Emamectin Benzoate

Emamectin Benzoate Technical – Acute Oral Toxicity Study in the Mouse (Up and Down Procedure)

Final Report

DATA REQUIREMENT(S): OECD Test Guideline 425 (2008)
EPA OPPTS 870.1100 (2002)

AUTHOR(S): Judit Tavaszi, M.Sc.

STUDY COMPLETION DATE: 26 August 2010

PERFORMING LABORATORY: LAB Research Ltd.
H-8200 Veszprém, Szabadságpuszta,
Hungary

LABORATORY PROJECT ID: Report Number: 10/036-001E
Study Number: 10/036-001E
Task Number: TK0022509

SPONSOR: Syngenta Ltd.
Jealott's Hill International Research Centre,
Bracknell, Berkshire, RG42 6EY, United Kingdom

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study has been performed in accordance with the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 9/2001. (III. 30.) EüM-FVM joint decree of the Minister of Health and the Minister of Agriculture and Regional Development which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17.).

This study was conducted in accordance with a written Study Plan and Amendments, authorized by the Sponsor and LAB Research Ltd. management, and followed applicable Standard Operating Procedures.

Signature: _____ Date: 16 August 2010

Judit Tavaszi, M.Sc.
Study Director

Performing Laboratory: LAB Research Ltd.
H-8200 Veszprém, Szabadságpuszta,
Hungary

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

Study Number: 10/036-001E

Study Title: Emamectin Benzoate Technical –
Acute Oral Toxicity Study in the Mouse (Up and Down Procedure)

Test Item: Emamectin Benzoate Technical

This study has been inspected, and this report audited by the Quality Assurance Unit in compliance with the Principles of Good Laboratory Practice. As far as it can be reasonably established the methods described and the results incorporated in this report accurately reflect the raw data produced during this study.

All inspections, data reviews and the report audit were reported in written form to the study director and to management. The dates of such inspections and of the report audit are given below:

Date of Inspection	Phase(s) Inspected/Audited	Date of report to	
		Management	Study Director
23 March 2010	Study Plan	23 March 2010	23 March 2010
08 April 2010	Necropsy	08 April 2010	08 April 2010
16 July 2010	Draft Report	16 July 2010	16 July 2010
25 August 2010	Final Report	25 August 2010	25 August 2010

Signature: Kiss Istvánné Date: 26 August 2010

Istvánné Kiss, M.Sc.
QA Inspector

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Syngenta Ltd. (as Sponsor) and LAB Research Ltd., the study titled "Emamectin Benzoate Technical - Acute Oral Toxicity Study in the Mouse (Up and Down Procedure) " was performed, in compliance with OECD 425 (October 2008), OPPTS 870.1100 (EPA 712-C-02-190, December 2002) and applicable SOP's of LAB Research Ltd.

Signature: _____ Date: 20 Aug 2010

Christopher Banks, DABT
Managing Director

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function
Judit Tavaszi, M.Sc.	Study Director
Viktória Zelenák, M.Sc.	Assistant scientist
István Pásztor, DVM	Veterinary control
Peter Maslej, DVM, PhD	Head of Pathology Unit
Tamás Mészáros, PhD	Head of Central Dispensary
Eric Yau	Syngenta Study Manager

Study dates

Experimental Starting Date	25 March 2010
Experimental Completion Date	05 May 2010
Reception of Animals	24 February 2010 and 14 April 2010
Acclimatization	At least 7 days
Treatment	25 March 2010 (female no. 4649) 26 March 2010 (female no. 4650) 30 March 2010 (female no. 4651) 31 March 2010 (female no. 4652) 21 April 2010 (female no. 4992) 23 April 2010 (female no. 4993)
Observation	25 March – 08 April 2010 (female no. 4649) 26 – 27 March 2010 (female no. 4650) 30 March – 01 April 2010 (female no. 4651) 31 March – 06 April 2010 (female no. 4652) 21 April – 05 May 2010 (female no. 4992) 23 – 24 April 2010 (female no. 4993)

Deviations from the study guideline

The relative humidity was out of the guideline range on 30 March 2010 (41 – 80 %).

This deviation is considered to have no impact on the outcome of the study and interpretation of the results.

