SYN524464

SYN524464 FS (A16148F) – Acute Dermal Toxicity Study in Rats

Final Report

DATA REQUIREMENT(S): EPA Health Effects Test Guidelines,
OPPTS 870.1200
OECD Guidelines for Testing of Chemicals,
Procedure 402

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STUDY COMPLETION DATE: August 27, 2008

PERFORMING LABORATORY: STILLMEADOW, Inc.
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LABORATORY PROJECT ID: Report Number: 11814-08
Study Number: 11814-08
Task Number: T001109-08

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STATEMENTS OF DATA CONFIDENTIALITY CLAIMS

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was designed and performed in STILLMEADOW, Inc.'s laboratory and was conducted in compliance with:

- United States Environmental Protection Agency FIFRA: Good Laboratory Practice Standards, 40 CFR 160
- United States Environmental Protection Agency TSCA 40 CFR 792
- Organization for Economic Cooperation and Development's Principles of Good Laboratory Practice, Annex 2, C(98)17
- Japan Ministry of Agriculture, Forestry and Fisheries, Notification 11-Nousan-6283, Director- General of Agricultural Production Bureau

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

Janice O Kuhn

Janice O. Kuhn, Ph.D., DABT
Study Director, STILLMEADOW, Inc.

27 Aug 08
Date

Performing Laboratory: STILLMEADOW, Inc.
12852 Park One Drive
Sugar Land, TX 77478 USA

QUALITY ASSURANCE STATEMENT

Test Substance: SYN524464 FS (500)
Study Title: SYN524464 FS (A16148F): Acute Dermal Toxicity Study in Rats

The study report and data have been audited in accordance with Good Laboratory Practice Standards and STILLMEADOW, Inc. Standard Operating Procedures (SOPs). The final report accurately reflects the study data. The Quality Assurance Unit has not been involved in the actual conduct of this study.

The Quality Assurance Unit performed a recent facility inspection on 30 Apr 08. All findings were reported to Management, and the report and responses are kept in the Quality Assurance files.

The findings from any study inspections and audits were reported to the Study Director and Management as follows:

Critical Phase Inspected	Date Inspected	Reported to Study Director	Reported to Management
Protocol Review	1 Apr 08	1 Apr 08	1 Apr 08
Dosing	1 May 08	1 May 08	1 May 08
Report/Data Audit	10 Jun 08	10 Jun 08	10 Jun 08

Richard L. Martin

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27 Aug 08
Date

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

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Study dates

Study initiation date: 14 Apr 08
Experimental start date: 1 May 08
Experimental termination date: 15 May 08

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1.0 EXECUTIVE SUMMARY

The test substance, SYN524464 FS (500) (A16148F), was evaluated for its dermal toxicity potential and relative skin irritancy when a single undiluted dose was applied to the intact skin of male and female albino rats, at a level of 5050 mg/kg. No mortality occurred during the study. There were no clinical signs of toxicity exhibited at any time throughout the study. The only signs of skin irritation was erythema on Day 1. There was no effect on body weight gain. The gross necropsy conducted at termination of the study revealed no observable abnormalities. The estimated acute dermal LD_{50}, as indicated by the data, was determined to be greater than 5050 mg/kg body weight.

2.0 INTRODUCTION

The objective of this study was to assess the systemic toxicity potential and relative skin irritancy of the test substance when administered to rats in accordance with US EPA OPPTS 870.1200, which is intended to meet testing requirements of FIFRA 7 USC 136, *et seq*, and TSCA 15 USC 2601. This study was conducted for Syngenta Crop Protection, Inc., according to the approved protocol and STILLMEADOW, Inc. SOP's. There were no deviations from the protocol which affected the quality or outcome of the study. All procedures in this study are in compliance with Animal Welfare Act Regulations. In the opinion of the sponsor, the study did not unnecessarily duplicate any previous work. The protocol, raw data, this report and a sample of test substance are archived at STILLMEADOW, Inc. The study was initiated on 14 Apr 08, the pre-dose experimental portion began on 30 Apr 08, and the animals were treated with the test substance between 1113 and 1120 on 1 May 08. The in-life portion of the study was terminated on 15 May 08.

