

Product Safety Labs

SYN549522

SYN549522 FS (A22417C) – Acute Dermal Toxicity – Fixed Dose Procedure in Rats

Final Report

DATA REQUIREMENT(S): OECD 402 (2017)

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COMPLETION DATE: April 26, 2019

PERFORMING LABORATORY: Product Safety Labs
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LABORATORY PROJECT ID: Report Number: 49378
Study Number: 49378
Task Number: TK0317075

SPONSOR(S): Syngenta Crop Protection, LLC
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VOLUME 1 OF 1 OF STUDY

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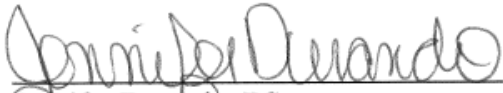
STATEMENT OF DATA CONFIDENTIALITY CLAIMS

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study meets the requirements of U.S. EPA GLP: Pesticide Programs (FIFRA): 40 CFR Part 160, 1989, which are compatible with OECD Principles of GLP (as revised in 1997): ENV/MC/CHEM(98)17, OECD, Paris, 1998, Japanese Ministry of Agriculture, Forestry and Fisheries: No. 23-Syouan-5173, 2 February, 2012, and EC Directive 2004/10/EC, Official Journal of the European Union, L50/44, Feb. 20, 2004. 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



Date

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FLAGGING STATEMENT

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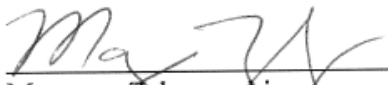
QUALITY ASSURANCE STATEMENT

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.

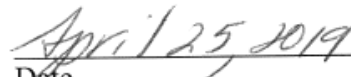
QA activities for this study:

QA Activity	Performed By	Date Conducted	Date Findings Reported To Study Director And Management
Protocol review	R. Krick; M. Zakrzewski	Aug 9, 2018 ¹ ; Jan 14, 2019	Aug 9, 2018; Jan 14, 2019
Critical phase inspection: <i>Day 14 in-life observations and body weights for Animal #3201</i>	B. Simms	Dec 18, 2018	Dec 18, 2018
Raw data audit	M. Zakrzewski	Jan 14, 2019	Jan 14, 2019
Draft report review	M. Zakrzewski	Jan 14, 2019	Jan 14, 2019

Final report reviewed by:



 Maryann Zakrzewski
 Quality Assurance Auditor
 Product Safety Labs



 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
Monique Inforzato, BS	Syngenta Study Monitor
Matthew Sorber, BS	Primary Scientist
Jonathan Bozzick, AS	Scientist
Harry Maselli, ALAT	Scientist
Amber Norton, BS	Scientist
Matthew Notta, BS	Laboratory Manager
Xiomara Portuguez, BS	Scientist

Study dates

Study initiation date: November 26, 2018

Experimental start date: December 4, 2018

Experimental termination date: December 20, 2018

Deviations from the Guidelines

None

Amendments to Final Protocol

None

Deviations from Final Protocol

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).

Other

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 (P322.FDM SYN), associated amendments and/or deviations if applicable, and all raw data generated at PSL, is maintained in the PSL Archives in Notebook No. 49378: pages 1-24. 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.

Any electronic raw data generated will be maintained on-site in accordance with GLP archiving procedures.

Performing laboratory test substance reference number

181105-1H

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1.0 EXECUTIVE SUMMARY

1.1 Study Design

An acute dermal toxicity test (Fixed Dose Procedure) was conducted with rats to determine the potential for SYN549522 FS (A22417C) to produce toxicity from a single topical application.

Initially, two thousand milligrams of the test substance per kilogram of body weight was applied to the skin of one healthy female rat for 24 hours. Due to the absence of extreme clinical signs or severe local signs of irritation, an additional two females were tested for the main test. The animals were observed for mortality, signs of gross toxicity, and behavioral changes at least once daily for 14 days. Body weights were recorded prior to application (initial), on Day 7 and Day 14 (terminal). Necropsies were performed on all animals.