Deviations from the study plan

Interpretation of the results will not be performed according to the EU labelling regulations.

The Draft Report was sent on 21 July 2010 instead of 25 June 2010 as indicated in the Study Plan.

The Study Plan and the Amendments will not be attached to the Report.

These deviations are considered to have no impact on the outcome of the study and interpretation of the results.

Performing laboratory test substance reference number

09/287K/1 100203

Other

The study documents:
- study plan and amendments,
- all raw data,
- sample of the test item,
- original final study report and any amendments,
- correspondence

will be archived according to the Hungarian GLP and to applicable SOP's in the archives of LAB Research Ltd. 8200 Veszprém, Szabadságpuszta, Hungary.

After the retention time of 15 years has elapsed all the archived materials listed above will be returned to the Sponsor or retained for a further period if agreed by a contract. Otherwise the materials will be discarded.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

1.1 Study Design

A single oral (gavage) dose was administered to mice followed by a 14 day observation period. The animals were fasted overnight prior to treatment. Animals were weighed before dosing and food was returned 2 hours after dosing.

Single animals were dosed sequentially at approximately 24 hour intervals. The time intervals between dosing were determined by the onset, duration and severity of toxic signs.

A limit test was not performed as the Sponsor had information which indicated the test item was likely to cause mortality at a dose level of 2000 mg/kg. The starting dose was 55 mg/kg bw as requested by the Sponsor.

Dosages

The test substance was formulated in 0.5% Carboxymethylcellulose.

Animal Number	Dosage [mg/kg body weight]	Volume [mL/kg body weight]
4649	55	10
4650	175	10
4651	55	10
4652	175	10
4992	55	10
4993	175	10

Observations

Surviving animals were observed individually after dosing at 30 minutes, 1, 2, 3, 4 and 6 hours post treatment and once each day for 14 days thereafter. Body weight was measured on Day -1 and just before treatment and weekly after. All surviving animals were examined macroscopically at the end of the study.

1.2 Results

Emamectin Benzoate Technical caused mortalities at 175 mg/kg bw (3/3) and 55 mg/kg bw (1/3).

Clinical signs included decreased activity (3/3), hunched back (3/3), incoordination (1/3), continuous tremors (1/3), intermittent tremors (1/3), prone position (1/3), piloerection (1/3) and prone position (1/3) at the dose level of 175 mg/kg bw. Animals dosed at 55 mg/kg were only observed with decreased activity (2/3), hunched back (2/3) and continuous tremors (1/3).

Body weight and body weight changes of the surviving animals during the study showed no indication of a treatment-related effect.

No treatment-related observations were found at necropsy. White discoloration of the digestive content in the stomach was observed in one mouse no. 4993, dosed at 175 mg/kg.

1.3 Conclusion

Under the conditions of this study, the acute oral median lethal dose (LD_{50}) of Emamectin Benzoate Technical was calculated to be 55 mg/kg bw in female CRL:(NMRI) BR mice.

2.0 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the oral toxicity of the test item Emamectin Benzoate Technical when administered as a single dose to mice. The results of the study allow the test item to be ranked according to most classification systems currently in use.

2.2 Guidelines

The study was performed according to the following guidelines:

OECD guideline reference 425 (2008): Acute Oral Toxicity - Up-and-Down Procedure.

United States Environmental Protection Agency, Health Effects Test Guidelines, OPPTS 870.1100 Acute Oral Toxicity EPA 712-C-02-190, December 2002.

2.3 Test Facility

This study was performed in an AAALAC-accredited laboratory. The Institutional Animal Care and Use Committee (IACUC) of LAB Research Ltd. Revewed the study plan and authorized the conduct of the study.

3.0 MATERIALS AND METHODS

3.1 Test Substance

Data as supplied by the Sponsor.

Name:	Emamectin Benzoate Technical
Batch number:	SNA6A015
Product code:	MK244G
Molecular mass:	1008.3
Appearance:	Powder/ white crystalline
Reanalysis date:	End of April 2011
Storage conditions:	< 10˚C
Safety Precautions:	Routine safety precautions (lab coat, safety glasses, gloves, face mask) for unknown materials were applied to assure personnel health and safety

The certificate of analysis for the test substance is attached in Appendix 2.

