citoxlab
Safety and Health Research

Isopyrazam/Difenoconazole

Isopyrazam/Difenoconazole SC (A21295D) - Acute Oral Toxicity Study in Rats (Up and Down Procedure)

Final Report

DATA REQUIREMENT(S): OECD Test Guideline 425 (2008)
EPA 870.1100 (2002)
Commission Regulation (EC) No 761/2009, ANNEX III, B.46
Guidance Document on Toxicology for Registration of Pesticides in India (2014)

AUTHOR(S): Ádám Appl, M.Sc.

COMPLETION DATE: 05 January 2018

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

LABORATORY PROJECT ID: Report Number: 17/135-001P
Study Number: 17/135-001P
Task Number: TK0296438

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: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17.).

This study was conducted in accordance with a written Study Plan, authorised by the Sponsor and CiToxLAB Hungary 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: 05 January 2018

Ádám Appl, M.Sc.
Study Director

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

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

Study Number: 17/135-001P

Study Title: Isopyrazam/Difenoconazole SC (A21295D) -
Acute Oral Toxicity Study in Rats (Up and Down Procedure)

Test Item: Isopyrazam/Difenoconazole SC (A21295D)

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
24 May 2017	Study Plan	24 May 2017	24 May 2017
30 May 2017	Treatment	30 May 2017	30 May 2017
19 August 2017	Draft Report	19 August 2017	19 August 2017
05 January 2018	Final Report	05 January 2018	05 January 2018

Signature: Schleicher Ph.D. Date: 05 January 2018

Ivett Schleicher, Ph.D.
QA Inspector

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Syngenta Ltd. (as Sponsor) and CiToxLAB Hungary Ltd. (as Test Facility) the study titled "Isopyrazam/Difenoconazole SC (A21295D) – Acute Oral Toxicity Study in Rats (Up and Down Procedure)" has been performed in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 05 Jan 2018

Alyson Leyshon, M.Sc.
Managing Director

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function
Ádám Appl, M.Sc.	Study Director
Máté Weisz, M.Sc.	Assistant Scientist
Ivett Schleicher, Ph.D.	Quality Assurance Unit
László Székelyhidi, D.V.M.	Veterinary Care
Gábor Boros, D.V.M.	Pathology
Peter Maslej, D.V.M., Ph.D.	Pathology
Tamás Mészáros, Ph.D.	Pharmacy
Ferenc Szűcs	Animal Service Laboratories
William Masinja, M.Sc.	Syngenta Study Manager

Other trained, competent personnel worked on the study.

Study dates

Study Initiation Date	24 May 2017
Experimental Starting Date	30 May 2017
Experimental Completion Date	27 June 2017
Draft Report Date	21 August 2017
Receipt of Animals	18 May 2017
Acclimatisation	At least 12 days
Treatment	30 May 2017 (female no. 9306) 01 June 2017 (female no. 9307) 06 June 2017 (female no. 9308) 08 June 2017 (female no. 9309) 13 June 2017 (female no. 9310)
Observation	30 May – 13 June 2017 (female no. 9306) 01 June – 15 June 2017 (female no. 9307) 06 June – 20 June 2017 (female no. 9308) 08 June – 22 June 2017 (female no. 9309) 13 June – 27 June 2017 (female no. 9310)

Necropsy	13 June 2017 (female no. 9306) 15 June 2017 (female no. 9307) 20 June 2017 (female no. 9308) 22 June 2017 (female no. 9309) 27 June 2017 (female no. 9310)

Deviation from the Study Plan

There was no deviation during the study.

Performing laboratory test substance reference number

170120

Other

The study documents and samples:

- Study Plan,
- all raw data,
- sample of the test item,
- original Study Report and any amendments,
- correspondence

will be archived according to the Hungarian GLP regulations and to applicable SOPs in the archives of CiToxLAB Hungary 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

In this acute oral toxicity study, 5 female Crl:WI Wistar rats were given a single oral (gavage) dose of Isopyrazam/Difenoconazole SC (A21295D) at a dose level of 2000 mg/kg body weight (bw). The animals were fasted overnight prior to treatment and food was returned 3 hours after dosing.

Individual animals were dosed sequentially at not less than 48-hour intervals, if no mortality occurred. The time intervals between doses were determined by the onset, duration and severity of clinical signs. The first animal was treated at a dose level of 2000 mg/kg bw. The dose selection for the next animal followed the recommendation of AOT425StatPgm software, based on available results.

