

Isopyrazam/Difenoconazole

**Isopyrazam/Difenoconazole SC (A21295D) -
Primary Skin Irritation Study in Rabbits**

Final Report

DATA REQUIREMENT(S): OECD 404 (2015)
Guidance Document on Toxicology for Registration
of Pesticides in India (2014).
EPA 870.2500 (1998)
EC No 440/2008, B.4 (2008)

AUTHOR(S): Ádám Appl, M.Sc.

COMPLETION DATE: 03 January 2018

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

LABORATORY PROJECT ID: Report Number: 17/135-006N
Study Number: 17/135-006N
Task Number: TK0296437

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

VOLUME 1 OF 1 OF STUDY
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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: 
Adám Appl, M.Sc.
Study Director

Date: 03 January 2018

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

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

Study Number: 17/135-006N
Study Title: Isopyrazam/Difenoconazole SC (A21295D) -
Primary Skin Irritation Study in Rabbits
Test Item: Isopyrazam/Difenoconazole SC (A21295D)

This study has been inspected, and this report was 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
28 June 2017	Study Plan	28 June 2017	28 June 2017
04 July 2017	Treatment	04 July 2017	04 July 2017
30 August 2017	Draft Report	30 August 2017	30 August 2017
02 January 2018	Final Report	02 January 2018	02 January 2018

Signature: _____

Merazga Leila
Leila Merazga, M.Sc.
On behalf of QA

Date: _____

02 January 2018

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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) - Primary Skin Irritation Study in Rabbits" was performed, in compliance with the Principles of Good Laboratory Practice.

Signature: _____



Date: 03 Jun 2018

Alyson Leyshon, M.Sc.
Managing Director

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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
Leila Merazga, M.Sc.	Quality Assurance Inspector
László Székelyhidi, D.V.M.	Veterinary Care
Tamás Mészáros, Ph.D.	Pharmacy
William Masinja, M.Sc.	Syngenta Study Manager

*Other trained, competent personnel may have worked on the study as required.

Study dates

Study Initiation Date:	28 June 2017
Experimental Starting Date:	04 July 2017
Experimental Completion Date:	09 July 2017
Acclimation:	14 June – 03/05 July 2017
Treatment:	04/06 July 2017
Observation of local findings:	For 72 hours after treatment. (04/06 July – 07/09 July 2017)

Deviations from the guideline

Due to technical reason, relative humidity values (minimum of 24.81% and maximum of 85.28%) outside the expected range of 30-70% were recorded occasionally during the study.

These minor differences of the environmental parameters were considered not to adversely affect the results or integrity of the study as confirmed by the clinical Veterinarian.

Performing laboratory test substance reference number

170120

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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.

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1.0 EXECUTIVE SUMMARY

1.1 Study Design

The primary skin irritation potential of Isopyrazam/Difenoconazole SC (A21295D) was investigated according to the following guidelines; OECD 404 (2015), OPPTS 870.2500 (1998) and EC No 440/2008, B.4 (2008). Three young adult New Zealand rabbits were treated by topical, semi-occlusive application of 0.5 mL test item to their intact shaved back. The duration of treatment was 4 hours. The scoring of skin reactions was performed at 1, 24, 48 and 72 hours after removal of the dressing. The primary irritation index (P.I.I.) was calculated by totalling the mean cumulative scores at 24, 48 and 72 hours and then dividing by the number of data points.

1.2 Results

The primary irritation index was 0.00.

The treated skin surface was examined at 1, 24, 48 and 72-hours after patch removal.

No local dermal signs were observed in the treated animals at 1, 24, 48 and 72-hours after patch removal through to the end of the observation period.

No clinical signs of systemic toxicity were observed in the animals during the study, and no mortality occurred.

As no clinical signs were observed at 72-hours after patch removal, the study was terminated after 72 hours of observation of the third rabbit.

The body weights of all rabbits were considered to be within the normal range of variability.

1.3 Conclusion

According to the Draize classification criteria, Isopyrazam/Difenoconazole SC (A21295D) is considered to be “non-irritant” to rabbit skin (P.I.I. = 0.00).

2.0 INTRODUCTION

2.1 Purpose

The purpose of this primary skin irritation study was to assess the irritation potential of Isopyrazam/Difenoconazole SC (A21295D) from a single application placed on the skin of rabbits for approximately 4 hours.

This study provides a rational basis for hazard classification.

