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SYN524464

SYN524464 FS (A16148F) – Acute Dermal Irritation Study in Rabbits

Final Report

DATA REQUIREMENT(S): OECD Guidelines for Testing of Chemicals, Procedure 404
EPA Health Effects Test Guidelines, OPPTS 870.2500

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STUDY COMPLETION DATE: August 27, 2008

PERFORMING LABORATORY: STILLMEADOW, Inc.
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LABORATORY PROJECT ID: Report Number: 11817-08
Study Number: 11817-08
Task Number: T001112-08

SUBMITTER/SPONSOR: Syngenta Crop Protection, Inc.
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VOLUME 1 OF 1 OF STUDY

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS UNDER SPECIFIED FIFRA PROVISIONS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Section 10(d)(1)(A) (discloses manufacturing or quality control processes), (B) (discloses the details of methods for testing, detecting or measuring the quantity of any deliberately added inert ingredient of a pesticide), or (C) (discloses the identity or percentage quantity of any deliberately added inert ingredient of a pesticide).

Company
Syngenta Crop Protection, Inc.

Company Agent: Adora Clark, Ph.D.

Adora Clark
U. S. Product Registration Manager

January 19, 2010
Date

Syngenta is the owner of this study. 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. Notwithstanding the wording of our marking TRADE SECRET, this marking, by itself, conveys no supplemental claims of confidentiality under FIFRA Sections 10(a) or 10(b) (addressing protection of trade secrets and commercial and financial information). In submitting this material to EPA according to method and format requirements contained in PR Notice 86-5, 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 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, Ph.D., DABT
Study Director, STILLMEADOW, Inc.

Date: 27 Aug 08

Performing Laboratory: STILLMEADOW, Inc.
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Odette Alexander, M.S.
Representative of Submitter/Sponsor

Date: 1/19/10

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QUALITY ASSURANCE STATEMENT

Test Substance: SYN524464 FS (500)
Study Title: SYN524464 FS (A16148F): Acute Dermal Irritation Study in Rabbits

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
Observations	30 Apr 08	30 Apr 08	30 Apr 08
Report/Data Audit	2 Jun 08	2 Jun 08	2 Jun 08

Richard L Martin
Richard L. Martin, M.S., C.Ph.T.
Quality Assurance, STILLMEADOW, Inc.

27 Aug 08
Date

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Study Director:	Janice O. Kuhn, Ph.D., DABT	
Technical Staff:	Carol Morris, B.A	Paul Siemens, B.A.
	Hector Fuentes	Robert Preston
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Data Services:	Connie Pavatte, Report Preparation	

Study dates

Study initiation date: 14 Apr 08
Experimental start date: 29 Apr 08
Experimental termination date: 2 May 08

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1.0 EXECUTIVE SUMMARY

A primary dermal irritation study was conducted on three albino rabbits using test substance SYN524464 FS (500) (A16148F). There was one intact test site per animal. Each test site was treated with 0.5 mL of undiluted test substance, which was maintained in contact with the skin for 4 hours. Observations for dermal irritation and defects were made at 1, 24, 48 and 72 hours after removal of the dressings. Irritation scores derived from the respective erythema and edema scores through the 72 hour observations for each animal are presented below.

	Erythema				Edema				
	Hours after Unwrap				Hours after Unwrap				Irritation
	1	24	48	72	1	24	48	72	Scores
2582-M	0	0	0	0	0	0	0	0	0.00
2584-M	0	0	0	0	0	0	0	0	0.00
2581-F	0	0	0	0	0	0	0	0	0.00

Based on the scores for the above observations, the Primary Irritation Index (PII) is 0.0. The test substance is therefore rated non-irritating. Based on the scores at the 72 hour observation only, the test substance is assigned to EPA Toxicity Category IV.

2.0 INTRODUCTION

The objective of this study was to assess the relative level of primary skin irritation of the test substance on rabbits in accordance with US EPA OPPTS 870.2500, 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 used 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, and the pre-dose experimental portion began on 28 Apr 08. The animals were treated with the test substance between 1000 and 1002 on 29 Apr 08. The in-life portion of the study was terminated on 2 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; 3691g (Gr.Wt.)
Physical Description:	Pink opaque liquid
Storage:	Room temperature
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 rabbit; New Zealand White
Justification of Species:	The rabbit is preferred by various regulatory agencies for use in primary dermal irritation testing.
Source:	Nichols Rabbitry Inc., Lumberton, TX
Date Born/Date Received:	27 Jan 08 / 18 Apr 08
Acclimation Period:	At least 5 days
Quantity & Sex:	2 males and 1 female (nulliparous and non-pregnant)
Initial Body Weight:	Males: 2.375-2.450 kg; Female: 2.250 kg
Final Body Weight:	Males: 2.500-2.600 kg; Female: 2.400 kg
Group/Animal Identification:	Cage cards/Ear tag

