Cyantraniliprole

Cyantraniliprole FS (A17960A) – Acute Oral Toxicity Study in the Rat (Up and Down Procedure)

Final Report

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

AUTHOR(S): István Buda, M.Sc.

STUDY COMPLETION DATE: 13 April 2011

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

LABORATORY PROJECT ID: Report Number: 11/013-001P
Study Number: 11/013-001P
Task Number: TK0015711

SPONSOR(S): 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, authorized by the Sponsor and LAB Research Ltd. management, and followed applicable Standard Operating Procedures.

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study.

Signature: _____ Date: 13 APRIL 2011

István Buda, 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: 11/013-001P

Study Title: Cyantraniliprole FS (A17960A) – Acute Oral Toxicity Study in the Rat (Up and Down Procedure)

Test Item: Cyantraniliprole FS (A17960A)

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
04 February 2011	Study Plan	04 February 2011	04 February 2011
15 February 2011	Body Weight measurement	15 February 2011	15 February 2011
19 March 2011	Draft Report	21 March 2011	19 March 2011
13 April 2011	Final Report	13 April 2011	13 April 2011

Signature: Kim Istvánné Date: 13 April 2011

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. (Test Facility) the study titled " Cyantraniliprole FS (A17960A) - Acute Oral Toxicity Study in the Rat (Up and Down Procedure)" has been performed in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 13 April 2011

Christopher Banks, DABT
Managing Director

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

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

Study dates

Experimental Starting Date	08 February 2011
Experimental Completion Date	25 February 2011
Reception of Animals	03 February 2011
Acclimatization	At least 5 days

Treatment	08 February 2011 (male no. 4430) 10 February 2011 (male no. 4435) 11 February 2011 (male no. 4436)
Observation	08 – 22 February 2011 (male no. 4430) 10 – 24 February 2011 (male no. 4435) 11 – 25 February 2011 (male no. 4436)

Deviations from the guidelines

During the study, the humidity value was in the range 24 – 87 %. This was a deviation from the range stated in the guidelines (30 – 70%) which was considered minor and with no impact on the objective of the study.

Performing laboratory test substance reference number

11002C

Other

The study documents:

- study plan,
- all raw data,

- sample of the test item,
- 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 limit test was performed with 3 animals. A single oral (gavage) administration was administered followed by a 14 day observation period. The animals were fasted overnight prior to treatment. Animals were weighed before dosing and food was returned 3 hours after dosing.

Single animals were dosed sequentially at no less than approximately 24 hour intervals. The time intervals between dosing were determined by the onset, duration and severity of clinical signs.

The first animal was treated at a dose level of 5000 mg/kg body weight (bw). As no mortality or significant clinical signs were observed, 2 additional animals were sequentially dosed at 5000 mg/kg bw such that a total of 3 animals were tested. No mortalities were observed, therefore the study was terminated.

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

1.2 Results

No deaths occurred during the study.

No clinical signs were observed following treatment at 5000 mg/kg.

There were no treatment related changes in the body weights. The body weights of the animals were within the range commonly recorded for this strain and age.

No treatment related macroscopic findings were observed.

1.3 Conclusion

Under the conditions of this study, the acute oral median lethal dose LD_{50} of the test item, Cyantraniliprole FS (A17960A), was greater than 5000 mg/kg bw in female RjHan:WI rats.

2.0 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the oral toxicity of the test item Cyantraniliprole FS (A17960A) when administered as a single oral gavage dose to rats at one defined dose level. The results of the study allowed 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.

3.0 MATERIALS AND METHODS

3.1 Test Substance

Data as supplied by the Sponsor.

Name:	Cyantraniliprole FS (A17960A)
Other Product Name(s):	Cyantraniliprole FS (600) SYN545377 FS (600)
Batch Number:	SMU1AP002
Product Code:	A17960A
Purity:	Cyantraniliprole – 49% w/w corresponding to 615g/L
Appearance:	Pink liquid
Density:	1255 kg/m^3
Recertification Date:	End of July 2013
Storage Conditions:	< 30˚C
Safety Precautions:	Routine safety precautions (lab coat, gloves, goggles, face mask) for unknown materials were applied to assure personnel health and safety

The Certificate of Analysis is attached in Appendix 2.

