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Difenoconazole/Mandipropamid/Sedaxane

Difenoconazole/Mandipropamid/Sedaxane FS (A22202A) - Acute Oral Toxicity - Up-And-Down Procedure in Rats

Final Report

DATA REQUIREMENT(S): OECD 425
EPA 870.1100

AUTHOR(S): Jennifer Durando, BS

COMPLETION DATE: March 10, 2017

PERFORMING LABORATORY: Product Safety Labs
2394 US Highway 130
Dayton, NJ 08810 USA

LABORATORY PROJECT ID: Report Number: 44571
Study Number: 44571
Task Number: TK0266092

SPONSOR(S): Syngenta Crop Protection, LLC
410 Swing Road
Post Office Box 18300
Greensboro, NC 27419-8300 USA

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

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: Patrick McCain Date: March 20, 2017

Patrick McCain

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 meets the requirements of OECD Principles of GLP (as revised in 1997): ENV/MC/CHEM(98)17, OECD, Paris, 1998; U.S. EPA GLP (FIFRA): 40 CFR Part 160, 1989; and JMAFF GLP: 11-Nousan-No. 6283, 1 October, 1999. Specific information related to the characterization of the test substance as received and tested is the responsibility of the study Sponsor (see Test Substance section).

I, the undersigned, declare that the methods, results and data contained in this report faithfully reflect the procedures used and raw data collected during the study.

Jennifer Durando, BS
Study Director, Product Safety Labs

03/10/2017
Date

Performing Laboratory: Product Safety Labs
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Dayton, NJ 08810 USA

Kristin Lichti-Kaiser, Ph.D.
Representative of Submitter/Sponsor

3/20/17
Date

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

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

The Product Safety Labs' Quality Assurance Unit has reviewed this final study report to assure the report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the study.

QA activities for this study:

QA Activity	**Performed By**	**Date Conducted**	**Date Findings Reported To Study Director And Management**
Protocol review	I. Stolyar; M. Zakrzewski	Aug 28, 2014[1]; Jan 10, 2017	Aug 28, 2014; Jan 10, 2017
In-process inspection: Initiation of dosing for Animal #3102	A. Adamiec	Dec 16, 2016	Dec 16, 2016
Raw data audit	M. Zakrzewski	Jan 10, 2017	Jan 10, 2017
Draft report review	M. Zakrzewski	Jan 10, 2017	Jan 10, 2017

Final report reviewed by:

Maryann Zakrzewski
Quality Assurance Auditor
Product Safety Labs

March 10, 2017
Date

[1] PSL's "generic" protocol used for this study was reviewed by the Quality Assurance group on this date.

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Title
Jennifer Durando, BS	Study Director
Kristin Lichti-Kaiser, PhD	Syngenta Study Monitor

Study dates

Study initiation date: December 14, 2016
Experimental start date: December 14, 2016
Experimental termination date: January 6, 2017

Deviations from the Guidelines

None

Retention of samples

The test substance is retained for at least 3 months following submission of the final report, unless otherwise specified by the Sponsor. All remaining test substance will be returned to the Sponsor or properly disposed. Records of sample disposition are maintained by Product Safety Labs (PSL).

Performing laboratory test substance reference number

161130-1H

Other

The original signed final report and electronic copies (in Microsoft Word and pdf) of the final report, including the signed QA and GLP Compliance pages will be sent to the Sponsor. A copy of the signed report, together with the protocol (P320.UDP SYN) and all raw data generated at PSL, is maintained in the PSL Archives in Notebook No. 44571: pages 1-30.

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1.0 EXECUTIVE SUMMARY

An acute oral toxicity test was conducted with rats to determine the potential for Difenoconazole/Mandipropamid/Sedaxane FS (076.7/153.4/076.7) A22202A to produce toxicity from a single dose via the oral route. Under the conditions of this study, the acute oral median lethal dose, LD_{50} of Difenoconazole/Mandipropamid/Sedaxane FS (076.7/153.4/076.7) A22202A is greater than 2000 mg/kg of body weight in female rats.

An initial limit dose of 2000 mg/kg was administered to one healthy female rat by oral gavage. Due to the absence of mortality in this animal, four additional females received the same dose level, sequentially. Since only one animal died, no additional animals were tested. Females were selected for the test because they are frequently more sensitive to the toxicity of test compounds than males. All animals were observed for mortality, signs of gross toxicity, and behavioral changes at least once daily for 14 days after dosing or until death occurred. Body weights were recorded prior to administration (initial) and again post dosing on Day 7 and Day 14 (terminal), or after death. Necropsies were performed on all animals.