Vehicle

Name:	0.5% Carboxymethylcellulose
Batch number:	1340439
Expiry Date:	30 January 2011
Produced by:	FLUKA
Dose volume:	10 mL/kg

3.1.1 Identification, receipt

The test item of a suitable chemical purity together with all precautions required in the handling and disposal of the test item were supplied by the Sponsor. The identification of test item was made in the Central Dispensary Unit of LAB Research Ltd. on the basis of the information provided by Sponsor.

3.1.2 Formulation

Emamectin Benzoate Technical was formulated for treatment doses at 55 and 175 mg/kg (dose volume of 10 mL/kg). The test substance was formulated in 0.5% Carboxymethylcellulose.

3.2 Experimental Animals

Species and strain:	CRL:(NMRI)BR mice
Source:	Toxi Coop, Cserkesz u. 90. 1103 Budapest, Hungary
Hygienic level at arrival:	SPF
Hygienic level during the study:	Standard housing conditions
Justification of strain:	Recognized by international guidelines as a recommended test system.
Number of animals:	1 animal/step
Sex:	Female mice, nulliparous and non-pregnant.
Age when treated:	Young adult mice, 8 – 11 weeks old.
Body weight (at dosing):	25.2 – 31.7 g
Randomization:	Selected by hand at time of delivery.
Acclimatization time:	At least 5 days under laboratory conditions, after health examination. Only animals without any visible signs of illness were used for the study.

3.2.1 Husbandry

Animal health:	Only healthy animals were used for the test. The health status was certified by the veterinarian.
Housing:	Individual caging
Cage type:	Type II. polypropylene/polycarbonate
Bedding:	Lignocel Bedding for Laboratory Animals was available to animals during the study.
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature:	22 ± 3 °C
Relative humidity:	30 - 80%
Ventilation:	15-20 air exchanges/hour

Enrichment:	Rodents were housed with deep wood sawdust bedding to allow digging and other normal rodent activities.

The temperature and relative humidity was recorded twice daily during the study and the acclimation period.

3.2.2 Food and water supply

Animals received ssniff® SM R/M-Z+H "Autoclavable complete feed for mice and mice – breeding and maintenance" produced by ssniff Spezialdiäten GmbH, D-59494 Soest Germany (batch: 476 3413 and 928 3711, exp. date: 06/2010 and 09/2010) *ad libitum*, and tap water from municipal supply, as for human consumption from 500 ml bottle *ad libitum*. The food was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study. Details of the diet are archived with the raw data.

Water quality control analysis is performed once every three months and microbiological assessment is performed monthly, by Veszprém County Institute of State Public Health and Medical Officer Service (ÁNTSZ, H-8201 Veszprém, József A.u.36., Hungary). The quality control results are retained in the archive at LAB Research Ltd.

3.2.3 Identification

Animals were individually identified by numbers written on the tail with a permanent marker pen. The numbers were given on the basis of the LAB Research Ltd. master file, for each animal allocated to the study.

The boxes were identified by cards holding information on the study code, the sex of animals, the dose group, the cage number and the individual animal number.

3.3 Experimental Design

3.3.1 Dosages

Justification of the doses:

Limit test was not performed. The starting dose in the main study was 55 mg/kg bw.

Rationale: Oral administration is considered to be an appropriate dose route as it is a possible route of human exposure.

3.3.2 Procedure

A single oral (gavage) administration was followed by a 14 day observation period. Before treatment the animals were fasted. Food, but not water, was withheld for 3 hours before

treatment. Animals were weighed before dosing and food was returned 2 hours after the treatment.

Single animals were dosed sequentially following an interval of approximately 24 hours. The time intervals between dosing were determined by the onset, duration and severity of toxic signs. Treatment of an animal at the next dose was performed when no significant clinical signs were noted in the previous animal.