Animals were observed individually at 30 minutes, and 1, 2, 3, 4 and 6 hours post treatment and once each day for 14 days thereafter. Body weight was measured on Day -1 (prior to removal of food), before dosing (on Day 0), on Day 7 and on Day 14. All animals were euthanised and examined macroscopically at the end of the observation period.

1.2 Results

There was no mortality during the study.

At the dose level of 2000 mg/kg bw, the following test item related symptoms were observed up to Day 2: slightly decreased activity (5 out of 5 animals), hunched back (5 out of 5 animals), slight or slight to moderate incoordination (5 out of 5 animals) and piloerection (2 out of 5 animals). From Day 3, all animals were symptom-free during the observation period.

There were no treatment related body weight changes. A slight decrease was detected in body weight between Day 7 and Day 14 in one animal (ID 9306). However, body weights were within the range commonly recorded for this strain and age.

There was no macroscopic findings at necropsy at the dose level of 2000 mg/kg bw.

1.3 Conclusion

Under the conditions of this study, the acute oral median lethal dose (LD_{50}) of the test item, Isopyrazam/Difenoconazole SC (A21295D) is greater than 2000 mg/kg bw in female Crl:WI Wistar rats.

2.0 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the acute oral toxicity of the test item Isopyrazam/Difenoconazole SC (A21295D) when administered as a single oral gavage dose to female rats at one defined dose level.

This study was performed with vertebrate animals as no *in vitro* alternative is available. The study was designed such that the minimum numbers of animals were used.

This study should provide a rational basis for hazard assessment.

2.2 Guidelines

The study was performed according to the following guidelines:

- OECD Guidelines Reference 425 (2008): Acute Oral Toxicity - Up-and-Down Procedure.
- Guidance Document on Toxicology for Registration of Pesticides in India (2014). Ministry of Agriculture Department of Agriculture & co-operation Central Insecticides Board & Registration Committee Directorate of Plant Protection Quarantine & Storage. NH-IV, Faridabad
- United States Environmental Protection Agency, Health Effects Test Guidelines, OPPTS 870.1100 Acute Oral Toxicity EPA 712-C-02-190, December 2002.
- Commission Regulation (EC) No 761/2009, ANNEX III, B.46

2.3 Test Facility

This study was performed in an AAALAC-accredited laboratory. The Institutional Animal Care and Use Committee (IACUC) of CiToxLAB Hungary Ltd. reviewed the Study Plan and authorised the conduct of the study.

3.0 MATERIALS AND METHODS

3.1 Test Substance

The following information was provided by the Sponsor:

Name:	Isopyrazam/Difenoconazole SC (A21295D)
Batch number:	JHU002-109-004
Active ingredient content*:	CGA169374 (difenoconazole), 11.9 % w/w corresponding to 129 g/L CGA185882 (cis isomer of difenoconazole), 6.97 % w/w corresponding to 76.0 g/L CGA185883 (trans isomer of difenoconazole), 4.89 % w/w corresponding to 53.3 g/L SYN520453 (isopyrazam) 11.9 % w/w corresponding to 130 g/L SYN534969 (syn isomer of isopyrazam) 10.1 % w/w corresponding to 110 g/L SYN534968 (anti isomer of isopyrazam) 1.82 % w/w corresponding to 19.9 g/L
Density:	1091 kg/m^3
Appearance:	Off-white liquid
Recertification date:	30 November 2018
Storage conditions:	Room temperature (<30°C)
Safety precautions:	Enhanced safety precautions were applied considering the supplied safety datasheet to assure personnel health and safety.
Hazards:	May cause an allergic skin reaction. Causes serious eye irritation. Suspected of damaging the unborn child.

**No adjustment for purity was applied.*

The Certificate of Analysis is presented in Appendix 2.

3.1.1 Identification and 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 Pharmacy of CiToxLAB Hungary Ltd. on the basis of the information provided by Sponsor.

3.1.2 Formulation

The test item was administered undiluted.

3.2 Experimental Design

3.2.1 Animals

Species and strain:	Crl:WI Wistar rats
Source:	Charles River Laboratories, Research Models and Services, Germany GmbH, Sandhofer Weg 7, D-97633 Sulzfeld, Germany
Hygienic level:	SPF at arrival, standard housing conditions during study
Justification of strain:	Recognized by international guidelines as a recommended test system.
Number of animals:	5
Sex:	Female rats, nulliparous and non-pregnant
Age when treated:	Young adult rats, 9-11 weeks old
Body weight (at dosing):	214 – 226 g
Identification:	The animals were identified by numbers written on the tail with an indelible pen. The cages were marked with individual identity cards with information about study number, sex, cage number, dose group and individual animal number.
Randomisation:	Selected by hand at time of delivery
Acclimatisation time:	At least 12 days

3.2.2 Husbandry

Animal health:	Only healthy animals were used for the test. The health status was certified by the Veterinarian.
Room number:	522/10
Housing / Enrichment:	Animals were housed individually in Type II. polypropylene/polycarbonate cages. Rodents were housed with deep wood sawdust bedding to allow digging and other normal rodent activities.