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 the 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

The test item was administered undiluted.

3.2 Experimental Animals

Species and strain:	RjHan:WI rats
Source:	Laboratoire Elevage Janvier, B.P. 4105, Route des Chênes Secs, 53940 Le Genest-St-Isle CEDEX FRANCE
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:	3
Sex:	Female rats, nulliparous and non-pregnant.
Age when treated:	Young adult rats, 8-9 weeks old.
Body weight (at dosing):	210-218 g
Randomization:	Selected by hand at time of delivery.
Acclimatization time:	At least 5 days

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:	24 – 87 %
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 rats and rats – breeding and maintenance" produced by ssniff Spezialdiäten GmbH, D-59494 Soest Germany *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 at LAB Research Ltd.

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 LAB Research Ltd.'s 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 Administration of the Test Item

3.3.1 Dosages

Justification of the doses:

A limit dose of 5000 mg/kg bw was selected as there is a specific regulatory requirement to test this dose level. The density of the test item is 1255 kg/m^3, therefore the applied dose volume was 3.98 mL/kg bw. The dose volumes used at these concentrations are shown below.

Animal Number	Dosage [mg/kg body weight]	Volume [mL/kg body weight]
4430	5000	0.84
4435	5000	0.87
4436	5000	0.85

Rationale: Oral administration was 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. The day before treatment the animals were fasted. The food, but not water, was withheld overnight. Animals were weighed before dosing and the food was returned 3 hours after the treatment.

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

3.4 Observations

3.4.1 Clinical observations

Animals were observed individually after dosing at 30 minutes, then 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 Days -1, 0 (beginning of the experiment), 7 and 14.

3.5 Necropsy

All animals were subjected to macroscopic examination. All animals were exsanguinated under pentobarbital anaesthesia (Euthasol® 40%, Lot No.: 10C25 7, Expiry Date: February 2013, Produced by: AST Beheer B.V. Oudewater Netherlands (Produlab Pharma, Raamsdonksveer). 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

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

4.1 Results

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.

4.2 Mortality

There were no mortalities observed.

4.3 Body Weights

The body weight and the body weight gain did not show any test item related effect.

4.4 Clinical Signs

No clinical signs were observed following treatment at 5000 mg/kg.

4.5 Macroscopic Findings

No treatment related macroscopic findings were observed.

5.0 CONCLUSIONS

Under the conditions of this study, the acute oral median lethal dose LD_{50} of the test item, Cyantraniliprole FS (A17960A), was greater than 5000 mg/kg bw in female RjHan:WI rats.

TABLES SECTION

TABLE 1 Individual Findings – Clinical Signs

DOSE LEVEL: 5000 mg/kg bw										SEX: FEMALE
Cage No.	Animal Number	Observations	Observation days							Frequency
			0						1	2-14	
			30'	1h	2h	3h	4h	6h			
1	4430	Symptom Free	+	+	+	+	+	+	+	+	20/20
2	4435	Symptom Free	+	+	+	+	+	+	+	+	20/20
3	4436	Symptom Free	+	+	+	+	+	+	+	+	20/20

Remarks: +: present

h=hour (s) 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: 5000 mg/kg bw									SEX: FEMALE
Cage No.	**Animal No.**	**Body Weight (g) Days**				**Body Weight Gain (g)**			
		-1	**0**	**7**	**14**	**-1-0**	**0-7**	**7- 14**	**-1 - 14**
1	4430	226	210	262	269	-16	52	7	43
2	4435	237	218	252	268	-19	34	16	31
3	4436	228	213	239	256	-15	26	17	28
Mean:		230.3	213.7	251.0	264.3	-16.7	37.3	13.3	34.0
Standard deviation:		5.9	4.0	11.5	7.2	2.1	13.3	5.5	7.9