One animal died within two days of test substance administration. Prior to death, the animal was hypoactive and exhibited irregular respiration, abnormal posture, piloerection, and reduced fecal volume. Following administration, three surviving animals exhibited irregular respiration including one animal that was also hypoactive. However, all three animals recovered by Day 1 and along with the remaining animal appeared active and healthy for the remainder of the 14-day observation period. Gross necropsy of the deceased animal revealed distention of the stomach and intestines and discoloration of the liver. No gross abnormalities were noted for any of the surviving animals when necropsied at the conclusion of the 14-day observation period.

2.0 INTRODUCTION

This study was conducted to provide information on potential health hazards from a short-term exposure to Difenoconazole/Mandipropamid/Sedaxane FS (076.7/153.4/076.7) A22202A by the oral route.

3.0 MATERIALS AND METHODS

3.1 Test Substance

The test substance was identified as: Difenoconazole/Mandipropamid/Sedaxane FS
(076.7/153.4/076.7)
A22202A
Batch ID 953755

It was received on November 30, 2016, and was further identified with PSL Reference Number 161130-1H. The test substance was stored at room temperature. Documentation of the methods of synthesis, fabrication, or derivation of the test substance is retained by the Sponsor.

Characterization of the test substance was provided to PSL by the Sponsor (see Appendix 1):

Composition: Difenoconazole (80.8 g/L), 7.44% w/w
Sedaxane (77.8 g/L), 7.16% w/w
Mandipropamid (147 g/L), 13.5% w/w

Physical Description: White liquid

Stability: Test substance was expected to be stable for the duration of testing.

Recertification Date: End of October 2019

3.2 Animals

Number of Animals: 5

Sex: Female, nulliparous and non-pregnant

Species/Strain: Rat/Sprague-Dawley derived, albino.

Age/Body weight: Young adult (10-12 weeks)/197-217 grams at experimental start.

Source: Received from SAGE® Labs on November 16 and 30, 2016.

Justification of Test System and Route of Exposure: The rat was the system of choice because, historically, it has been the preferred and most commonly used species for acute oral toxicity tests. The oral route of administration was used because human exposure may occur via this route.

3.3 Husbandry

Housing: The animals were singly housed in suspended stainless steel caging, which conforms to the size recommendations in the most recent *Guide for the Care and Use of Laboratory Animals* (Natl. Res. Council, 2011). Enrichment (e.g., toy) was placed in each cage. Litter paper was placed beneath the cage and was changed at least three times per week.

Animal Room Temperature: 19-23ºC

Animal Room Relative Humidity: 39-60%

Animal Room Air Changes: 13/hour. Airflow measurements are evaluated regularly and the records are kept on file at PSL.

Photoperiod: 12-hour light/dark cycle

Acclimation Period: 16-29 days

Food: Envigo Teklad Global 16% Protein Rodent Diet® #2016. The diet was available *ad libitum*, except during fasting.

Water: Filtered tap water was supplied *ad libitum*.

Contaminants: There were no known contaminants reasonably expected to be found in the food or water at levels which would have interfered with the results of this study. Analyses of the food and water are conducted regularly and the records are kept on file at PSL.

3.4 Identification

Cage: Each cage was identified with a cage card indicating at least the study number and identification and sex of the animal.

Animal: A number was allocated to each rat on receipt and a stainless steel ear tag bearing this number was attached to the rat. This number, together with a sequential animal number assigned to study number 44571, constituted unique identification.

3.5 Selection of Animals

Prior to each dosing, experimentally naive rats were fasted overnight by removing the feed from their cages. During the fasting period, the rats were examined for health and weighed. Five healthy, naive female rats (not previously tested) were selected for test.

3.6 Preparation of Test Substance

The test substance was administered as received and mixed well prior to use.

3.7 Dose Calculations

Individual doses were calculated based on the initial body weights, taking into account the density (determined by PSL) of the test substance.

3.8 Dosing

The test substance was administered to the stomach using a stainless steel ball-tipped gavage needle attached to an appropriate syringe. Following administration, each animal was returned to its designated cage. Feed was replaced approximately 3-4 hours after dosing.