3.4 Observations

3.4.1 Clinical observations

Surviving animals were observed individually after dosing at 30 minutes, 1, 2, 3, 4, and 6 hours after dosing and once each day for 14 days thereafter. Individual observations were performed on the skin and fur, eyes and mucous membranes and also respiratory, circulatory, autonomic and central nervous system, somatomotor activity and behaviour pattern. Particular attention was directed to observation of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

3.4.2 Body weight measurement

The body weights were recorded on Day -1 and Days 0 (beginning of the experiment) 7 and 14 (surviving animals).

3.5 Necropsy

All animals were subjected to macroscopic examination. Surviving animals were exsanguinated under pentobarbital anaesthesia (Euthasol, Batch no.: 07K05 7, Exp. date: 10/2010). After examination of the external appearance, the cranial, thoracic and abdominal cavities were opened and the appearance of the tissues and organs were observed. All gross pathological changes were recorded for each animal on the post mortem record sheets.

3.6 Data Evaluation

The type, severity and duration of clinical observations are described. Body weight and body weight changes are summarised in tabular form. Necropsy findings are described and summarised in tabular form.

4.0 RESULTS AND DISCUSSION

Individual clinical observations and mortality results are presented in Table 1. Individual body weights and necropsy results are presented in Tables 2 and 3, respectively.

4.1 Mortality

Emamectin Benzoate Technical caused mortalities at 175 mg/kg bw (3/3) and at 55 mg/kg bw (1/3).

4.2 Body Weights

Body weight and body weight changes of the surviving animals during the study showed no indication of a treatment-related effect.

4.3 Clinical Signs

Clinical signs included decreased activity (3/3), hunched back (3/3), incoordination (1/3), continuous tremors (1/3), intermittent tremors (1/3), prone position (1/3), piloerection (1/3) and prone position (1/3) at the dose level of 175 mg/kg bw. Animals dosed at 55 mg/kg were only observed with decreased activity (2/3), hunched back (2/3) and continuous tremors (1/3).

4.4 Macroscopic Findings

No treatment-related observations were found at necropsy. White discoloration of the digestive content in the stomach was observed in one mouse 4993, dosed at 175 mg/kg.

5.0 CONCLUSIONS

Under the conditions of this study, the acute oral median lethal dose (LD_{50}) of Emamectin Benzoate Technical was calculated to be 55 mg/kg bw in female CRL:(NMRI) BR mice.

TABLES SECTION

TABLE 1 Individual Findings – Clinical Signs

DOSE LEVEL: 55 mg/kg

SEX: FEMALE

Group No.	Animal No.	Observations	Observation days																			Frequency
			0						1	2	3	4	5	6	7	8	9	10	11	12	13	14	
			30'	1h	2h	3h	4h	6h															
1	4649	Symptom Free	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	19/20
		Hunched back	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	1/20
		Activity Decreased	-	-	-	-	-	-	-1	-	-	-	-	-	-	-	-	-	-	-	-	-	1/20
		Tremors (continuous)	-	-	-	-	-	-	+1	-	-	-	-	-	-	-	-	-	-	-	-	-	1/20
3	4651	Symptom Free	+	+	+	+	+	+	-														6/7
		Activity Decreased	-	-	-	-	-	-	-1														1/7
		Hunched back	-	-	-	-	-	-	+														1/7
		Found dead	-	-	-	-	-	-	-	+													-
5	4992	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20

Remarks:

+: present; -: absent

Frequency of observation = number of occurence of observation / total number of observations

' = minutes

h = hour(s)

Treatment day = Day 0

TABLE 1 Individual Findings – Clinical Signs (Continued)

DOSE LEVEL: 175 mg/kg

SEX: FEMALE

Group No.	Animal No.	Observations	30'	1h	2h	3h	4h	6h	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Frequency
2	4650	Symptom Free	+	-	-	-	-	-															1/6
		Activity Decreased	-	-1	-1	-2	-2	-3															5/6
		Hunched back	-	-	+	+	+	+															4/6
		Incoordination	-	-	-	-	+	-															1/6
		Tremors (continuous)	-	-	-	+1	+2	+3															3/6
		Found dead	-	-	-	-	-	-	+														-
4	4652	Symptom Free	+	+	+	-	-	-	-	-	-	-	-										3/11
		Activity Decreased	-	-	-	-1	-3	-3	-2	-3	-2	-2	-2										8/11
		Hunched back	-	-	-	+	+	+	+	+	+	+	+										8/11
		Tremors (intermittent)	-	-	-	+1	+3	+3	+1	+1	+1	+1	+1										8/11
		Piloerection	-	-	-	-	-	-	-	+	+	+	+										4/11
		Found dead	-	-	-	-	-	-	-	-	-	-	-	+									-
6	4993	Symptom Free	+	+	+	-	-	-															3/6
		Activity Decreased	-	-	-	-1	-3	-3															3/6
		Hunched back	-	-	-	+	-	-															1/6
		Prone position	-	-	-	-	+	+															2/6
		Found dead	-	-	-	-	-	-	+														-