Remark: Treatment day= Day 0

TABLE 3 Macroscopic Findings

DOSE LEVEL: 5000 mg/kg bw					SEX: FEMALE
Cage No.	**Animal ID**	**Necropsy Date**	**External Observations**	**Internal Observations**	**Organ/Tissue**
1	4430	22 February 2011	No external observations recorded	No internal observations recorded	Not applicable
2	4435	24 February 2011	No external observations recorded	No internal observations recorded	Not applicable
3	4436	25 February 2011	No external observations recorded	No internal observations recorded	Not applicable

APPENDICES SECTION

APPENDIX 1 Pathology Report

LAB Study code. 11/013-001P

PATHOLOGY REPORT

INTRODUCTION

The objective of the study was to assess the acute oral toxicity of Cyantraniliprole FS (A17960A) when administered in a single dose to female rats at one or more defined doses. 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

All rats survived until the scheduled termination of the study.

All animals were euthanized upon completion of the treatment period on Day 14. Rats 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.

TERMINAL (DAY 14)

Macroscopic Findings

There was no evidence of the macroscopic observations at a dose level of 5000 mg/kg bw.

CONCLUSION

A single oral gavage of Cyantraniliprole FS (A17960A) to the RjHan: WI female rat at a dose level of 5000 mg/kg bw with a 14 day observation period, was not associated with any macroscopic findings.

13 April 2011

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

APPENDIX 2 Certificate of Analysis

syngenta

GLP Testing Facility WMU
Analytical Development
& Product Chemistry

Syngenta Crop Protection Münchwilen AG
Breitenloh 5
CH-4333 Münchwilen

Certificate of Analysis

A17960A
SYN545377 FS (600)
SMU1AP002

Batch Identification	**SMU1AP002**
Product Code	**A17960A**
Product Name	SYN545377 FS (600)
Other Product Name	Cyantraniliprole FS (600)

Chemical Analysis
(Active Ingredient Content)

– **Identity of SYN545377 ***	**confirmed**
– **Content of SYN545377 ***	**49.0 % w/w corresponding to 615 g/l**

The Active Ingredient content is within the FAO limits.

Methodology used for Characterization / Recertification	HPLC

Physical Analysis

– **Appearance**	**pink liquid**
– **Density ***	**1255 kg/m^3**

Stability:

– **Storage Temperature**	**< 30 °C**
– **Recertification Date**	**End of July 2013**

If stored under the conditions given above, this test substance can be considered stable until the recertification date is reached.

This Certificate of Analysis summarizes data which originate 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 Muenchwilen AG.

Study number of batch characterization:	122193
Study number(s) of batch recertification:	----

Authorisation:

28 January 2011 Robi Das

Robin Das
Analytical Development & Product Chemistry

APPENDIX 3 GLP Certificate

ORSZÁGOS GYÓGYSZERÉSZETI INTÉZET
National Institute of Pharmacy

FŐIGAZGATÓ
1051 Budapest, Zrínyi u. 3.
tel: (1) 8869-320
fax: (1) 8869-480
e-mail: szepezdi.zsuzsanna@ogyi.hu

Ref. no: OGYI/8242-11/2010
Admin.: Urbin Magdolna Zita
Date: 16 December, 2010

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

It is hereby certified that the test facility

LAB Research Kft.

(Base facility: H-8201 Veszprém, Szabadságpuszta, Hungary)

is able to carry out

physico-chemical testing, toxicity studies, mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air;bio-accumulation , safety pharmacology testing, reproduction toxicology, inhalation toxicology, analytical chemistry and contract archiving

in compliance with the Principles of GLP (Good Laboratory Practice) and also complies with the corresponding OECD/European Community requirements.

Date of the inspection: **4-8 October, 2010.**

Zsuzsanna Szepezdi, Ph. D.
Director-General