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Difenoconazole/Fludioxonil/Metalaxyl-M/Cyclobutrifluram FS

Difenoconazole/Fludioxonil/Metalaxyl-M/Cyclobutrifluram FS (A23793B) – Acute Dermal Toxicity Study in Rats

Final Report

TEST GUIDELINE(S): OECD 402 (2017)
EPA 870.1200 (1998)
EC 440/2008, B.3 (2008)

AUTHOR(S): Balázs Mráz, M.Sc.

COMPLETION DATE: 07 March 2022

PERFORMING LABORATORY: Charles River Laboratories Hungary Kft.
H-8200 Veszprém, Szabadságpuszta, hrsz. 028/1.,
Hungary

LABORATORY PROJECT ID: Report Number: 21/245-002P
Study Number: 21/245-002P
Task Number: TK0518484

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: _____ Date: 07. March 2022

Balázs Mráz, M.Sc.
Study Director

Performing Laboratory: Charles River Laboratories Hungary Kft.
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 Code: 21/245-002P

Study Title: Difenoconazole/Fludioxonil/Metalaxyl-M/Cyclobutrifluram FS (A23793B) - Acute Dermal Toxicity Study in Rats

Test Item: Difenoconazole/Fludioxonil/Metalaxyl-M/Cyclobutrifluram FS (A23793B)

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
06 December 2021	Study Plan	06 December 2021	06 December 2021
14 December 2021	Treatment	14 December 2021	14 December 2021
08 February 2022	Draft Report	08 February 2022	08 February 2022
04 March 2022	Final Report	04 March 2022	04 March 2022

Signature: Nyitrai Ildikó Date: 07. March 2022

Ildikó Nyitrai, M.Sc.
On behalf of QA

STATEMENT OF THE MANAGEMENT

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 "Difenoconazole/Fludioxonil/Metalaxyl-M/Cyclobutrifluram FS (A23793B) - Acute Dermal Toxicity Study in Rats" was performed, in compliance with the Principles of Good Laboratory Practice.

Signature: Balázs Tóth Date: 07 March 2022

Balázs Tóth, Ph.D.
General Manager

GENERAL INFORMATION

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

Name	Function or Department
Balázs Mráz, M.Sc	Study Director
Ivett Orosz, M.Sc.	Assistant Scientist
Ildikó Nyitrai, M.Sc.	Quality Assurance Unit
Eszter Sebestyén, B.Sc.	Quality Assurance Unit
László Székelyhidi, D.V.M.	Veterinary Control
Ferenc Szűcs	Animal Service Laboratories
Tamás Mészáros, Ph.D.	Pharmacy
Carolina Vaccari, M.Sc.	Syngenta Study Manager

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

Study dates

Study initiation date:	07 December 2021
Acclimatization period:	02 December – 14/16 December 2021
Experimental start date:	15 December 2021
Treatment date:	15 / 17 December 2021
Observation period:	15 / 17 December – 29 / 31 December 2021
Experimental termination date:	31 December 2021
Draft Report:	09 February 2021
Final Report:	07 March 2021

Deviations from the guidelines and Study Plan
Due to technical reason, relative humidity values (minimum of 28%) outside the expected range of 30-70% were recorded during the study. This difference of the environmental parameter was considered not to adversely affect the results or integrity of the study as confirmed by the clinical Veterinarian.

Performing laboratory test substance reference number
210563

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

Three female Crl:WI rats were treated with a single dermal application of difenoconazole/fludioxonil/metalaxyl-M/cyclobutrifluram FS (A23793B) at a dose level of 2000 mg/kg body weight (bw). The application period was 24 hours, followed by a 14-day observation period.

Clinical observations along with a check of viability and mortality were performed on all animals at 30 minutes, 1, 2 and 5 hours after dosing and daily for 14 days thereafter. Body weight was measured prior to dosing on Day 0, and on Days 7 and 14. Rats were euthanized and subjected to a gross macroscopic examination at the end of the 2-week observation period (Day 14).

