplemented Humic Acid 40 ml/kg	280/280	280/280

Comment: SF = Symptom Free

Table 3.1.

STATISTICAL ANALYSIS OF BODYWEIGHT

Males

Group	Bodyweight [g]			
	before the treatment	24th hour	7th day	14th day
Control				
Group size:	10	10	10	10
Mean:	20,590	24,540	30,180	33,870
±SD:	0,740	1,385	1,502	1,910
Supplemented Humic Acid 40 ml/kg				
Group size:	10	10	10	10
Mean:	20,560	24,510	29,990	33,800
±SD:	0,595	1,515	1,727	2,900

Comment: SD = Standard Deviation

Table 3.2.

STATISTICAL ANALYSIS OF BODYWEIGHT

Females

Group	Bodyweight [g]				
	before the treatment	24th hour	48th hour	7th day	14th day
Control					
Group size:	10	10	10	10	10
Mean:	19,470	21,920	23,030	24,960	26,860
± SD:	0,478	1,186	1,173	1,426	1,648
Supplemented Humic Acid 40 ml/kg					
Group size:	10	10	10	10	10
Mean:	19,750	21,610	22,860	24,340	26,440
± SD:	0,588	1,271	1,107	1,527	2,068

Comment: SD = Standard Deviation

ORAL ACUTE TOXICITY STUDY OF SUPPLEMENTED HUMIC ACID (DHS) IN MICE WITH "LIMIT TEST" METHOD

Table 4.

NECROPSY MACROSCOPIC ALTERATIONS

Sex	Males		Females	
Group	Control	Supplemented Humic Acid 40 ml/kg	Control	Supplemented Humic Acid 40 ml/kg
FINDINGS				
	findings / group size			
LUNG: - haemorrhage	1/10	0/10	0/10	0/10
- emphysema	0/10	2/10	1/10	0/10
THYMUS: - haemorrhage	1/10	0/10	2/10	0/10
SPLEEN: - hyperaemia	1/10	2/10	0/10	0/10
OVARY: - hyperaemia	---	---	1/10	1/10
- hydrometra	---	---	4/10	3/10

Comment: --- = no data

Appendices

1.1.

LETHALITY DURING THE STUDY

Males - Individual Data

Group / Animal code	Treatment day	The days of the posttreatment observation period													
		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.
Control															
621	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
622	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
623	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
624	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
625	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
626	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
627	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
628	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
629	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
630	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Supplemented Humic Acid 40 ml/kg															
631	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
632	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
633	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
634	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
635	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
636	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
637	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
638	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
639	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
640	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Comment: - = No Lethality

BODYWEIGHTS DURING THE STUDY

Males - Individual Data

Group / Animal code	Bodyweight [g]			
	before the treatment	24th hour	7th day	14th day
Control				
621	22,5	25,6	32,6	36,9
622	20,7	23,9	31,7	32,1
623	20,1	27,8	30,3	36,1
624	20,1	23,4	28,4	34,1
625	20,1	23,2	29,4	33,5
626	20,4	24,8	27,9	30,7
627	20,4	24,9	30,2	34,8
628	20,3	24,5	30,7	32,0
629	21,1	24,0	29,1	33,7
630	20,2	23,3	31,5	34,8
Supplemented Humic Acid 40 ml/kg				
631	21,4	25,8	31,6	34,9
632	20,6	24,1	29,0	31,7
633	19,9	24,4	32,7	36,1
634	20,1	22,3	26,4	27,9
635	20,0	23,3	28,7	32,9
636	21,5	26,8	30,0	32,6
637	21,1	25,3	30,8	35,9
638	20,4	25,6	30,8	35,3
639	20,6	25,2	29,9	38,2
640	20,0	22,3	30,0	32,5

BODYWEIGHTS DURING THE STUDY

Females - Individual Data

Group / Animal code	Bodyweight [g]				
	before the treatment	24th hour	48th hour	7th day	14th day
Control					
641	20,3	24,1	24,5	26,7	27,7
642	19,3	22,8	23,7	24,5	25,3
643	19,2	22,4	24,2	26,0	28,5
644	19,1	21,2	23,2	25,6	26,9
645	19,6	21,8	23,4	24,5	26,7
646	20,0	19,9	20,4	23,1	24,6
647	20,0	20,6	22,2	25,5	28,9
648	19,2	21,6	22,3	25,8	24,2
649	19,1	22,4	23,1	22,1	27,7
650	18,9	22,4	23,3	25,8	28,1
Supplemented Humic Acid 40 ml/kg					
651	20,6	22,6	23,8	24,8	27,3
652	19,3	21,9	23,2	23,5	24,5
653	20,6	21,8	23,5	23,8	25,6
654	20,0	20,0	21,3	22,7	23,7
655	20,1	18,8	20,6	22,3	23,4
656	19,2	22,9	24,1	26,4	29,1
657	19,7	21,9	22,6	23,0	26,7
658	19,5	22,6	23,0	24,8	27,3
659	18,8	22,1	23,5	26,7	29,1
660	19,7	21,5	23,0	25,4	27,7

NECROPSY MACROSCOPIC ALTERATIONS

Males - Individual Data

Group	Control										Supplemented Humic Acid 40 ml/kg									
Animal code	621	622	623	624	625	626	627	628	629	630	631	632	633	634	635	636	637	638	639	640

FINDINGS

LUNG: - haemorrhage	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
- emphysema	-	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-
THYMUS: - haemorrhage	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SPLEEN: - hyperaemia	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	+	-	-	-

Comment: - = no findings
 + = findings

NECROPSY MACROSCOPIC ALTERATIONS

Females - Individual Data

Group	Control										Supplemented Humic Acid 40 ml/kg									
Animal code	641	642	643	644	645	646	647	648	649	650	651	652	653	654	655	656	657	658	659	660

FINDINGS

LUNG: - haemorrhage	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
- emphysema	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
THYMUS: - haemorrhage	-	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-
SPLEEN: - hyperaemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OVARY: - hyperaemia	-	-	-	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-
- hydrometra	-	-	+	+	+	-	-	-	+	-	-	-	-	-	+	+	+	-	-	-

Comment: - = no findings
+ = findings