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Difenoconazole/Fludioxonil/Metalaxyl-M/Cyclobutrifluram

Difenoconazole/Fludioxonil/Metalaxyl-M/Cyclobutrifluram FS (A23793B) – Acute Oral Toxicity Study in Rats (Up and Down Method)

Final Report

TEST GUIDELINE(S): OECD 425 (2008)
EPA 870.1100 (2002)

AUTHOR(S): Krisztina Sipos, M.Sc.

COMPLETION DATE: 13 April 2022

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

LABORATORY PROJECT ID: Report Number: 21/245-001P
Study Number: 21/245-001P
Task Number: TK0518487

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.

No chemical analysis of the dose formulation was performed as part of this study. Traceability (equipment used, quantities of test item weighed) of dosing form preparations was checked and revealed no abnormalities of consequence. Furthermore, for this study, the formulations were prepared just before the treatment. Consequently, the absence of dose formulation analysis data was considered not to prejudice the overall GLP status of the study and the scientific reliability of the study conclusions.

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: 13 April 2022

Krisztina Sipos, 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 Number: 21/245-001P

Study Title: Difenoconazole/Fludioxonil/Metalaxyl-M/Cyclobutrifluram FS (A23793B) – Acute Oral Toxicity Study in Rats (Up and Down Method)

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
03 November 2021	Study Plan	03 November 2021	03 November 2021
04 November 2021	Treatment	04 November 2021	04 November 2021
26 January 2022	Draft Report	26 January 2022	26 January 2022
03 February 2022	Amendment 1 to the Study Plan	03 February 2022	03 February 2022
08 April 2022	Final Report	08 April 2022	08 April 2022

Signature: Nyitrai Ildikó Date: 13. april 2022.

Ildikó Nyitrai, 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 "Difenoconazole/Fludioxonil/Metalaxyl-M/Cyclobutrifluram FS (A23793B) – Acute Oral Toxicity Study in Rats (Up and Down Method)" has been performed in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 13 April 2022

Balázs Tóth, Ph.D.
General Manager

GENERAL INFORMATION

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

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

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

Study dates

Study Initiation Date	03 November 2021
Experimental Starting Date	04 November 2021
Experimental Completion Date	02 December 2021
Draft Report	03 February 2022
Amendment 1 to the Study Plan	03 February 2022
Final Report	13 April 2022
Receipt of Animals	14 October 2021
Treatment	04 November 2021 (female no. 1448) 09 November 2021 (female no. 1459) 11 November 2021 (female no. 1450) 16 November 2021 (female no. 1451) 18 November 2021 (female no. 1452)
Observation	04 November - 18 November 2021 (female no. 1448) 09 November - 23 November 2021 (female no. 1459) 11 November - 25 November 2021 (female no. 1450) 16 November - 30 November 2021 (female no. 1451) 18 November - 02 December 2021 (female no. 1452)
Necropsy	18 November 2021 (female no. 1448) 23 November 2021 (female no. 1459) 25 November 2021 (female no. 1450) 30 November 2021 (female no. 1451) 02 December 2021 (female no. 1452)

Deviation from the guideline and Study Plan
There was no deviation from the guideline or Study Plan.

Performing laboratory test substance reference number
210563

Other
The study documents and samples:
- Study Plan and amendment,
- 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.

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 (up and down procedure) study, five female Crl:WI rats were given a single oral (gavage) dose of difenoconazole/fludioxonil/metalaxyl-M/cyclobutrifluram FS (A23793B) at dose level of 2000 mg/kg body weight (bw), followed by a 14 day observation period. The animals were fasted overnight prior to treatment and food was returned 3 hours after dosing.

Individual animals were dosed sequentially at no less than 48-hour intervals. 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.

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

1.2 Results

No mortality was observed at the dose level of 2000 mg/kg bw during the study.

Slight to moderate ataxia 2/5, hunched back (4/5), piloerection (3/5) and decreased activity (5/5) was observed at Day 0. Decreased activity was still present (2/5) in some animals on Day 1, and from Day 2 all animals were symptom-free.

There was no test item related effect on body weight or body weight gain at 2000 mg/kg bw. Body weights were within the range commonly recorded for this strain and age.

A single oral gavage of difenoconazole/fludioxonil/metalaxyl-M/cyclobutrifluram FS (A23793B) to Crl:WI female rats at a dose level of 2000 mg/kg bw was not associated with any gross observations at necropsy.