1.2 Results

No mortality occurred during the study.

After the treatment with the test item 3/3 animals had areas of red discolouration of skin on Day 1 – 3 due to test item. Animals were symptom free from Day 4.

The body weights of the animals were within the range commonly recorded for this strain and age.

There was no evidence of any gross macroscopic changes at necropsy at a dose level of 2000 mg/kg bw.

1.3 Conclusion

Under the conditions of this study, the median lethal dose (LD_{50}) of difenoconazole/fludioxonil/metalaxyl-M/cyclobutrifluram FS (A23793B) after a single dermal administration was considered to be greater than 2000 mg/kg bw in female Crl:WI rats.

2.0 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the acute dermal toxicity of difenoconazole/fludioxonil/metalaxyl-M/cyclobutrifluram FS (A23793B) when administered to rats by a 24-hour dermal application, followed by an observation period of 14 days.

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.

2.2 Guidelines

The study was performed according to the following guidelines:

- OECD Guidelines for Testing of Chemicals, Section 4, Number 402 "Acute Dermal Toxicity", adopted 2017

  Note: The 2 following guidelines have not yet been revised in line with the OECD 2017 version. The study does not fully comply with the older version of the guidelines below, but the study design is considered to be acceptable for all OECD countries.

- United States Environmental Protection Agency Health Effects Division Test Guidelines, OPPTS 870.1200 Acute Dermal Toxicity EPA 712-C-98-192, 1998

- Commission Regulation (EC) No 440/2008, B.3 (L 142, 2008)

This study was being performed to meet safety assessment requirements outside the EU, hence the Commission regulation (EU) 2016/863 of 2016 restricting the performance of acute dermal toxicity studies did not apply.

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 authorized the conduct of the study.

3.0 MATERIALS AND METHODS

3.1 Test Substance

The following information was provided by the Sponsor.

Name:	Difenoconazole/fludioxonil/metalaxyl-M/cyclobutrifluram FS (A23793B)
Batch/Lot number:	1200767
Other name:	A23793B
Active ingredient content*:	Difenoconazole 5.45 % w/w, 64.0 g/L, fludioxonil 4.37 % w/w, 51.3 g/L, metalaxyl-M 4.31 % w/w, 50.6 g/L, cyclobutrifluram 21.0 % w/w, 247 g/L
Density:	1.174 g/cm^3
Appearance:	Red liquid
Recertification date:	31 August 2024
Storage conditions:	Room temperature (< 30°C)
Safety precautions:	Routine safety precautions (gloves, goggles, face mask, lab coat)

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

The Certificate of Analysis is attached in Appendix 1.

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 provided 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 the Sponsor.

3.1.2 pH of test item

If the pH is 2 or less or 11.5 or greater, a study cannot be conducted, unless there is evidence that the test item is not severely irritating or corrosive to the skin. The pH of the test item in this study was determined prior to the initiation of the experiment and it was found to be 6.53, therefore the experiment could be started.

3.1.3 Formulation

The test item was administered as supplied without dilution.

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:	The Wistar rat as a rodent is one of the standard species of acute toxicity studies.
Number of animals:	Range finding study: 1 animal/ step Main Study: 2 animals at the selected dose level
Sex:	Female rats, nulliparous and non-pregnant.
Age at dosing:	Young adult rats (9 weeks)
Body weight at dosing:	Between 233 g and 242 g
Identification:	Animals were individually identified by numbers written on the tail with an indelible pen. The numbers were given on the basis of Charles River Laboratories Hungary Kft.'s master file, for each animal allocated to the study. The housing 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.
Randomisation:	Selected by hand at time of delivery. No computer generated randomization program.
Acclimatisation time:	13 and 15 days