1.2 Results

Range-Finding Study 2000 mg/kg (1 animal); the animal survived test substance administration, gained body weight, and appeared active and healthy during the study. There were no signs of gross toxicity, dermal irritation, adverse clinical effects, or abnormal behavior. No gross abnormalities were noted for the animal when necropsied at the conclusion of the 14-day observation period.

Main Study 2000 mg/kg (2 animals); both animals survived test substance administration, and appeared active and healthy during the study. There were no signs of gross toxicity, dermal irritation, adverse clinical effects, or abnormal behavior. Although one animal lost body weight, the other animal gained body weight during the study. No gross abnormalities were noted for the animals when necropsied at the conclusion of the 14-day observation period.

1.3 Conclusion

Under the conditions of this study, the single dose acute dermal LD₅₀ of SYN549522 FS (A22417C) is greater than 2000 mg/kg of body weight in female rats.

2.0 INTRODUCTION

2.1 Purpose

This study was conducted to provide information on potential health hazards from a short-term exposure to SYN549522 FS (A22417C) by the dermal route.

2.2 Regulatory Guidelines

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. 402 (2017)

2.3 Test Facility

This study was conducted at Product Safety Labs' (PSL) test facility at 2394 US Highway 130, Dayton, New Jersey 08810. In the opinion of the Sponsor and the Study Director, this study did not unnecessarily duplicate any previous work.

3.0 MATERIALS AND METHODS

3.1 Test Substance

The test substance was identified as: SYN549522 FS
A22417C
Batch ID SMU8IP001

It was received on November 5, 2018, and was further identified with PSL Reference Number 181105-1H. 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: SYN549522 (498 g/L), 41.4% w/w (a mixture of SYN547386 and SYN548941):
SYN547386 (448 g/L), 37.2% w/w
SYN548941 (50.0 g/L), 4.16% w/w

Physical Description: Red liquid

pH: Not available

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

Recertification Date: End of October 2021

3.2 Experimental Design

3.2.1 Animals

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

Sex: 3 Females, nulliparous and non-pregnant.

3.2.4 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 animal. This number, together with a sequential animal number assigned to study 49378, constituted unique identification. Only the sequential animal number is presented in this report.

3.3 Preparation and Selection of Animals

On the day prior to application, a group of animals were prepared by clipping the dorsal area and the trunk. After clipping, but prior to application, the animals were examined for health, weighed (initial) and the skin checked for any abnormalities. Three healthy, naive female rats (not previously tested) were selected for test.

3.4 Preparation of Test Substance

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

3.5 Dose Calculations

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

3.6 Application of Test Substance

Initial testing was conducted on one female rat to determine extreme clinical signs or severe irritation potential of the test substance. Due to the absence of extreme clinical signs or severe local signs of irritation, an additional two females were tested. Two thousand milligrams of the test substance per kilogram of body weight was applied evenly over a dose area of approximately 2 inches x 3 inches (approximately 10% of the body surface) and covered with a 2-inch x 3-inch, 4-ply gauze pad. The gauze pad and entire trunk of each animal were then wrapped with 3-inch Durapore tape to avoid dislocation of the pad and to minimize loss of the test substance. The rats were then returned to their designated cages. The day of application was considered Day 0 of the study.

After 24 hours of exposure to the test substance, the pads were removed and the test sites were gently cleansed with a 3% soap solution followed by tap water and a clean paper towel to remove any residual test substance.

3.7 In-life Observations

The animals were observed for mortality, signs of gross toxicity, and behavioral changes during the first several hours after application, after patch removal, and then at least once daily thereafter for 14 days. 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.

3.8 Body Weights

Individual body weights of the animals were recorded prior to test substance application (initial), on Day 7, and Day 14 (terminal).

3.9 Necropsy

All rats were euthanized via CO₂ inhalation at the end of the 14-day observation period. Gross necropsies were performed on all animals. Tissues and organs of the thoracic and abdominal cavities were examined.

3.10 Statistical Analysis

Statistical analysis was not employed during this study.

4.0 RESULTS AND DISCUSSION

Individual body weights and doses, in-life and necropsy observations are presented in Tables 1 through 3. The Certificate of Analysis is presented in Appendix 1.