1.3 Conclusion

Under the conditions of this study, the stopping criteria was met and the estimated acute oral median lethal dose (LD_{50}) of the test item difenoconazole/fludioxonil/metalaxyl-M/cyclobutrifluram FS (A23793B) was found to be 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 difenoconazole/fludioxonil/metalaxyl-M/cyclobutrifluram FS (A23793B) when administered as a single oral gavage dose to female rats at one or more defined dose levels.

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 Reference 425 (2008): Acute Oral Toxicity - Up-and-Down Procedure.
- United States Environmental Protection Agency, Health Effects Test Guidelines, OPPTS 870.1100 Acute Oral Toxicity EPA 712-C-02-190, December 2002.

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)
Other name:	A23793B
Batch number:	1200767
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/cm³
Appearance:	Red liquid
Recertification date:	31 August 2024
Storage conditions:	Room temperature (15-25°C, ≤70% relative humidity)

Safety precautions:	Routine safety precautions (gloves, goggles, face mask, lab coat) were applied to ensure personnel health and safety.

**Note: No adjustment for active ingredient content was applied.*
[#]Note: Test Item name in the title of the Amendment 1 to the Study Plan listed incorrectly. It is only a typo as the correct name can be seen inside the document as well as in the draft report.

The Certificate of Analysis is presented 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 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 the Sponsor.

3.1.2 Formulation

The test item was undiluted and used as supplied by the Sponsor.

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 (1 animal/step)
Sex:	Female rats, nulliparous and non-pregnant
Age when treated:	Young adult rats, 10-12 weeks old
Body weight (at dosing):	229 – 270 g (the weight variation in animals in the study did not exceed ± 20 % of the mean weight)
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.
Randomization:	Selected by hand at time of delivery
Acclimatisation time:	At least 5 days

3.2.2 Husbandry

Animal health:	Only healthy animals were used for the test. The health status was certified by the Veterinarian.
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. Additional enrichment (hiding tunnels) was also used during the study.
Bedding / Nesting:	SAFE 3/4 S certified wooden chips and SAFE 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 Certificate of Analysis are retained in the Archive at Charles River Laboratories Hungary Kft.
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature:	21.1 - 24.4°C
Relative humidity:	32 - 69%
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" (Batch no.: 187 76795; 536 84829, Expiry date: 31 October 2021; 31 May 2022, respectively) produced by ssniff Spezialdiäten GmbH, *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 diets are archived with the raw data at Charles River Laboratories Hungary Kft.

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. The quality control results are retained in the archive at Charles River Laboratories Hungary Kft.

3.3 Administration of the Test Item

3.3.1 Dosages

Justification of the doses:

The starting dose of the main test was 2000 mg/kg bw was selected by the Study Director after a discussion with the Sponsor.

The animals were treated with a single oral (gavage) dose of difenoconazole/fludioxonil/metalaxyl-M/cyclobutrifluram FS (A23793B) at a dose level of 2000 mg/kg bw. Test item was administered undiluted at a constant concentration adjusting for the specific gravity of the test material.

The density of the test item was 1174 kg/m³ as provided by the Sponsor, therefore the dose volume for the animals was 1.70 mL/kg bw. The individual dose volumes used are shown below.

Animal Number	Dose [mg/kg body weight]	Applied volume [mL]	Bodyweight [g]	Mortality
1448	2000	0.42	248	Survived
1459	2000	0.42	248	Survived
1450	2000	0.39	229	Survived
1451	2000	0.46	270	Survived
1452	2000	0.43	252	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 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, 1, 2, 3, 4 and 6 hours after dosing, then once each day for 14 days. Individual observations were performed on the skin, fur, eyes, mucous membranes, somatomotor activity and behaviour pattern as well as respiratory, circulatory, autonomic, and central nervous systems.

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) in all animals until termination.

3.5 *Post Mortem* Investigations

All animals were subjected to gross macroscopic evaluation. All animals were euthanised under pentobarbital anaesthesia (Euthanimal 40%, details in section 3.5.1) at the end of the observation period. After examination of the external appearance, the cranial, thoracic, and abdominal cavities were opened then 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:	Euthanimal 40% (sodium pentobarbital)
Lot No.:	2001004-06
Expiry Date:	31 January 2023
Produced by:	Alfasan Nederland BV, Kuipersweg 9, Woerden, The Netherlands

3.6 Data Evaluation

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

Data were 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 v.9.