3.2.2 Husbandry

Animal health:	Only healthy animals were used for the study. The staff Veterinarian certified health status.
Room number:	522/1
Housing / Enrichment:	Group caging apart from during the 24-hour exposure period where animals were caged individually in Type II polypropylene/polycarbonate cages. Rodents were housed with deep wood sawdust bedding to allow digging and other normal rodent activities. Additional enrichment (GLP MaxiFun Tunnels, LBS UK) was also used.
Bedding and nesting:	SAFE 3/4-S Bedding and SAFE crinklets natural nesting for Laboratory Animals (*produced by J. Rettenmaier & Söhne GmbH + Co. KG, Germany*) were available to animals during the study. Copies of Certificate of analysis are retained in the raw data.
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature:	19.1– 22.7°C
Relative humidity:	28 – 70%
Ventilation:	15-20 air exchanges per hour

The temperature and relative humidity were recorded twice daily during the acclimatisation and experimental phases of the study. Fresh bedding was provided for the animals twice a week.

3.2.3 Food and feeding

The 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, *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 and details of the lot 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 500 mL bottles. 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. 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

3.3.1 Doses

Justification of the doses:
In an acute oral toxicity study (study code: 21/245-001P), no mortality was observed at 2000 mg/kg bw. Experiences show that the acute dermal toxicity is lower than the acute oral toxicity, therefore in this dermal acute study a limit dose of 2000 mg/kg bw was chosen and agreed by the Sponsor.

3.3.2 Experimental design

A single administration was performed by the dermal route and was followed by a fourteen-day observation period.

One female rat was dosed initially in the dose range finding part of the test and the remaining 2 female rats were dosed 2 days later (main test) when it was clear there were no adverse effects.

3.3.3 Procedure

The backs of the animals were shaved (approximately 10% area of the total body surface) approximately 24 hours prior to the treatment. Only those animals without injury or irritation on the skin were used in the test.

On Day 0, the test item was applied at a single dose of 2000 mg/kg bw uniformly over the shaved skin (approximately 10 % area of the total body surface) and remained on the skin throughout a 24-hour exposure period. The appropriate amount of test item was distributed as uniformly as possible onto the skin and then covered with sterile gauze pads. Sterile gauze pads were placed on the skin of rats at the site of application. These gauze pads were kept in contact with the skin using adhesive hypoallergenic plasters. The entire trunk of the animal was then wrapped with semi occlusive plastic wrap for 24 hours. At the end of the exposure period, residual test item was removed, using body temperature water.

During the 24-hour exposure period animals were caged individually in order to avoid oral ingestion of the test chemical by other animals in the cage.

3.4 Observations

3.4.1 Clinical observations

A clinical examination was performed on the day of treatment (Day 0), approximately at 30 minutes, 1, 2 and 5 hours after the application of the test item, and once each day for 14 days thereafter.

Observations included the skin and fur, eyes and mucous membranes, respiratory, circulatory, autonomic and central nervous system, as well as somatomotor activity and behaviour pattern. Particular attention was directed to the observation of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

3.4.2 Skin irritation

Adverse skin reactions at the site of application were recorded daily following the removal of the dressing.

3.4.3 Measurement of body weight

The body weight of all animals was recorded on Day 0 (before treatment), on Day 7 and Day 14.

3.5 *Post Mortem* Investigations

All animals were subjected to gross macroscopic examination. All animals were anaesthetised with sodium pentobarbital (details in 3.5.1.) and exsanguinated. After examination of the external appearance, the cranial, thoracic and abdominal cavities were opened and the appearance of the tissues and organs were observed. Any gross macroscopic findings were recorded.

3.5.1 Materials used for euthanasia

Name:	Euthanimal 40% (Sodium Pentobarbital)
Lot No.:	2001004-06
Expiry Date:	31 January 2023
Produced by:	AlfasanNederland BV, Kuipersweg 9, 3449 JA Woerden, The Netherlands

3.6 Data Evaluation

The type, severity and duration of clinical observations will be described and be summarised in a tabular form. Data will be recorded on the appropriate forms from the relevant SOPs of Charles River Laboratories Hungary Kft., and then tabulated using the Microsoft Office Word and/or Excel or collected using the software PROVANTIS 10 (to be documented in the raw data and reported), as appropriate.
Body weight and body weight changes will be summarised in a tabular form.
Necropsy findings will be described and summarised in a tabular form.