An *in vitro* skin irritation study in the EPISKIN model (CiToxLAB study code: 17/135-043B) with the test item Isopyrazam/Difenoconazole SC (A21295D) (Batch number: JHU002-109-004) was performed. Based on the results of this test, the test item was non-irritant to skin and thus is considered to be very unlikely to cause severe skin irritation or skin damage, hence this *in vivo* study can be conducted for classification of skin irritation.

The study was designed such that the minimum numbers of animals were used.

The test item was administered at 0.5 mL/animal, the dose specified in the test guidelines for a liquid test item.

2.2 Guidelines

The study was conducted according to the following guidelines:

- OECD Guidelines for Testing of Chemicals, Section 4, Number 404 “Acute Dermal Irritation / Corrosion”, adopted July 28, 2015.
- 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 Division Test Guidelines, OPPTS 870.2500 Acute Dermal Irritation EPA 712-C-98-196, August 1998.
- Commission Regulation (EC) No 440/2008, B.4 (L 142, 30 May 2008).

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 correction for purity of the test item was applied.

The pH of the test item was measured and was found to be 5.5.

The Certificate of Analysis is shown in Appendix 1.

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 applied undiluted as supplied by the Sponsor.

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3.2 Experimental Design

3.2.1 Animals

Species and strain:	New Zealand White Rabbit
Source:	S&K-LAP Kft. 2173 Kartal, Császár út 135, Hungary
Number of animals:	3
Sex:	Male
Age when treated:	Young Adult, ~12 weeks
Body weight at dosing:	3448 g – 3507 g
Identification:	The animals were identified by engraved ear tags. The cages were marked with individual identity cards with information about study code, sex, cage number, dose and individual animal number.
Acclimation:	Under laboratory conditions after health examination. Only animals without any visual signs of illness were used for the study.
Acclimation time:	20 or 22 days

3.2.2 Husbandry

Animal health:	Only healthy animals were used for the study, as certified by the staff Veterinarian.
Room number:	032
Housing / Enrichment:	Animals were housed individually in AAALAC approved metal wire rabbit cages. Cages are of an open wire structure, and cages are placed together to allow some social interaction with rabbit(s) in adjoining cages.
Lighting periods:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature:	17.84 – 22.56°C
Relative humidity:	24.81 – 85.28%
Ventilation:	15-20 air exchanges/hour.

The temperature and relative humidity values were measured continuously. The measured range was checked regularly during the acclimation and experimental phases.

3.2.3 Food and feeding

The animals received UNI diet for rabbits produced by Cargill Takarmány Zrt., *ad libitum*. The batch numbers of the lots used in the study were: 0003992970, expiry date: 20 June 2017 and 0004181216, expiry date: 06 September 2017. The food was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study. A detailed description of the contents of the lots used is archived with the raw data at CiToxLAB Hungary's Ltd.

3.2.4 Water supply and quality control

The animals received tap water, fit for human consumption, *ad libitum*, from the automatic system supplied by the communal water network. The water was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study.

The 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). Copies of the relevant Certificates of Analysis are retained in the archives at CiToxLAB Hungary Ltd.

3.3 Administration of the Test Item

According to EC 2004/73, B.4. and OECD Guidelines 404, a study doesn't need to be conducted if the pH-value is equal/less than 2 or equal/greater than 11.5, owing to its predictable corrosive properties. The pH of the test item was measured before the study initiation date and was found to be 5.5.

Approximately 24 hours prior to the test, the hair was clipped from the back of the animals with an electric clipper, exposing an area of approximately 100 cm² (10 cm x 10cm).

Animals with overt signs of skin injury or marked irritation which may have interfered with the interpretation of the results were not used in the test.

On the day of treatment, 0.5 mL of test item was placed on a surgical gauze pad (*ca.* 2.5 cm x 2.5 cm). This gauze pad was applied to the intact skin of the clipped area and was kept in contact with the skin by a patch with a surrounding adhesive hypoallergenic plaster. The entire trunk of the animals was then wrapped with plastic wrap held in place with an elastic stocking.

Untreated skin served as a control.

The duration of treatment was 4 hours. The dressing was then removed and the skin was flushed with lukewarm tap water to clean the application site.

Initially, a single animal was treated. As neither a corrosive effect nor a severe irritant effect were observed after the 24-hour observation, the test was completed using the 2 remaining animals with an exposure period of 4 hours.

Clinical signs, including viability/mortality, were recorded daily from the day of application of the animals to the termination of the test.