Remarks:

+: present; -: absent ‘ = minutes h = hours Treatment day = Day 0
Frequency of observation = number of occurence of observation / total number of observations

TABLE 2 Body Weight and Body Weight Gain

DOSE LEVEL: 55 mg/kg SEX: FEMALE

Group No.	Animal No.	Body weight (g) Days				Body Weight Gain (g)			
		-1	0	7	14	-1-0	0-7	7- 14	-1 - 14
1	4649	33.2	31.7	32.8	31.9	-1.5	1.1	-0.9	-1.3
3	4651	32.2	31.3	-	-	-0.9	-	-	-
5	4992	27.5	25.2	27.1	29.4	-2.3	1.9	2.3	1.9
Mean:		31.0	29.4	30.0	30.7	-1.6	1.5	0.7	0.3
SD:		3.0	3.6	4.0	1.8	0.7	0.6	2.3	2.3

DOSE LEVEL: 175 mg/kg SEX: FEMALE

Group No.	Animal No.	Body weight (g) Days				Body Weight Gain (g)			
		-1	0	7	14	-1-0	0-7	7- 14	-1 - 14
2	4650	32.1	30.3	-	-	-1.8	-	-	-
4	4652	30.2	28.6	-	-	-1.6	-	-	-
6	4993	28.5	26.2	-	-	-2.3	-	-	-
Mean:		30.3	28.4	-	-	-1.9	-	-	-
SD:		1.8	2.1	-	-	0.4	-	-	-

TABLE 3 Macroscopic Findings

DOSE LEVEL: 55 mg/kg SEX: FEMALE

Group No.	Animal No.	Necropsy Date	External Observations	Internal Observations	Organ/Tissue
1	4649	08 April 2010	No external observations	No internal observations	Not applicable
3	4651*	01 April 2010	No external observations	No internal observations	Not applicable
5	4992	05 May 2010	No external observations	No internal observations	Not applicable

DOSE LEVEL: 175 mg/kg SEX: FEMALE

Group No.	Animal No.	Necropsy Date	External Observations	Internal Observations	Organ/Tissue
2	4650*	27 March 2010	No external observations	No internal observations	Not applicable
4	4652*	06 April 2010	No external observations	No internal observations	Not applicable
6	4993*	24 April 2010	No external observations	White discoloration, stomach	Digestive content

Remarks:

*: Found dead

**: Moribund

APPENDICES SECTION

APPENDIX 1 Pathology Report

LAB Study code. 10/036-001E

PATHOLOGY REPORT

INTRODUCTION

The objective of the study was to identify the acute oral toxicity Emamectin Benzoate Technical when administered in a single dose to mice. The results of the study allows the calculation of the estimated oral LD_{50} of the test item and permits the test item to be ranked according to most classification systems currently in use.

RESULTS AND DISCUSSION

Surviving animals were euthanized upon completion of the treatment period on Day 14. Mice were anesthetized with pentobarbital, followed by exsanguination. Gross pathology consisted of an external examination, including identification of all clinically-recorded lesions, as well as a detailed internal examination. Histopathological examination was not performed.

MORTALITY

A total 4 animals were found dead. Affected animals included 1/3 (55 mg/kg) died on Day 2 and 3/3 (175 mg/kg) on Day 1 or 6.

FOUND DEAD

Macroscopic Findings

No treatment-related observations were found at necropsy. White discoloration of the digestive content in the stomach was observed in one mouse no. 4993.

