charles river

Isocycloseram/Emamectin Benzoate

Isocycloseram/Emamectin Benzoate SC (A23220A) - Primary Skin Irritation Study in Rabbits

Final Report

TEST GUIDELINE(S):	OECD 404 (2015) EPA 870.2500 (1998) EC No 440/2008, B.4 (2008)
AUTHOR(S):	Ivett Orosz, M.Sc.
COMPLETION DATE:	03 August 2020
PERFORMING LABORATORY:	Charles River Laboratories Hungary Kft. (formerly Citoxlab Hungary Ltd.) H-8200 Veszprém, Szabadságpuszta, hrsz. 028/1., Hungary
LABORATORY PROJECT ID:	Report Number: 20/080-006N Study Number: 20/080-006N Task Number: TK0416695
SPONSOR(S):	Syngenta Ltd. Jealott's Hill International Research Centre Bracknell, Berkshire, RG42 6EY, United Kingdom

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

The Following Statement Applies To The United States of America:

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS
UNDER SPECIFIED FIFRA PROVISIONS

No claim of confidentiality, on any basis whatsoever, is made for any information contained in this document. I acknowledge that information not designated as within the scope of FIFRA sec. 10(d)(1)(A), (B), or (C) and which pertains to a registered or previously registered pesticide is not entitled to confidential treatment and may be released to the public, subject to the provisions regarding disclosure to multinational entities under FIFRA 10(g).

Company: Syngenta Crop Protection, LLC
410 Swing Road
Post Office Box 18300
Greensboro, NC 27419-8300 USA

Submitter: _____ Date: _____

Syngenta is the owner of this information and data. Syngenta has submitted this material to the United States Environmental Protection Agency specifically under the provisions contained in FIFRA as amended and, hereby, consents to use and disclosure of this material by EPA according to FIFRA. In submitting this material to EPA according to method and format requirements contained in PR Notice 2011-3, we do not waive any protection or right involving this material that would have been claimed by the company if this material had not been submitted to the EPA, nor do we waive any protection or right provided under FIFRA Section 3 (concerning data exclusivity and data compensation) or FIFRA Section 10(g) (prohibiting disclosure to foreign and multinational pesticide companies or their agents).

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, authorized by the Sponsor and Charles River Laboratories Hungary Kft. 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. By virtue of my dated signature I accept the responsibility for the validity of the data.

Signature: Orosz Ivett Date: 03 August 2020

Ivett Orosz, M.Sc.
Study Director

Performing Laboratory: Charles River Laboratories Hungary Kft.
(formerly Citoxlab Hungary Ltd.)
H-8200 Veszprém, Szabadságpuszta, hrsz. 028/1.,
Hungary

To be completed for USA EPA submission only:
Representative of Submitter/Sponsor:

_____ _____

Date

Submitter/Sponsor: Syngenta Crop Protection, LLC
410 Swing Road
Post Office Box 18300
Greensboro, NC 27419-8300 USA

FLAGGING STATEMENT

This page is intentionally left blank. It will be replaced by an appropriate Flagging statement by the Sponsor.

QUALITY ASSURANCE STATEMENT

Study Number: 20/080-006N

Study Title: Isocycloseram/Emamectin Benzoate SC (A23220A) - Primary Skin Irritation Study in Rabbits

Test Item: Isocycloseram/Emamectin Benzoate SC (A23220A)

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
01 July 2020	Study Plan	01 July 2020	01 July 2020
07 July 2020	Observation	07 July 2020	07 July 2020
24 July 2020	Draft Report	24 July 2020	24 July 2020
03 August 2020	Final Report	03 August 2020	03 August 2020

Signature: Merazga Leila Date: 03 August 20

Leila Merazga, M.Sc.
On behalf of QA

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Syngenta Ltd. (as Sponsor) and Charles River Laboratories Hungary Kft. (as Test Facility) the study titled "Isocycloseram/Emamectin Benzoate SC (A23220A) - Primary Skin Irritation Study in Rabbits" was performed, in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 03 August 2020

Balázs Tóth, Ph.D.
General Manager

GENERAL INFORMATION

Contributors
The following contributed to this report in the capacities indicated:

Name	Function or Department
Ivett Orosz, M.Sc.	Study Director
Zsolt Tarcai, M.Sc.	Assistant Scientist
Leila Merazga, M.Sc.	Quality Assurance
László Székelyhidi, D.V.M.	Veterinary Control
Carolina Vaccari	Syngenta Study Manager

Other competent personnel worked on the study as required.