4.1 In-Life Observations

Range-Finding Study 2000 mg/kg

The animal survived test substance administration. There were no signs of gross toxicity, dermal irritation, adverse clinical effects, or abnormal behavior.

Main Study 2000 mg/kg

Both animals survived test substance administration. There were no signs of gross toxicity, dermal irritation, adverse clinical effects, or abnormal behavior.

4.2 Bodyweight

Range-Finding Study 2000 mg/kg

The animal gained body weight during the study.

Main Study 2000 mg/kg

Although one animal lost body weight, the other animal gained body weight during the study.

4.3 Necropsy

Range-Finding Study 2000 mg/kg

No gross abnormalities were noted for the animal when necropsied at the conclusion of the 14-day observation period.

Main Study 2000 mg/kg

No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

5.0 CONCLUSIONS

Under the conditions of this study, the single dose acute dermal LD₅₀ of SYN549522 FS (A22417C) 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/Weight Gains And Doses

Range Finding Study 2000 mg/kg

Animal No.	Sex	Body Weight (g)					Dose ¹
		Initial	Day 7	Gain*	Day 14	Gain*	g
3201	F	270	282	12	292	22	0.46

* - Body weight gain from Day 0.

F – Female

Main Study 2000 mg/kg

Animal No.	Sex	Body Weight (g)					Dose ¹
		Initial	Day 7	Gain*	Day 14	Gain*	g
3202	F	261	262	1	280	19	0.45
3203	F	256	240	-16	252	-4	0.44

* - Body weight gain from Day 0.

F - Female

¹ The test substance was applied as received. Density - 1.171 g/mL.

TABLE 2 Individual In-life Observations

Range-Finding Study 2000 mg/kg

Animal Number	Animal Sex	Dose Level (mg/kg)	Observation	Color	Day of Observation (x=observation is present)															
					0(1 hr)	0(3 hrs)	0(4 hrs)	1	2	3	4	5	6	7	8	9	10	11	12	13
3201	F	2000	Active and healthy		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
			Staining at the dose site	Red				x	x	x	x	x								

Main Study 2000 mg/kg

Animal Number	Animal Sex	Dose Level (mg/kg)	Observation	Color	Day of Observation (x=observation is present)																
					0(1 hr)	0(3 hrs)	0(4 hrs)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
3202	F	2000	Active and healthy		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
			Staining at the dose site	Red				x	x	x	x	x									
3203	F	2000	Active and healthy		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
			Staining at the dose site	Red				x	x	x	x	x									

TABLE 3 Individual Necropsy Observations

Range-Finding Study 2000 mg/kg

Animal Number	Animal Sex	Dose Level (mg/kg)	Organ / Tissue	Observation
3201	F	2000	All tissues and organs	No gross abnormalities

Main Study 2000 mg/kg

Animal Number	Animal Sex	Dose Level (mg/kg)	Organ / Tissue	Observation
3202	F	2000	All tissues and organs	No gross abnormalities
3203	F	2000	All tissues and organs	No gross abnormalities

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis



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

Certificate of Analysis

A22417C
SYN549522 FS (500)
SMU8IP001

Batch Identification	SMU8IP001
Other Batch ID	1058463
Product Code	A22417C
Other Product Code(s)	SYN549522 FS (500)
Chemical Analysis	
(Active Ingredient content)	
- Identity of the Active Ingredient(s)*	confirmed
- Content of SYN549522*	41.4 % w/w corresponding to 498 g/l
- Content of SYN547386*	37.2 % w/w corresponding to 448 g/l
- Content of SYN548941*	4.16 % w/w corresponding to 50.0 g/l
The Active Ingredient(s) content is within the FAO limits.	
Methodology used for Characterization / Recertification	HPLC, chiral HPLC, oscillating density meter
Physical Analysis	
- Appearance	red liquid
- Density*	1203 kg/m ³
Stability:	
- Storage Temperature	< 30 °C
- Recertification Date	End of October 2021

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: CHMU180671
Study number(s) of batch recertification: ---

Authorization: 17-Oct-2018

Daniel Jenniches
Analytical Development & Product Chemistry