Bedding / Nesting:	"Lignocel 3/4-S Hygienic Animal Bedding" and "Arbocel crinklets natural" nest building material produced by J. Rettenmaier & Söhne GmbH + CO.KG (D-73494 Rosenberg, Germany) were available to animals during the study. Copies of the Certificates of Analyses are retained in the archive at CiToxLAB Hungary Ltd.
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature:	20.5 – 25.0 °C
Relative humidity:	31 – 64 %
Ventilation:	15-20 air exchanges/hour

The temperature and relative humidity were recorded twice daily during the acclimatisation period and throughout the study.

3.2.3 Food and feeding

Animals received ssniff® SM R/M "Autoclavable complete diet for rats and mice – breeding and maintenance" produced by ssniff Spezialdiäten GmbH, D-59494 Soest, Germany (Lot number: 285 17890, Expiry date: 31 August 2017), *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 CiToxLAB Hungary Ltd.

3.2.4 Water supply and quality control

Animals received tap water from the municipal supply from 500 mL bottles *ad libitum*. The water was fit for human consumption and was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study.

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 Attila utca 36, Hungary). The quality control results are retained in the archive at CiToxLAB Hungary Ltd.

3.3 Administration of the Test Item

3.3.1 Dosage

Justification of the dose:

A limit dose of 2000 mg/kg bw was selected by the Study Director after discussion with the Sponsor. The density of the test item is 1091 kg/m^3 as provided by the Sponsor, therefore the dose volume for the first animal was 1.83 mL/kg bw. The individual dose volumes used are shown below.

Animal Number	Dose [mg/kg body weight]	Volume Dosed [mL]	Bodyweight [g]	Mortality
9306	2000	0.39	214	Survived
9307	2000	0.41	226	Survived
9308	2000	0.39	214	Survived
9309	2000	0.40	218	Survived
9310	2000	0.40	219	Survived

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) dose was followed by a 14-day observation period. The animals were fasted overnight prior to treatment. Water was still available, *ad libitum* overnight. Animals were weighed before dosing and the food was returned 3 hours after the treatment.

Individual animals were dosed sequentially following an interval of at least 48 hours. The time intervals between doses were determined by the onset, duration and severity of toxic signs.

3.4 Observations

3.4.1 Clinical observations

Animals were observed individually at 30 minutes and then at 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 (prior to removal of food), on Day 0 (before dosing), on Day 7 and on Day 14 (before necropsy).

3.5 *Post Mortem* Investigations

All animals were subjected to gross macroscopic evaluation. All animals were euthanised under pentobarbital anaesthesia (Release®, details in 3.5.1) at the end of the observation period. 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 and the animals were discarded.

3.5.1 Material used for euthanasia

Name:	Release® (pentobarbital sodium)
Lot No.:	106075
Expiry Date:	31 July 2018
Produced by:	Wirtschaftsgenossenschaft deutscher Tierärzte eG Siemensstr. 14, 30827 Garbsen, Germany

3.6 Data Evaluation

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

The LD_{50} was calculated using the AOT425StatPgm program. This program was prepared for the US Environmental Protection Agency by Westat, May 2001 and updated by the US EPA June 2003. This program was constructed using the most appropriate method to estimate the LD_{50}.

4.0 RESULTS AND DISCUSSION

4.1 Mortality

There was no mortality during the study.

4.2 Clinical Signs

At the dose level of 2000 mg/kg bw, the following test item related symptoms were observed up to Day 2: slightly decreased activity (5 out of 5 animals), hunched back (5 out of 5 animals), slight or slight to moderate incoordination (5 out of 5 animals) and piloerection (2 out of 5 animals). From Day 3, all animals were symptom-free during the observation period.

Individual clinical observations and mortality results are presented in Table 1.

4.3 Body Weights

There were no treatment related body weight changes. A slight decrease was detected in body weight between Day 7 and Day 14 in one animal (ID 9306). However, body weights were within the range commonly recorded for this strain and age.

Individual body weights and body weight gains are presented in Table 2.