4.0 RESULTS AND DISCUSSION

4.1 Mortality

No mortality occurred during the study.

4.2 Clinical Signs

After the treatment with the test item 3/3 animals had areas of red discolouration of skin on Day 1 – 3 due to test item. Animals were symptom free from Day 4.

The body weights of the animals were within the range commonly recorded for this strain and age.

Individual clinical observations are presented in Table 1.

4.3 Local Dermal Signs

No dermal sign was observed on any animal. Observations are presented in Table 1.

4.4 Body Weight

The body weights of the animals were within the range commonly recorded for this strain and age.

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

4.5 Necropsy

There was no evidence of any gross changes at a dose level of 2000 mg/kg bw (Table 3).

5.0 CONCLUSIONS

Under the conditions of this study, the median lethal dose (LD_{50}) of difenoconazole/fludioxonil/metalaxyl-M/cyclobutrifluram FS (A23793B) after a single dermal administration was considered to be greater than 2000 mg/kg bw in female Crl:WI rats.

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

TABLE 1 Clinical Observation

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	8	9	10	11	12	13	14	
			30'	1h	2h	5h															
1	2395	Symptom Free	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	16/18
		Skin, Discolored, Dorsal Thoracic, Red	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	2/18
2	2396	Symptom Free	+	+	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+	+	15/18
		Skin, Discolored, Dorsal Thoracic, Red	-	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	3/18
3	2397	Symptom Free	+	+	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+	+	15/18
		Skin, Discolored, Dorsal Thoracic, Red	-	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	3/18

Note: Animals were group housed after patch removal.

Standard footnotes:

+ = present - = absent
h = hour (s) ' = minute
# = Found dead
/ = not applicable
Frequency of observation = number of occurrence of observation / total number of observations

Severities: Sl = Slight/Small/Few/Small amount
Mo = Moderate/Several/Moderate amount
Ex = Severe/Large/Many/Large/Extreme amount

Local dermal 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	8	9	10	11	12	13	14	
			30'	1h	2h	5h															
1	2395	Skin- Erythema (Draize) - Treated area	/	/	/	/	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14/18
		Skin- Oedema (Draize) - Treated area	/	/	/	/	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14/18
2	2396	Skin- Erythema (Draize) - Treated area	/	/	/	/	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14/18
		Skin- Oedema (Draize) - Treated area	/	/	/	/	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14/18
3	2397	Skin- Erythema (Draize) - Treated area	/	/	/	/	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14/18
		Skin- Oedema (Draize) - Treated area	/	/	/	/	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14/18

Note: Animals were group housed after patch removal.

Standard footnotes:

+ = present - = absent
h = hour (s) ' = minute
# = Found dead
/ = not applicable
Frequency of observation = number of occurrence of observation / total number of observations

Severities: Sl = Slight/Small/Few/Small amount
Mo = Moderate/Several/Moderate amount
Ex = Severe/Large/Many/Large/Extreme amount

Severities: Erythema severities: 0 = No erythema; 1 = Very slight; 2 = Well-defined; 3 = Moderate to severe; 4 = Severe + Slight eschar formation
Oedema severities: 0 = No oedema; 1 = Very slight; 2 = Slight; 3 = Moderate; 4 = Severe

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)			Body Weight Gain (g)		
		0	7	14	0-7	7- 14	0 - 14
1	2395	242	254	268	12	14	26
2	2396	234	241	264	7	23	30
3	2397	233	240	254	7	14	21
Mean:		236.3	245.0	262.0	8.7	17.0	25.7
Standard deviation:		4.9	7.8	7.2	2.9	5.2	4.5

Note: Animals were group housed after patch removal.