3.0 MATERIALS AND METHODS

3.1 Test Substance

Reference Name:	SYN524464 FS (500)
Label Identification:	SYN524464 FS (500) ID 533158 A16148F
Date & Quantity Received:	14 Apr 08; 3691 g (Gr.Wt.)
Physical Description:	Pink opaque liquid
Storage:	Room temperature
Density:	1.1265 g/mL
Purity (w/w):	45.6% active ingredient
Stability:	Reassay: Mar 2009

Records pertaining to stability, characterization, identity, synthesis methods and location of documentation are the responsibility of the sponsor. A copy of the sponsor's Analytical Report is retained in the study file.

3.2 Experimental Animals

Species & Strain:	Albino rat; Sprague-Dawley
Justification of Species:	The rat is a representative rodent species preferred by various regulatory agencies for acute dermal testing.
Source:	Texas Animal Specialties, Humble, TX
Date Born/Date Received:	3 Mar 08 / 24 Apr 08
Acclimation Period:	At least 5 days
Quantity & Sex:	5 males and 5 females (nulliparous and non-pregnant)
Group/Animal Identification:	Cage cards/Ear punch
Weight on Dosing Day:	Males: 268-305 g; Females: 196-230 g

3.3 Animal Husbandry

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Controls Set to Maintain:	•Temperature 22°C±3° •Relative Humidity 30-70% •12-hour light/dark cycle •10-12 air changes/hour
Actual Temp/Rel. Humidity:	20-22° C / 43-93% Protocol deviation: humidity was outside protocol range but did not affect study outcome.
Food:	Purina Formulab Chow #5008; available *ad libitum*
Water Type:	Municipal water supply, analyzed by TCEQ Water Utilities Division; available *ad libitum* from automatic water system

Animal husbandry and housing at STILLMEADOW, Inc. comply with standards outlined in the "Guide for the Care and Use of Laboratory Animals" (NRC Publ.). No contaminants were expected to have been present in the feed or water that would have interfered with or affected the results of the study.

3.4 Test Substance Administration

Healthy albino rats were released from quarantine. Each animal was prepared on the day prior to treatment by clipping the dorsal surface of the trunk free of hair to expose not less than 10% of the total body surface area. Care was taken to avoid abrading the skin. Only those animals with exposure areas free of pre-existing skin irritation or defects were used for this study. All animals were treated with 5050 mg/kg (4.48 mL/kg) of undiluted test substance. An individual dose was calculated for each animal based on its Day 0 body weight just before exposure. The test substance was applied to each exposure area in a thin, uniform layer. The area of application was covered with an appropriately sized surgical gauze patch (2 x 4 in) and secured with non-irritating adhesive tape. The trunk of each animal was then wrapped with vet wrap which was secured in place with non-irritating adhesive tape to prevent possible ingestion of the test substance.

3.5 Removal of Test Substance

After 24 hours, the wrappings were removed. The test sites were gently washed with room temperature tap water and a clean cloth to remove as much residual test substance as possible.

3.6 In-life Observations

Observations for mortality and clinical/behavioral signs of toxicity were made at least three times on the day of dosing (Day 0) and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to dosing and on Days 7 and 14. Observations for dermal irritation at the test site were made on Days 1, 4, 7, 11 and 14.

3.7 Post-mortem Observations

On Day 14 after dosing, each animal was euthanized by an overdose of CO_2. All study animals were subjected to gross necropsy and all abnormalities were recorded.

4.0 RESULTS AND DISCUSSION

4.1 Mortality/Estimated LD_{50} Values

There was no mortality during the study. The estimated acute dermal LD_{50}, as indicated by the data, was determined to be greater than 5050 mg/kg body weight.

4.2 Body Weights

Individual body weights are presented in Table 1. Body weight gain was unaffected by the administration of the test substance.

4.3 Clinical Signs/Dermal Irritation

A summary of clinical signs is presented in Table 2. All animals appeared normal for the duration of the study. Signs of skin irritation are presented in Table 3, and included very slight erythema in three animals on Day 1; test substance staining of the site was also noted.

4.4 Necropsy Findings

Individual necropsy findings are presented in Table 1. The gross necropsy conducted at termination of the study revealed no observable abnormalities.

