# Product Safety Labs

**SYN549522**

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

**Final Report**

**DATA REQUIREMENT(S):** OECD 402 (2017)

**AUTHOR(S):** Jennifer Durando, BS

**COMPLETION DATE:** April 26, 2019

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

**LABORATORY PROJECT ID:** Report Number: 49378
Study Number: 49378
Task Number: TK0317075

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

**VOLUME 1 OF 1 OF STUDY**

## 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

04/26/2019
Date

Performing Laboratory: Product Safety Labs
2394 Highway 130
Dayton, NJ 08810 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 | R. Krick; M. Zakrzewski | Aug 9, 2018[1]; Jan 14, 2019 | Aug 9, 2018; Jan 14, 2019 |
| Critical phase inspection: *Day 14 in-life observations and body weights for Animal #3201* | 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

April 25, 2019
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

# TABLE OF CONTENTS

# 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 $LD_{50}$ 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.

Number of Animals/Dose Level: Range-Finding Study: 1 / 2000 mg/kg
Main Study: 2 / 2000 mg/kg

Age/Body Weight: Young adult (12 weeks)/ 256-270 grams at experimental start.

Source: Received from SAGE® Labs on November 7, 2018.

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 dermal toxicity tests. The topical route of administration was used because human exposure may occur via this route.

### 3.2.2 Husbandry

Housing: The animals were housed in caging which conforms to the size recommendations in the most recent *Guide for the Care and Use of Laboratory Animals* (Natl. Res. Council, 2011). Animals were group housed, except on the day of application, at which time they were singly housed until the animals were deemed acceptable, based on observations, to return to group housing. Enrichment (e.g., toy) was placed in each cage and litter was changed at least once per week.

Animal Room Temperature: 20-22ºC

Animal Room Relative Humidity: 38-58%

Animal Room Air Changes: 12/hour. Airflow measurements are evaluated regularly and the records are kept on file at PSL.

Photoperiod: 12-hour light/dark cycle

Acclimation Period: 27 or 29 days

### 3.2.3 Food and feeding

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

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.

### 3.2.4 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 $CO_2$ 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 $LD_{50}$ 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 ($8^{th}$ 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 | 14 |
| 3201 | 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 | 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 | 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 | 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

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/m³** |
| **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

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