The LD_{50} was determined directly from the raw data due to the lack of effects.

4.0 RESULTS AND DISCUSSION

4.1 Mortality

No mortality was observed at the dose level of 2000 mg/kg bw during the study.

4.2 Clinical Signs

Slight to moderate ataxia 2/5, hunched back (4/5), piloerection (3/5) and decreased activity (5/5) was observed at Day 0. Decreased activity was still present (2/5) in some animals on Day 1, and from Day 2 all animals were symptom-free.

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

4.3 Body Weights

There was no test item related effect on body weight or body weight gain at 2000 mg/kg bw. Body weights were within the range commonly recorded for this strain and age.

Individual body weights are presented in Table 2.

4.4 Macroscopic Findings

A single oral gavage of difenoconazole/fludioxonil/metalaxyl-M/cyclobutrifluram FS (A23793B) to Crl:WI female rats at dose level of 2000 mg/kg bw was not associated with any gross observations at necropsy.

Macroscopic findings are presented in Table 3.

5.0 CONCLUSIONS

Under the conditions of this study, the stopping criteria was met and the estimated acute oral median lethal dose (LD_{50}) of the test item difenoconazole/fludioxonil/metalaxyl-M/cyclobutrifluram FS (A23793B) was found to be 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	2-14	
			30'	1h	2h	3h	4h	6h			
1	1448	Symptom Free	-	-	-	-	-	-	-	+	13/20
		Activity decreased	Sl	Sl	Sl	Sl	Sl	Sl	Sl	-	7/20
		Ataxia	Sl	Mo	Mo	Sl	Sl	-	-	-	6/20
		Hunched back	-	-	-	+	+	+	-	-	3/20
2	1459	Symptom Free	+	-	-	-	-	-	+	+	15/20
		Activity decreased	-	Sl	Sl	Mo	Sl	Sl	-		5/20
		Hunched back	-	-	+	+	+	+	-		4/20
		Piloerection	-	-	+	+	+	-	-		3/20
4	1450	Symptom Free	+	-	-	-	-	-	+	+	15/20
		Activity decreased	-	Sl	Sl	Sl	Sl	Sl	-		5/20
		Piloerection	-	+	+	+	+	-	-		4/20
5	1451	Symptom Free	+	+	-	-	-	-	+	+	16/20
		Activity decreased	-	-	Sl	Sl	Sl	Sl	-		4/20
		Hunched back	-	-	-	+	-	-	-		1/20
6	1452	Symptom Free	-	-	-	-	-	-	-	+	13/20
		Activity decreased	Sl	Sl	Sl	Sl	Sl	Sl	Sl		7/20
		Ataxia	-	-	Sl	Sl	Sl	-	-		3/20
		Hunched back	-	+	+	+	+	+	-		5/20
		Piloerection	-	-	-	+	+	+	-		3/20

Standard Footnotes:

+ = present - = absent

h = hour (s) ' = minute

= Found dead M = Moribund

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

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) between days		
		-1	0	7	14	0-7	7-14	0-14
1	1448	262	248	274	279	26	5	31
2	1459	258	248	272	287	24	15	39
3	1450	243	229	255	255	26	0	26
4	1451	286	270	299	300	29	1	30
5	1452	271	252	283	286	31	3	34
Mean:		229.6	264.0	249.4	276.6	281.4	27.2	4.8
Standard deviation:		18.0	15.9	14.6	16.1	16.6	2.8	6.0

Standard Footnotes: **# = Found dead** **M = Moribund**

Note: Day -1 prior to fasting, Day 0 prior to administration

TABLE 3 Macroscopic 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	1448	Day 14	No external observations recorded	No internal observations recorded	Not applicable
2	1449	Day 14	No external observations recorded	No internal observations recorded	Not applicable
4	1450	Day 14	No external observations recorded	No internal observations recorded	Not applicable
5	1451	Day 14	No external observations recorded	No internal observations recorded	Not applicable
6	1452	Day 14	No external observations recorded	No internal observations recorded	Not applicable

Standard Footnotes:
 # = Found dead **M = Moribund**

Note: Day -1 prior to fasting, Day 0 prior to administration

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

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

Page 2 of 2

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 9450
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”).