5.0 CONCLUSIONS

The test substance, SYN524464 FS (500) (A16148F), was evaluated for its acute dermal toxicity potential and relative skin irritancy in albino rats when administered as a single dose of 5050 mg/kg. The acute dermal LD_{50} is greater than 5050 mg/kg in males and females.

TABLES SECTION

TABLE 1 Body Weights, Time of Death and Gross Necropsy

ACUTE DERMAL TOXICITY IN RATS
Test Substance: SYN524464 FS (500)
Dose Level: 5050 mg/kg (4.48 ml/kg)

Animal Number	Dose Amt (mL)	Body Weights (g)			Time of Death*	Gross Necropsy Findings
		Day 0	Day 7	Final		
151-M	1.29	287	303	353	Day 14	NOA
152-M	1.31	292	307	334	Day 14	NOA
153-M	1.21	270	294	304	Day 14	NOA
154-M	1.20	268	291	315	Day 14	NOA
155-M	1.37	305	320	341	Day 14	NOA
	Mean Wt:	284	303	329		
156-F	0.879	196	207	213	Day 14	NOA
157-F	1.03	230	239	255	Day 14	NOA
158-F	0.923	206	216	226	Day 14	NOA
159-F	0.955	213	221	238	Day 14	NOA
160-F	0.897	200	212	220	Day 14	NOA
	Mean Wt:	209	219	230		

* - Day of dosing considered Day 0; Day 14 is terminal sacrifice.
M - Male; F - Female; NOA - No Observable Abnormalities

TABLE 2 Summary of Pharmacologic and/or Toxicologic Signs

ACUTE DERMAL TOXICITY IN RATS
Test Substance: SYN524464 FS (500)
Dose Level: 5050 mg/kg (4.48 mL/kg)
Sex: Males and Females

	Time After Treatment															
	DAY 0			DAYS												
Reaction and Severity	1st	2nd	3rd	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Males																	
Appeared normal at each observation.																	
Females																	
Appeared normal at each observation.																	

TABLE 3 Signs of Dermal Irritation

ACUTE DERMAL TOXICITY IN RATS
Test Substance: SYN524464 FS (500)
Dose Level: 5050 mg/kg (4.48 mL/kg)

Animal Num.	Day 1			Day 4			Day 7			Day 11			Day 14		
	Er	Ed	Other	Er	Ed	Other	Er	Ed	Other	Er	Ed	Other	Er	Ed	Other
151-M	1	0	-	0	0	-	0	0	-	0	0	-	0	0	-
152-M	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-
153-M	1	0	-	0	0	-	0	0	-	0	0	-	0	0	-
154-M	0	0	T	0	0	-	0	0	-	0	0	-	0	0	-
155-M	0	0	T	0	0	-	0	0	-	0	0	-	0	0	-
156-F	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-
157-F	1	0	-	0	0	-	0	0	-	0	0	-	0	0	-
158-F	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-
159-F	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-
160-F	0	0	-	0	0	-	0	0	-	0	0	-	0	0	-

Er = Erythema: 0 = None, 1 = Very slight, 2 = Well-defined, 3 = Moderate, 4 = Severe
Ed = Edema: 0 = None, 1 = Very slight, 2 = Slight, 3 = Moderate, 4 = Severe
Other = - A dash (-) is used if there are no other signs of dermal irritation.
T = Test site staining

APPENDICES SECTION

APPENDIX 1 Analytical Report

syngenta

A16148F
Batch ID 533158 (GP-080305)

Batch Identification	533158
Product Design Code	A16148F
Product Denomination	SYN524464 FS (500)
Product by Common Name	SYN524464 FS (500)
Other Product Code(s)	GP-080305
Source	Technology & Projects, Syngenta Crop Protection, Inc.
Chemical Analysis (Active Ingredient Content)	
Identity of the Active Ingredient*	Confirmed
Content of SYN524464*	45.6% (wt/wt) or 534 g/L
Methodology Used for Characterization	HPLC
The Active Ingredient content is within the FAO limits.	
Physical Analysis	
Appearance*	pink opaque liquid
Density*	1171 g/L
Stability:	
Storage Temperature	< 30°C
Expiration date	March 2009

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

This Certificate of Analysis is summarizing data (marked with an asterisk) 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.

Authorization:

26 Mar 2008

Dorothea Jeffery
Group Leader I
Analytical & Product Chemistry Department

Date