Standard footnotes: **# = Found dead** **M = Moribund** **- = No data**

TABLE 3 **Necropsy Findings**

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

Cage No.	Animal Number	Necropsy Day	External Observations	Internal Observations	Organ/Tissue
1	2395	Day 14	No external observations recorded	No internal observations recorded	Not applicable
2	2396	Day 14	No external observations recorded	No internal observations recorded	Not applicable
3	2397	Day 14	No external observations recorded	No internal observations recorded	Not applicable

Note: Animals were group housed after patch removal.

Standard footnotes: **# = Found dead** **M = Moribund** **- = No data**

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis

syngenta

Syngenta Crop Protection, LLC
Analytical and Product Chemistry
Greensboro, NC 27409

Certificate of Analysis

A23793B
Batch ID 1200767 (GP210610)

Test Substance Name:	CGA169374/CGA173506/CGA329351/SYN549522 FS (062.51/049.93/050.05/250.08)
Common Name:	Difenoconazole/Fludioxonil/Metalaxyl-M/Cyclobutrifluram FS (062.51/049.93/050.05/250.08)
Material ID:	A23793B
Batch ID:	1200767
Other ID:	GP210610
Source:	Syngenta Crop Protection LLC., 410 Swing Road, Greensboro, NC 27409, US

Chemical Analysis

AI	% w/w	g/L
Difenoconazole	5.45	64.0
Fludioxonil	4.37	51.3
Metalaxyl-M	4.31	50.6
Cyclobutrifluram	21.0	247

Identity of the Active Ingredients: Confirmed

Methodology Used for Characterization: LC, mass spectrometry, oscillating density meter.

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

Isomer Assay

Analyte	Isomer	% w/w
CGA329351	D-alanine, N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-, Methyl Ester	4.15
CGA351920	L-alanine, N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-, Methyl Ester	0.15

COA Number: USGR210208

APPENDIX 1 Certificate of Analysis (continued)

Physical Analysis

Analyte	Value	Units
Density	1.174	g/cm3

Appearance: red liquid

Storage Temperature: <30°C

Re-certification Date:End of Aug/2024

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

The stability of this test substance will be determined concurrently through reanalysis of material held in inventory under GLP conditions at Syngenta Crop Protection, LLC, Greensboro, NC.

This Certificate of Analysis is summarizing data from a study that has been performed in compliance with Good Laboratory Practices per 40 CFR Part 160. Raw data, documentation, protocols, any amendments to study protocols and reports pertaining to this study are maintained in the Syngenta Crop Protection Archives in Greensboro, NC.

Study Number: USGR210208

Authorization: Sherry Perine

Sherry C Perine

Sherry Perine

Analytical and Product Chemistry Department

Aug 24, 2021

Date

COA Number: USGR210208

APPENDIX 2 GLP Certificate

OGYÉI Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet
Hatósági Ellenőrzési Főosztály

1051 Budapest, Zrínyi utca 3.
Levélcím: 1372 Postafiók 450
Tel.: +36 1 886 9300, Fax: +36 1 886 9460
E-mail: ogyei@ogyei.gov.hu
Web: www.ogyei.gov.hu

Ref. no: OGYÉI/-29520-2/2021
Admin.: Dr. Szaller Zoltán

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

It is hereby certified that the test facility

Charles River Laboratories Hungary Kft.

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.**

This certificate is valid up to 11th of May, 2022.

Dr. Lukács Ferenc József
Digitálisan aláírta: Dr. Lukács Ferenc József
Dátum: 2021.05.06 13:04:14 +02'00'

Dr. Ferenc Lukács
Head of Inspectorate

Note: Translation of the text of the certificate in the header: ("Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet") - ("National Institute of Pharmacy and Nutrition"); (“Hatósági Ellenőrzési Főosztály”) - (Inspectorate Division) and at the signature: (“Digitálisan aláírta”) - (Digitally signed); (“Dátum”) - (“Date”).