4.4 Macroscopic Findings

There was no evidence of any macroscopic findings at necropsy at the dose level of 2000 mg/kg bw.

Macroscopic findings are presented in Table 3. The Pathology Report is presented in Appendix 1.

5.0 CONCLUSIONS

Under the conditions of this study, the acute oral median lethal dose (LD_{50}) of the test item, Isopyrazam/Difenoconazole SC (A21295D) is greater than 2000 mg/kg bw in female Crl:WI Wistar rats.

TABLES SECTION

TABLE 1 Individual Findings – Clinical Signs

DOSE LEVEL: 2000 mg/kg bw, Treatment on Day 0 **SEX: FEMALE**

Cage No.	Animal Number	Observations	Observation days													Frequency
			0						1	2	3	4	5	6	7-14	
			30'	1h	2h	3h	4h	6h								
1	9306	Symptom Free	+	-	-	-	-	-	-	+	+	+	+	+	+	14/20
		Activity decreased	-	1	1	1	1	1	-	-	-	-	-	-	-	5/20
		Hunched back	-	+	+	+	+	+	+	-	-	-	-	-	-	6/20
		Incoordination	-	-	-	1	-	-	-	-	-	-	-	-	-	1/20
2	9307	Symptom Free	-	-	-	-	-	-	-	+	+	+	+	+	+	13/20
		Activity decreased	-	1	1	1	1	1	1	-	-	-	-	-	-	6/20
		Hunched back	-	-	+	+	+	+	-	-	-	-	-	-	-	4/20
		Incoordination	1	1	1	1	2	2	-	-	-	-	-	-	-	6/20
		Piloerection	-	-	-	-	+	+	-	-	-	-	-	-	-	2/20
3	9308	Symptom Free	-	-	-	-	-	-	+	+	+	+	+	+	+	14/20
		Activity decreased	-	1	1	1	-	-	-	-	-	-	-	-	-	3/20
		Hunched back	-	+	+	+	+	+	-	-	-	-	-	-	-	5/20
		Incoordination	1	1	-	-	-	-	-	-	-	-	-	-	-	2/20

Remarks: + = present - = absent

h = hour (s) ' = minute

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

Severities: 1 = Slight/Small/Few; 2 = Moderate/Medium; 3 = Marked/Large/Many

TABLE 1 Individual Findings – Clinical Signs (Continued)

DOSE LEVEL: 2000 mg/kg bw, Treatment on Day 0 **SEX: FEMALE**

Cage No.	Animal Number	Observations	Observation days													Frequency
			0						1	2	3	4	5	6	7-14	
			30'	1h	2h	3h	4h	6h								
4	9309	Symptom Free	-	-	-	-	-	-	-	-	+	+	+	+	+	12/20
		Activity decreased	-	1	1	1	1	1	1	1	-	-	-	-	-	7/20
		Hunched back	-	+	+	+	+	+	+	+	-	-	-	-	-	7/20
		Incoordination	1	1	2	2	1	1	-	-	-	-	-	-	-	6/20
		Piloerection	-	-	-	+	+	+	+	-	-	-	-	-	-	4/20
5	9310	Symptom Free	-	-	-	-	-	+	+	+	+	+	+	+	+	15/20
		Activity decreased	-	1	1	1	1	-	-	-	-	-	-	-	-	4/20
		Hunched back	-	+	+	+	+	-	-	-	-	-	-	-	-	4/20
		Incoordination	1	2	1	1	1	-	-	-	-	-	-	-	-	5/20

Remarks: + = present - = absent

h = hour (s) ' = minute

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

Severities: 1 = Slight/Small/Few; 2 = Moderate/Medium; 3 = Marked/Large/Many

TABLE 2 Body Weight and Body Weight Gain

DOSE LEVEL: 2000 mg/kg bw, Treatment on Day 0 **SEX: FEMALE**

Cage No.	Animal Number	Body weight (g) Days				Body Weight Gain (g)			
		-1	0	7	14	-1-0	0-7	7- 14	-1 - 14
1	9306	235	214	234	233	-21	20	-1	-2
2	9307	246	226	245	260	-20	19	15	14
3	9308	223	214	242	247	-9	28	5	24
4	9309	234	218	238	255	-16	20	17	21
5	9310	234	219	239	248	-15	20	9	14
Mean:		234.4	218.2	239.6	248.6	-16.2	21.4	9.0	14.2
Standard deviation:		8.1	4.9	4.2	10.2	4.8	3.7	7.3	10.1