Study dates

Study Initiation Date:	02 July 2020
Experimental Starting Date:	07 July 2020
Experimental Completion Date:	12 July 2020
Animal receipt:	17 June 2020
Acclimatization:	17 June 2020 – 06 / 08 July 2020
Removing of hair [2nd and 3rd animals]:	08 July 2020
Treatment:	07 / 09 July 2020
Observation of local findings:	For 72 hours after treatment. (07 / 09 July – 10 / 12 July 2020)
Animal skin examination and assignment to study (pre-treatment) [2nd and 3rd animals]:	08 July 2020
Initial body weight measurement [2nd and 3rd animals]:	09 July 2020
Draft Report:	24 July 2020
Final Report:	03 August 2020

Performing laboratory test substance reference number
200164

Deviations from the guideline or Study Plan
Due to a technical reason, relative humidity values (maximum of 72%) outside the expected range of 30-70% were recorded during the study. However, these deviations have no effect on the outcome of the study.

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 Charles River Laboratories Hungary Kft., H-8200 Veszprém, Szabadságpuszta, hrsz. 028/1., Hungary. This is for a period of 15 years.

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

The primary skin irritation potential of isocycloseram/emamectin benzoate SC (A23220A) 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 application of 0.5 mL test item to their intact shaved dorsal area. The duration of treatment was 4 hours. The scoring of skin reactions was performed at approximately 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.

No local dermal signs were observed in the treated animals throughout the study.

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 second and third rabbits.

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

1.3 Conclusion

Under the conditions of this study and according to the Draize classification criteria, isocycloseram/emamectin benzoate SC (A23220A) 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 isocycloseram/emamectin benzoate SC (A23220A) from a single dose placed on the skin of rabbits for 4 hours.

The New Zealand white rabbit has been shown to be a suitable model for this type of study and is recommended in the test guideline. The results of the study are believed to be of value in predicting the likely skin irritancy potential of the test material to man.

Based on an *in vitro* skin irritation study that was conducted using the EpiDerm^{TM} model (EPI-200-SIT) (study number: 20/080-043B) with isocycloseram/emamectin benzoate SC (A23220A) the test item is indicated to be irritant to skin. However, based on the justification of the Sponsor, the test item is non-irritant/corrosive to skin and thus is considered to be very unlikely to cause severe skin irritation or skin damage, hence this *in vivo* study was conducted for classification of skin irritation, for regional registration purposes.

The study was designed such that the minimum number of animals were used. As specified in the test guidelines, the test item was administered undiluted at 0.5 mL/animal.

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.

- 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 Charles River Laboratories Hungary Kft. 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:	Isocycloseram/Emamectin Benzoate SC (A23220A)
Batch number:	TSC002-041-001
Product code:	A23220A
Active ingredient content*:	Isocycloseram: 17.5 % w/w corresponding to 201 g/L emamectin benzoate: 4.18 % w/w corresponding to 48.1 g/L
Appearance:	Brown liquid
Recertification date:	31 January 2023
Storage conditions:	Room temperature (<30°C)
Safety precautions:	Enhanced safety precautions (half mask at least with P3 filter cartridge, nitrile gloves, lab coat) for unknown materials were applied to assure personnel health and safety.

**No adjustment for the active ingredient content was applied.*

The Certificate of Analysis is shown in Appendix 1.

The integrity of supplied data relating to the identity, purity and stability of the test material is the responsibility of the Sponsor.

3.1.1 Identification and receipt

The test item of a suitable active ingredient content 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 Charles River Laboratories Hungary Kft. on the basis of the information provided by Sponsor.