TERMINAL (DAY 14)

Macroscopic Findings

There was no evidence of test item-related macroscopic observations in remaining 2 animals at a dose level of 55 mg/kg.

APPENDIX 1 Pathology Report (Continued)

CONCLUSION

A single oral gavage of Emamectin Benzoate Technical to the CRL: (NMRI) BR mouse led to the death of 3 animals at a dose level of 55 and 175 mg/kg bw on Day 1, 2 or 6. A specific cause of death was not determined for these mice.

In animals surviving to the termination on Day 14, no macroscopic findings were present.

25 August 2010

Peter Maslej, D.V.M., Ph.D. Date
Head, Pathology Department

APPENDIX 2 Certificate of Analysis

10/036-001E

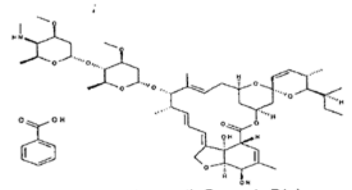
syngenta

GLP Testing Facility WMU
Analytical Development & Product Chemistry

Syngenta Crop Protection Münchwilen AG
Breitenloh 5
CH-4333 Münchwilen

Certificate of Analysis

MK244G



(shown as Emamectin Benzoate B1a)

SNA6A015, purity 96.6 %

Batch Identification	**SNA6A015**
Product Code	**MK244G**
Origin	**Syngenta, Nantong, China**
Other Product Code(s)	---
ISO Common Name	emamectin benzoate
CA Reg. No.	155569-91-8
CA Index Name	avermectin B1, 4''-deoxy-4''-(methylamino)-(4''R)-, benzoate (salt)
IUPAC Name	---
Molecular formula	$C_{56}H_{81}NO_{15}$
Molecular mass	1008.3
Chemical Analysis	
– **Identity***	**confirmed**
– **Content of MK244***	**96.6 %**
Methodology used for Characterization	HPLC, GC
Physical Analysis	
– **Appearance ***	**white crystalline powder**
Stability:	
– **Storage Temperature**	**< 10 °C**
– **Reanalysis date**	**End of April 2011**

5. It's a true copy / Hiteles másolat
Date / Dátum: 2010 FEBR 24.
Signature/Aláírás: TM
Eredeti helye: 6.sz. dosszié

The stability of this test substance will be controlled by reanalysis of material held in the inventory at Syngenta Crop Protection Münchwilen AG at the appropriate time.
This Certificate of Analysis summarizes data which originates either from a single study or from several individual studies. Tests marked with an asterisk (*) have been conducted in compliance with GLP. Raw data, documentation, study plans, any amendments to study plans and reports pertaining to this/these study/studies are stored under the study number(s) referenced below within the archives of the GLP Testing Facility WMU at Syngenta Crop Protection Münchwilen AG.

Characterization: 115982 (cf. report for 5 representative batches)

Reanalysis: ---

Authorization:

10-Dec-2009

Dr. K. Heintz
Analytical Development & Product Chemistry

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APPENDIX 3 GLP Certificate

ORSZÁGOS GYÓGYSZERÉSZETI INTÉZET
National Institute of Pharmacy

H-1051 Budapest, Zrinyi u. 3.
Mail: 1372 P.O. Box 450.
Phone: +36 1 8869-300
Fax: +36 1 8869-460
E-mail: ogyi@ogyi.hu

Budapest, 20th December 2008
No: 38625/48/2007
Our ref.: Szilvia Karsai
Subject: GLP Certificate

GOOD LABORATORY PRACTICE (GLP)
CERTIFICATE

Based on the Inspection report and the discussion of follow up activities it is hereby certified that the test facility

LAB Research Ltd.
H-8201 Veszprém, Szabadságpuszta, Hungary

is able to carry out **Physical-chemical testing, Toxicity studies, Mutagenicity studies, Environmental toxicity studies on aquatic and terrestrial organisms, Studies on behaviour in water, soil and air; bioaccumulation, Bioanalytical, Analytical and clinical chemistry testing** compliance with the Principles of GLP (Good Laboratory Practice).

Date of the inspection: **13-22 October 2008.**

This GLP Certificate is valid for 2 years.

Zsuzsanna Szepezdi, Ph. D.
Director-General