Individual animals were dosed as follows:

Limit Test

Dosing Sequence	Animal No.	Dose Level (mg/kg)	Short-Term Outcome	Long-Term Outcome
1	3101	2000	S	S
2	3102		S	S
3	3103		S	S
4	3104		D	D
5	3105		S	S

S – Survival D – Death

3.9 Cage-Side Observations

The animals were observed for mortality, signs of gross toxicity, and behavioral changes approximately 30 minutes post-dosing, during the first several hours post-dosing and at least once daily thereafter for 14 days after dosing or until death occurred. Observations included gross evaluation of skin and fur, eyes and mucous membranes, respiratory, circulatory, autonomic and central nervous systems, somatomotor activity and behavior pattern. Particular attention was directed to observation of tremors, convulsions, salivation, diarrhea, and coma.

3.10 Body Weights

Individual body weights of the animals were recorded prior to test substance administration (initial) and again post dosingon Day 7 and Day 14 (terminal), or after death.

3.11 Necropsy

Surviving rats were euthanized on Day 14 via CO_2 inhalation. Gross necropsies were performed on all decedents and euthanized animals. Tissues and organs of the thoracic and abdominal cavities were examined.

3.12 Statistical Analysis

Statistical analysis was limited to the calculation of the mean density value for dosing.

3.13 Study Conduct

This study was conducted at Product Safety Labs' test facility at 2394 US Highway 130, Dayton, New Jersey 08810. The Study Director for this study was Jennifer Durando, BS. The

primary scientist for this study was Harry Maselli, ALAT, with contributions from Cynthia Bodnar, Stephanie De Carlo, BS, Mark Schooley, Matthew Sorber, BS, and Shannon Stevens, BS, CVT. This study was conducted to comply with the most recent version of the Good Laboratory Practice (GLP) regulations as defined in:

- OECD Principles of GLP (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris
- 40 CFR Part 160: U.S. EPA GLP Standards: Pesticide Programs (FIFRA)
- 11-Nousan-No. 6283: JMAFF GLP Standards

The procedures as described in this protocol are based on the most recent version of the following testing guidelines:

- OECD Guidelines for the Testing of Chemicals, Test No. 425 (2008)
- U.S. EPA Health Effects Test Guidelines, OPPTS 870.1100 (2002)

In the opinion of the Sponsor and the Study Director, this study did not unnecessarily duplicate any previous work.

3.14 Quality Assurance

The final report was audited for agreement with the raw data records and for compliance with the protocol, PSL Standard Operating Procedures and appropriate Good Laboratory Practice Standards. Dates of inspections and audits performed during the study and the dates of reporting of the inspection and audit findings to the Study Director and Facility Management are presented in the Quality Assurance Statement.

3.15 Amendments to Final Protocol

None

3.16 Deviations from Final Protocol

None

3.17 Records to be Maintained

Information on care of the test system, equipment maintenance and calibration, storage, usage, and disposition of the test substance, and all other records that would demonstrate adherence to the protocol will be maintained. Facility records which are not specific to the subject study will be maintained by the testing facility and archived according to PSL SOP.

The original signed final report and electronic copies (in Microsoft Word and pdf) of the final report, including the signed QA and GLP Compliance pages will be sent to the Sponsor. A copy of the signed report, together with the protocol (P320.UDP SYN) and all raw data generated at PSL, is maintained in the PSL Archives in Notebook No. 44571: pages 1-30. PSL will maintain these records for a period of at least five years. After this time, the Sponsor will be offered the opportunity to take possession of the records or may request continued archiving by PSL.

4.0 RESULTS AND DISCUSSION

Individual body weights and doses are presented in Table 1. Individual cage-side and necropsy observations are presented in Tables 2 and 3, respectively. The Certificate of Analysis is presented in Appendix 1.

One animal died within two days of test substance administration. Prior to death, the animal was hypoactive and exhibited irregular respiration, abnormal posture, piloerection, and reduced fecal volume. Following administration, three surviving animals exhibited irregular respiration including one animal that was also hypoactive. However, all three animals recovered by Day 1 and along with the remaining animal appeared active and healthy for the remainder of the 14-day observation period. Gross necropsy of the deceased animal revealed distention of the stomach and intestines and discoloration of the liver. No gross abnormalities were noted for any of the surviving animals when necropsied at the conclusion of the 14-day observation period.

5.0 CONCLUSIONS

Under the conditions of this study, the acute oral median lethal dose, LD_{50} of Difenoconazole/Mandipropamid/Sedaxane FS (076.7/153.4/076.7) A22202A is greater than 2000 mg/kg of body weight in female rats.