3.1.2 Formulation

The undiluted test item was administered as a single dose, as supplied.

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:	~12 weeks
Body weight at dosing:	3337 g – 3810 g
Identification:	The animals were identified by ear tag. The cages were marked with individual identity cards with information about study number, sex, cage number, dose and individual animal number.
Acclimatization:	Under laboratory conditions after health examination. Only animals without any visual signs of illness were used for the study.
Acclimatization time:	20 days

3.2.2 Husbandry

Animal health:	Only healthy animals were used for the study, as certified by the staff Veterinarian.
Room number:	034, 030
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. Additional environmental enrichment (Bunny Blocks and Dumbbell Devices) was provided for all animals.
Lighting periods:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature:	19.1 – 21.0°C
Relative humidity:	46-72%
Ventilation:	15-20 air exchanges/hour.

Environmental parameters (temperature and relative humidity) were continuously monitored and the minimum and maximum values were recorded twice a day during the study. The actual temperature and humidity range during the acclimatisation and experimental phases was reported.

3.2.3 Food and feeding

The animals received UNI diet for rabbits produced by Cargill Takarmány Zrt., *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. Batch numbers of the diet, detailed descriptions of the contents of the lots used are archived with the raw data at Charles River Laboratories Hungary Kft.

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-8200 Veszprém, József A.u.36., Hungary). Copies of the relevant Certificates of Analysis are retained in the archives at Charles River Laboratories Hungary Kft.

3.3 Administration of the Test Item

According to OECD Guidelines 404, a test item does not need to be tested 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 8.78. This was within the acceptable range given by the OECD guideline, therefore the test item was permitted for use in this study. Patch testing was used to detect primary irritating effects of the test item. The dermal route was selected because it is a potential route of human exposure.

Approximately 24 hours prior to the test, the hair was clipped from the dorsal area of the trunk of the animals with an electric clipper, exposing an area of approximately 100 cm^2 (10 cm x 10 cm).

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 animal was then wrapped with plastic wrap held in place with an elastic stocking.

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 was 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 euthanized by intravenous sodium pentobarbital 40% (Euthanimal) 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 Material for euthanasia

Name: Euthanimal 40% (sodium pentobarbital)
Lot No.: 1811347-03
Expiry Date: 31 December 2021
Produced by: Alfasan Netherland BV, Kuipersweg 9, Woerden, The Netherlands

3.5 Data Evaluation

The skin reaction was assessed according to the numerical scoring system listed in the OECD 404 (28 July 2015) which was based on the Draize scoring system. The skin reaction was assessed at approximately 1, 24, 48 and 72 hours after the end of exposure (removal of the dressing, gauze patch and test item).

Summarized in tables, the data reported includes 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 (approximately 24, 48 and 72 hours after patch removal) for each animal for erythema/eschar grades and for oedema grades, separately. An animal was positive 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.

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 throughout the study.

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 clinical signs were observed at 72 hours after patch removal, the study was terminated after the 72-hour observation time point of the second and third rabbits.

4.4 Body Weight

The body weights of all rabbits were considered to be within the normal range of variability (Table 4).

5.0 CONCLUSIONS

According to the Draize classification criteria, isocycloseram/emamectin benzoate SC (A23220A) 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. (13250): 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.

Internal references

Balázs Orovecz, B.Sc., (2020) Isocycloseram/Emamectin Benzoate SC (A23220A) − *In Vitro* Skin Irritation Test in the EpiDerm™ Model (EPI -200-SIT). Charles River Laboratories Hungary Kft. (formerly Citoxlab Hungary Ltd.) H-8200 Veszprém, Szabadságpuszta, hrsz. 028/1., Hungary 20/080-043B.