Body weights were recorded on the day of application and at the end of the observation period.

3.4 *Post Mortem Investigations*

At the end of the observation period, animals were euthanised by intramuscular injections of Ketamine 10% and Xylazine 2% followed by i.v. pentobarbital sodium anaesthesia. Following confirmation of death, the carcasses were discarded without further examination. Details of materials employed for euthanasia are retained in the raw data and detailed in Section 3.4.1.

3.4.1 **Materials used for euthanasia**

Name: Ketanest (100 mg/mL Ketamine)
Batch No.: H1023-10
Expiry Date: 31 March 2019
Produced by: bela-pharm GmbH & Co. KG, Lohner Straße 19, D-49377 Vechta, Germany

Name: Nerfasin (20 mg/mL Xylazine)
Batch No.: 16A134
Expiry Date: 31 December 2018
Produced by: Le Vet B.V., Wilgenweg 7, 3421 TV Oudewater, The Netherlands

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

3.5 **Data Evaluation**

The skin reaction was assessed according to the numerical scoring system listed in the Commission Directive 2004/73/EC, April 29, 2004 which was based on the Draize scoring system. The animals skin reaction to the test item was assessed at approximately 1, 24, 48 and 72 hours after the end of exposure (removal of the dressing, gauze patch and test item).

Summarised in tables, data reported included the irritation scores for erythema and oedema for each individual animal at all measurement intervals. Lesions, if observed, were described by the degree and nature of irritation, corrosion or any other toxic effects, and their reversibility.

The mean score was calculated across 3 scoring times (24, 48 and 72 hours after patch removal) for each animal for erythema/eschar grades and for oedema grades, separately. An animal had a positive reaction when the mean score was 2 or greater. The test was positive for irritation when at least 2 animals were positive for the same endpoint (erythema/eschar or oedema).

The Cumulative Scores for the Skin Irritation Scores were calculated and represent the sum of all numerical scores for each animal at each time point. The resulting Mean Cumulative Skin Irritation Score was calculated for all animals at each time point.

The Primary Irritation Index (P.I.I.) was calculated by totalling the mean cumulative scores at 24, 48 and 72 hours and then dividing by the number of data points.

The irritation was classified according to the following criteria:

P.I.I. = 0	Not irritant
$0 < P.I.I. \leq 2$	Mild irritant
$2 < P.I.I. \leq 5$	Moderate irritant
$5 < P.I.I.$	Severe irritant

Viability/mortality, clinical signs and dermal findings were recorded on data sheets as appropriate.

Body weights were recorded on the day of the treatment and at the end of the observation period of each animal.

No statistical analysis was performed.

4.0 RESULTS AND DISCUSSION

4.1 Skin Irritation

Individual and mean skin irritation scores are presented in Tables 1 and 2. Individual local findings are shown in Appendix 2.

The primary irritation index was 0.00 (out of a maximum score of 8.0). No corrosive effects were noted on the treated skin of any animal at any of the observation intervals.

No local dermal signs were observed in the treated animals at the observation time points of 1, 24, 48 and 72-hours after patch removal.

4.2 Clinical Observations

No clinical signs of systemic toxicity were observed in the animals during the study, and no mortality occurred (Table 3).

4.3 Duration of the In-Life Phase

As no local or clinical signs were observed at 72-hour after patch removal, the study was terminated after the 72-hour observation time point of the second and third rabbits.

4.4 Body Weight

There were no treatment related body weight changes. Body weights were within the range commonly recorded for this strain and age (Table 4).

5.0 CONCLUSIONS

According to the Draize classification criteria, Isopyrazam/Difenoconazole SC (A21295D) is considered to be “non-irritant” to rabbit skin (P.I.I. = 0.00).

6.0 REFERENCES

Literature references listed are available upon request.

External references

Draize, J.H. (1959): Dermal Toxicity. In Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, pp. 46-49. Austin, Texas: Association of Food and Drug Officials of the United States.

Draize, J.H., Woodward, G. & Calvery, H.O. (1944): Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J. Pharmacol. Exper. Therap. 83: 377-390.

Commission Directive 2004/73/EC of 29 April 2004.