6.0 REFERENCES

National Research Council. (2011). *Guide for the Care and Use of Laboratory Animals (8th ed.)*. Washington, DC: The National Academies Press.

TABLES SECTION

TABLE 1 Individual Body Weights, Doses, and Mortalities

Animal No.	Sex	Dose Level (mg/kg)	Body Weight (g)					Dose[1] mL	Mortalities	
			Day 0 Weight	Day 7 Weight	Gain*	Day 14 Weight	Gain*		Day	Weight (g)
3101	F	2000	210	226	16	256	46	0.40	E	-
3102	F		215	243	28	255	40	0.41	E	-
3103	F		200	246	46	252	52	0.38	E	-
3104	F		197	-	-	-	-	0.37	2	186
3105	F		217	230	13	240	23	0.41	E	-

E - Euthanized via CO_2 inhalation after weighing on Day 14
* - Body weight gain from Day 0.
F - Female

[1] The test substance was administered as received. Density – 1.058 g/mL.

TABLE 2 Individual Cage-Side Observations

Animal Number	Animal Sex	Dose Level (mg/kg)	Observation	Day of Observation (x=observation is present)																
				0(0.5 hr)	0(3 hrs)	0(3.5 hrs)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
3101	F	2000	Active and healthy	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
3102	F	2000	Irregular respiration	x	x															
			Active and healthy				x	x	x	x	x	x	x	x	x	x	x	x	x	x
3103	F	2000	Active and healthy	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x
			Irregular respiration		x															
3104	F	2000	Active and healthy	x																
			Hypoactivity			x														
			Hunched posture			x														
			Piloerection			x														
			Irregular respiration			x	x													
			Prone				x													
			Reduced fecal volume				x													
			Dead					x												

Shaded boxes represent no observation taken for the specified animal.

TABLE 2 Individual Cage-Side Observations (Continued)

Animal Number	Animal Sex	Dose Level (mg/kg)	Observation	Day of Observation (x=observation is present)															
				0(0.5 hr)	0(3 hrs)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
3105	F	2000	Active and healthy	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
			Irregular respiration		x														
			Hypoactivity		x														

TABLE 3 Individual Necropsy Observations

Animal Number	Animal Sex	Dose Level (mg/kg)	Organ / Tissue	Grade	Observation	Modifier	Color	Location
3101	F	2000	All tissues and organs		No gross abnormalities			
3102	F	2000	All tissues and organs		No gross abnormalities			
3103	F	2000	All tissues and organs		No gross abnormalities			
3104	F	2000	Stomach	Moderate	Distention			
			Intestines	Slight	Distention			
			Lungs		Discoloration	Dark	Red	Around edges
3105	F	2000	All tissues and organs		No gross abnormalities			

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis

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

Certificate of Analysis

A22202A

Batch ID 953755 (GP160857)

Test Substance Name:	CGA169374/NOA446510/SYN524464 FS (076.7/153.4/076.7)
Common Name:	Difenoconazole/Mandipropamid/Sedaxane FS (076.7/153.4/076.7)
Design Code:	A22202A
Batch ID:	953755
Other ID:	GP160857
Source:	Syngenta Crop Protection LLC.,US ,410 Swing Road,Greensboro, NC 27409,

Chemical Analysis

AI	% w/w	g/L
Difenoconazole	7.44	80.8
Sedaxane	7.16	77.8
Mandipropamid	13.5	147

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
CGA185882		3.88
CGA185883		3.56
SYN508210	1H-pyrazole-4-carboxamide, N-[2-(1R,2S)-[1,1'-bicyclopropyl]-2-ylphenyl]-3-(difluoromethyl)-1-methyl-, rel-	6.40
SYN508211	1H-pyrazole-4-carboxamide, N-[2-(1R,2R)-[1,1'-bicyclopropyl]-2-ylphenyl]-3-(difluoromethyl)-1-methyl-, rel-	0.76

COA Number: USGR160216

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Physical Analysis

Property	Value	Units
Density	1.086	g/cm3

Appearance: white liquid

Storage Temperature: <30°C

Re-certification Date:End of Oct/2019

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: USGR160216

Authorization: Sherry Perine

Sherry C Perine

Sherry Perine

Analytical and Product Chemistry Department

Oct. 11, 2016

Date