TABLE 3 Macroscopic Findings

DOSE LEVEL: 2000 mg/kg bw, Treatment on Day 0 **SEX: FEMALE**

Cage No.	Animal Number	Necropsy Date/ Necropsy Day	External Observations	Internal Observations	Organ/Tissue
1	9306	13 June 2017 Day 14	No external observations recorded	No internal observations recorded	Not applicable
2	9307	15 June 2017 Day 14	No external observations recorded	No internal observations recorded	Not applicable
3	9308	20 June 2017 Day 14	No external observations recorded	No internal observations recorded	Not applicable
4	9309	22 June 2017 Day 14	No external observations recorded	No internal observations recorded	Not applicable
5	9310	27 June 2017 Day 14	No external observations recorded	No internal observations recorded	Not applicable

APPENDICES SECTION

APPENDIX 1 Pathology Report

CiToxLAB Hungary Ltd. Study code 17/135-001P

PATHOLOGY REPORT

INTRODUCTION

The objective of the study was to assess the acute oral toxicity of the test item Isopyrazam/Difenoconazole SC (A21295D) when administered via a single oral gavage dose to female rats. Five rats were dosed at 2000 mg/kg bodyweight with the test item.

METHODS

All animals were euthanized upon completion of the observation period on Day 14. Rats were anaesthetized 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 2000 mg/kg bw.

CONCLUSION

A single oral gavage of Isopyrazam/Difenoconazole SC (A21295D) to the female Crl:WI rats at a dose level of 2000 mg/kg bw with a 14-day observation period, was not associated with any macroscopic findings.

Gábor Boros, D.V.M.
Histopathologist

08. Dec. 17.
Date

APPENDIX 2 Certificate of Analysis

GLP Testing Facility WMU
Analytical Development &
Product Chemistry GS2131

Syngenta Crop Protection
Münchwilen AG
Im Breitenloh 5
4333 Münchwilen, Switzerland

Certificate of Analysis

A21295D
CGA169374/SYN520453 SC (125/125)
JHU002-109-004

Batch Identification	**JHU002-109-004**
Product Code	**A21295D**
Other Product Code(s)	CGA169374/SYN520453 SC (125/125)

Chemical Analysis
(Active Ingredient Content)

– **Identity of the Active Ingredients***	**Confirmed**
– **Content of CGA169374 (difenoconazole)***	**11.9 % w/w corresponding to 129 g/l**
– **Content of CGA185882 (cis isomer of difenoconazole)***	**6.97 % w/w corresponding to 76.0 g/l**
– **Content of CGA185883 (trans isomer of difenoconazole)***	**4.89 % w/w corresponding to 53.3 g/l**
– **Content of SYN520453 (isopyrazam)***	**11.9 % w/w corresponding to 130 g/l**
– **Content of SYN534969 (syn isomer of isopyrazam)***	**10.1 % w/w corresponding to 110 g/l**
– **Content of SYN534968 (anti isomer of isopyrazam)***	**1.82 % w/w corresponding to 19.9 g/l**

The Active Ingredient(s) content is within the FAO limits.

Methodology used for Characterization	HPLC, OECD 109 (oscillating density meter)

Physical Analysis

– **Appearance**	**Off-white liquid**
– **Density***	**1091 kg/m^3**

Stability:

– **Storage Temperature**	**< 30 °C**
– **Recertification Date**	**End of November 2018**

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 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, Switzerland.

syngenta

GLP Testing Facility WMU
Analytical Development &
Product Chemistry GS2131

Syngenta Crop Protection Münchwilen AG
Im Breitenloh 5
4333 Münchwilen, Switzerland

Certificate of Analysis

Study number of batch characterization: CHMU151002
Study number(s) of batch recetification: ---

Authorisation: 14-Dec-2015

Elke Ebi
Analytical Development & Product Chemistry

APPENDIX 3 GLP Certificate

OGYÉI
National Institute of
Pharmacy and Nutrition

H-1051 Budapest, Zrínyi u. 3.
1372 P.O. Box:450.
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Ref. no: OGYI/19440-7/2015
Admin.: Szatmári Andrea
Date: 22 September, 2015

GOOD LABORATORY PRACTICE (GLP)
CERTIFICATE

It is hereby certified that the test facility

CiToxLAB Hungary Ltd.

H-8200 Veszprém, Szabadságpuszta

is able to carry out

physico-chemical testing, toxicity studies, in vitro studies and mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, 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: **02-04. June 2015.**

Dr. József Reiter
Deputy Director-General

Note: Translation of the Stamp on the official document ("Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet"): ("National Institute of Pharmacy and Nutrition")