TABLES SECTION

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
$0 < P.I.I. \leq 2$	Mild Irritant
$2 < P.I.I. \leq 5$	Moderate Irritant
$5 < P.I.I.$	Severe Irritant

TABLE 1 Skin Irritation Scores - Individual Values

Animal Number	Sex	Evaluation Interval*	Erythema	Oedema	Cumulative	
					Score	Mean
5711	male	1 hour	0	0	0.00	0.00
5709	male		0	0	0.00	
5716	male		0	0	0.00	
5711	male	24 hours	0	0	0.00	0.00
5709	male		0	0	0.00	
5716	male		0	0	0.00	
5711	male	48 hours	0	0	0.00	0.00
5709	male		0	0	0.00	
5716	male		0	0	0.00	
5711	male	72 hours	0	0	0.00	0.00
5709	male		0	0	0.00	
5716	male		0	0	0.00	

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

Animal Number	Sex	Erythema	N	Oedema	N	Primary Skin Irritation Index
5711	male	0	3	0	3	0
5709	male	0	3	0	3	
5716	male	0	3	0	3	
Mean score		0		0		

N: number of available data points

TABLE 3 Clinical Signs

Animal Number	Sex	Observations	Observation time*			
			Day 0	Day 1	Day 2	Day 3
5711	male	Symptom free	+	+	+	+
5709	male	Symptom free	+	+	+	+
5716	male	Symptom free	+	+	+	+

*: relative to the day of treatment
+: present

TABLE 4 Body Weights

Animal No.	Sex	Body weight (g)	
		Day of Treatment	End of observation period
5711	male	3490	3634
5709	male	3337	3434
5716	male	3810	3862

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis

syngenta

Syngenta Crop Protection AG
GLP Testing Facility WMU
Analytical Development & Product Chemistry
Breitenloh 5
4333 Münchwilen, Switzerland

Certificate of Analysis

A23220A

isocycloseram/emamectin benzoate SC (200/050)

TSC002-041-001

Batch Identification	**TSC002-041-001**
Other Batch ID	1122866
Product Code	**A23220A**
Other Product Code(s)	isocycloseram/emamectin benzoate SC (200/050)
Chemical Analysis (Active Ingredient content)	
- **Identity of the Active Ingredient(s)***	**confirmed**
- **Content of isocycloseram***	**17.5 % w/w corresponding to 201 g/l**
- **Content of emamectin benzoate***	**4.18 % w/w corresponding to 48.1 g/l**
	The Active Ingredient(s) content is within the FAO limits.
Methodology used for Characterization / Recertification	LC, chiral LC, oscillating density meter
Physical Analysis	
- **Appearance**	**brown liquid**
- **Density***	**1150 kg/m³**
Stability:	
- **Storage Temperature**	**< 30°C**
- **Recertification Date**	**End of January 2023**

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 AG, Switzerland.

Study number of batch characterization: CHMU200180
Study number(s) of batch recertification:

Authorization: 19-Feb-2020

Dr. Karine Heintz
Analytical Development & Product Chemistry

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APPENDIX 2 Individual Local Findings

Animal No. 5711, Male

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

Animal No. 5709, Male

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

Animal No. 5716, Male

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

APPENDIX 3 Structured Study Summary

Structured Study Summary Table

Test substance design code	A23220A
Test substance batch code	TSC002-041-001
Test substance purity (% w/w)	Isocycloseram: 17.5 % w/w corresponding to 201 g/L emamectin benzoate: 4.18 % w/w corresponding to 48.1 g/L
Study number	20/080-006N
Study type	SKIN IRRITATION (DRAIZE)
Lab Reference	Charles River Laboratories Hungary Kft.
Study guidelines	OECD 404 (2015), OPPTS 870.2500 (1998), EC No 440/2008, B.4 (2008).
Nonstandard elements	
Species	Rabbit
Strain	New Zealand White

Structured Study Results Table

Animal number	Clinical Observations	Mortality
5711	No clinical signs were observed	No
5709	No clinical signs were observed	No
5716	No clinical signs were observed	No

APPENDIX 4 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: OGYÉI/22762-5/2018
Admin.: Dr. Juhász Uzonka
Date: 03 August 2018

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, mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, analytical and clinical chemistry, pathology studies, preparation of microscopic tissue sections, reproduction toxicology, in vitro studies, inhalation toxicology, 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: **07-11 May 2018.**

Tarjáni Ibolya
Head of Inspectorate

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