Orovecz, B. (2017): Isopyrazam/Difenoconazole SC (A21295D) - *In Vitro* Skin Irritation Test in the EPISKIN™ Model. CiToxLAB Hungary Ltd. Study Code: 17/135-043B, Syngenta Task Number: TK0296437

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TABLES SECTION

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GLOSSARY FOR TABLE 1

Grading of Skin Reactions

ERYTHEMA AND ESCHAR FORMATION

No erythema.....	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beef redness) or eschar formation (injuries in depth preventing erythema) reading	4

OEDEMA FORMATION

No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well-defined by definite raising).....	2
Moderate oedema (edges raised approximately 1 mm).....	3
Severe oedema (raised more than 1 mm and extending beyond the area of exposure)	4

Primary Irritation Index (P.I.I.)

The irritation was classified according to the following criteria:

P.I.I. = 0	Not irritant
$0 < \text{P.I.I.} \leq 2$	Mild irritant
$2 < \text{P.I.I.} \leq 5$	Moderate irritant
$5 < \text{P.I.I.}$	Severe irritant

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TABLE 1 Skin Irritation Scores - Individual Values

Animal Number	Sex	Evaluation Interval*	Erythema	Oedema	Cumulative	
					Score	Mean
741	male	1 hour	0	0	0.00	0.00
754	male		0	0	0.00	
749	male		0	0	0.00	
741	male	24 hours	0	0	0.00	0.00
754	male		0	0	0.00	
749	male		0	0	0.00	
741	male	48 hours	0	0	0.00	0.00
754	male		0	0	0.00	
749	male		0	0	0.00	
741	male	72 hours	0	0	0.00	0.00
754	male		0	0	0.00	
749	male		0	0	0.00	

* Examinations were performed at the specified times after removal of the dressing.

TABLE 2 Skin Irritation Scores - Mean Values after 24, 48 and 72 Hours

Animal Number	Sex	Erythema	N	Oedema	N	Primary Skin Irritation Index
741	male	0.00	3	0.00	3	0.00
754	male	0.00	3	0.00	3	
749	male	0.00	3	0.00	3	
Mean score		0.00		0.00		
N= number of available data points.						

TABLE 3 Clinical Signs

Animal Number	Sex	Observations	Observation time*				Frequency
			Day 0	Day 1	Day 2	Day 3	
741	male	Symptom free	+	+	+	+	4/4
754	male	Symptom free	+	+	+	+	4/4
749	male	Symptom free	+	+	+	+	4/4

Remarks: + = present, Frequency: number of occurrence of observation/total number of observations
*: relative to the day of treatment

TABLE 4 Body Weights

Animal No.	Sex	Body weight (g)	
		Day of Treatment	End of observation period
741	male	3483	3544
754	male	3507	3569
749	male	3448	3490

RESULTADOS DE TESTES E OUTROS DADOS NÃO DIVULGADOS

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Todos os infratores poderão ser processados civil e criminalmente

APPENDICES SECTION

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APPENDIX 1 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.

RESULTADOS DE TESTES E OUTROS DADOS NÃO DIVULGADOS

Os resultados de testes e outros dados não divulgados são confidenciais e de propriedade da SYNGENTA PROTEÇÃO DE CULTIVOS LTDA., protegidos na forma da Lei 10.603/02 e do artigo 195, XIV da Lei 9.279/96

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APPENDIX 1 Certificate of Analysis (Continued)



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 recertification: --

Authorisation: 14-Dec-2015

Elke Ebi
Analytical Development & Product Chemistry

RESULTADOS DE TESTES E OUTROS DADOS NÃO DIVULGADOS

Estes e outros dados não divulgados são confidenciais e de propriedade da SYNGENTA PROTEÇÃO DE CULTIVOS LTDA., protegidos na forma da Lei 10.603/02 e do artigo 195, XIV da Lei 9.279/96

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APPENDIX 2 Individual Local Findings

Animal No. 741, Male

After 1 hour:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 24 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 48 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 72 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented

RESULTADOS DE TESTES E OUTROS DADOS NÃO DIVULGADOS

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APPENDIX 2 Individual Local Findings (Continued)

Animal No. 754, Male

After 1 hour:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 24 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 48 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 72 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented

RESULTADOS DE TESTES E OUTROS DADOS NÃO DIVULGADOS

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APPENDIX 2 Individual Local Findings (Continued)

Animal No. 749, Male

After 1 hour:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 24 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 48 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 72 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented

RESULTADOS DE TESTES E OUTROS DADOS NÃO DIVULGADOS

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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.**



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

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RESULTADOS DE TESTES E OUTROS DADOS NÃO DIVULGADOS

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