3.3 Animal Husbandry

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Conditions Set to Maintain:	•Temperature 20°C±3° •Relative Humidity 30-70% •12-hour light/dark cycle •10-12 air changes/hour
Actual Temp/Rel. Humidity:	18-22° C / 46-98% Protocol deviation: humidity was outside protocol range but did not affect study outcome.
Food:	PMI Feeds, Inc.™ Lab Rabbit Diet #5321, 8 oz. daily
Water:	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

Prior to starting the study, the pH of the test substance was determined to be 6.02. Each animal was prepared on the day prior to treatment by clipping the dorsal area of the trunk free of hair to expose an area at least 8 x 8 cm. Only those animals with exposure areas free of pre-existing skin irritation or defects were selected for testing. A single intact exposure site was selected as the test site while the contralateral intact site served as a control site.

On Day 0, 0.5 mL of the undiluted test substance was applied to each test site and covered with a surgical gauze patch measuring 2.5 x 2.5 cm and four single layers thick. Each patch was secured in place with a strip of non-irritating adhesive tape. The entire trunk of each animal was loosely wrapped with a semi-permeable dressing (orthopedic stockinette) and secured on both edges with strips of tape to retard evaporation of volatile substances and to prevent possible ingestion of the test substance.

3.5 Removal of Test Substance

After four hours, the patches and 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 Observations

The test sites were observed for erythema and edema formation, and any other dermal defects or irritation at 1, 24, 48 and 72 hours after unwrap.

3.7 Irritation Scoring Method

The scoring scale used to rate dermal irritation is presented in the Legend to Table 1. For each animal, all of the erythema and edema scores through 72 hours were added, and the sum was divided by 4 to obtain an individual irritation score. The primary irritation index was determined by calculating the mean of the irritation scores for all the animals and was used to obtain a rating for the test substance.

4.0 RESULTS AND DISCUSSION

4.1 Evaluation

Signs of dermal irritation or defects are presented in Table 1. Erythema and edema were not observed at any time throughout the study.

5.0 CONCLUSIONS

The primary irritation index of 0.0 out of a possible 8.0 was obtained from the 1, 24, 48 and 72 hour observations and was used to give SYN524464 FS (500) (A16148F) a descriptive rating of non-irritating. Based on the 72 hour observations only, SYN524464 FS (500) is assigned to EPA Toxicity Category IV.

TABLES SECTION

TABLE 1 Signs of Dermal Irritation

ACUTE DERMAL IRRITATION IN RABBITS
Test Substance: SYN524464 FS (500)

Animal Number	Erythema							Edema										Primary Irritation Scores
	Hours				Days			Hours				Days						
	1	24	48	72	7	10	14	1	24	48	72	7	10	14				
2582-M	0	0	0	0				0	0	0	0				0	/4	=	0.00
2584-M	0	0	0	0				0	0	0	0				0	/4	=	0.00
2581-F	0	0	0	0				0	0	0	0				0	/4	=	0.00
Primary Irritation Index* =					0.00		/3=	0.0										
Descriptive Rating =								Non-irritating										

* - Only the first four observation times are used for calculations.

M – Male; F – Female Study Duration: 72 Hrs

Animal Number	Other Observations						
	Hours				Days		
	1	24	48	72	7	10	14
2582-M	T	-	-	-			
2584-M	T	-	-	-			
2581-F	T	T	T	-			

T - Test site staining

Note: A dash (-) is used if there are no other signs of dermal irritation.

APPENDICES SECTION

APPENDIX 1 Legend to Table 1

ACUTE DERMAL IRRITATION IN RABBITS

Evaluation of Skin Reactions

Erythema Formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Maximum Possible	4

Edema Formation

No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond the area of exposure)	4
Maximum Possible	4

Classification of Test Substance

Descriptive Rating	Primary Irritation Index
Non-Irritating	0.0
Practically Non-irritating	0.1 - 0.4
Slightly Irritating	0.5 - 2.0
Moderately Irritating	2.1 - 5.0
Severely Irritating	5.1 - 8.0

The primary irritation index is calculated using only the first four observations.

EPA Dermal Irritation Toxicity Categories

Toxicity Category	Criteria
I	Corrosive
II	Severe irritation at 72 hours
III	Moderate irritation at 72 hours
IV	Non-irritating, mild, or slight irritation at 72 hours

APPENDIX 2 Analytical Report

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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 Jeffers
Group Leader I
Analytical & Product Chemistry Department

Date