Ametryn/NOA449280

Ametryn/NOA449280 SC (A16361B) – Acute Oral Toxicity Study in Rats

Final Report

DATA REQUIREMENT(S): OECD Guidelines for Testing of Chemicals, Procedure 425
EPA Health Effects Test Guidelines, OPPTS 870.1100

AUTHOR(S): Janice O. Kuhn, PhD, DABT

STUDY COMPLETION DATE: June 22, 2009

PERFORMING LABORATORY: STILLMEADOW, Inc.
12852 Park One Drive
Sugar Land, TX 77478 USA

LABORATORY PROJECT ID: Report Number: 12821-09
Study Number: 12821-09
Task Number: T007139-06

SPONSOR: Syngenta Crop Protection, Inc.
410 Swing Road
Post Office Box 18300
Greensboro, NC 27419-8300 USA

STATEMENTS OF DATA CONFIDENTIALITY CLAIMS

This page intentionally left blank.

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, PhD, DABT
Study Director, STILLMEADOW, Inc.

22 Jan 09
Date

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

QUALITY ASSURANCE STATEMENT

Test Substance: Ametryn/NOA449280 SC (428.57/57.14)
Study Title: Ametryn/NOA449280 SC (A16361B): Acute Oral 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 13 Jan 09. 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	13 Feb 09	13 Feb 09	13 Feb 09
Observations/Body Weights	2 Apr 09	2 Apr 09	2 Apr 09
Report/Data Audit	22 Apr 09	22 Apr 09	22 Apr 09

Teresa Hughes
Quality Assurance, STILLMEADOW, Inc.

22 June 09
Date

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Title
Janice O. Kuhn, PhD, DABT	Study Director
Carol Morris, BA	Quality Control
Paul Siemens, BA	Technician
Hector Fuentes	Technician
Robert Preston	Technician
Nancy Casajuana, LAT	Technician
Connie Pavatte	Report Preparation

Study dates

Study initiation date: 2 Mar 09
Experimental start date: 24 Mar 09
Experimental termination date: 9 Apr 09

TABLE OF CONTENTS

STATEMENTS OF DATA CONFIDENTIALITY CLAIMS **2**

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT **3**

QUALITY ASSURANCE STATEMENT **4**

GENERAL INFORMATION **5**

TABLE OF CONTENTS **6**

1.0 EXECUTIVE SUMMARY **7**

2.0 INTRODUCTION **7**

3.0 MATERIALS AND METHODS **7**

3.1 Test Substance 7

3.2 Experimental Animals 8

3.3 Animal Husbandry 8

3.4 Test Substance Administration 8

3.5 In-life Observations 8

3.6 Post-mortem Observations 9

4.0 RESULTS AND DISCUSSION **9**

4.1 Mortality/Estimated Lethality Values 9

4.2 Body Weights 9

4.3 Clinical Signs 9

4.4 Necropsy Findings 9

5.0 CONCLUSIONS **9**

TABLES SECTION **10**

TABLE 1 Body Weights, Time of Death and Gross Necropsy 10

TABLE 2 Pharmacologic and/or Toxicologic Signs 11

APPENDICES SECTION **12**

APPENDIX 1 Analytical Report 12

1.0 EXECUTIVE SUMMARY

The test substance, Ametryn/NOA449280 SC (428.57/57.14) (A16361B), was evaluated for its acute oral toxicity potential in female albino rats when administered as a gavage dose at a level of 5000 mg/kg. The study was terminated following the stopping rules of this procedure. No mortality occurred during the study. Clinical signs included crusted muzzle, piloerection and alopecia around eye, which were observed in only one animal. There was no effect on body weight gain. The gross necropsy conducted at termination of the study revealed no observable abnormalities. The acute oral LD_{50} was estimated to be greater than 5000 mg/kg.

2.0 INTRODUCTION

The objective of this study was to assess the acute oral toxicity potential of the test substance when administered by gavage to rats in accordance with US EPA OPPTS 870.1100, 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. SOPs. 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 2 Mar 09, the pre-dose experimental portion began on 23 Mar 09, and the animals were treated as follows:

Dose Level (mg/kg)	Treatment		Animal Number	In-life Termination Date
	Date	Time		
5000	24 Mar 09	1013	191	7 Apr 09
5000	26 Mar 09	0918	192	9 Apr 09
5000	26 Mar 09	0918	193	9 Apr 09

3.0 MATERIALS AND METHODS

3.1 Test Substance

Reference Name:	Ametryn/NOA449280 SC (428.57/57.14)
Label Identification:	G34162/NOA449280 SC (428.57/057.14) ID 555418 A16361B
Date & Quantity Received:	16 Feb 09; 4609.9 g (GW)
Physical Description:	Tan liquid
Storage:	Room temperature
Density:	1.0968 g/mL
Purity (w/w):	38.2% Ametryn; 5.30% NOA449280
Stability:	Reassay: May 2010

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 use in an acute oral study.
Source:	Texas Animal Specialties, Humble, TX
Date Born/Date Received:	26 Jan 09 / 19 Mar 09
Quarantine Period:	5 days
Quantity & Sex:	3 females (nulliparous and non-pregnant)
Animal Identification:	Ear punch
Day -1 Wt/Day 0 (fasted) Wt:	175-201 g / 160-186 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 / 29-89% Protocol deviation: humidity was outside protocol range but did not affect study outcome.
Food:	PMI Feeds Inc.™ Formulab #5008; available *ad libitum* except for approximately 16 hours before dosing
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

The test substance was administered as received and was not diluted. An individual dose was calculated for each animal based on its fasted body weight and administered by gavage at a volume of 4.56 mL/kg. Each dose was administered using an appropriately sized syringe and stainless steel ball-tipped intubation needle. The animals were returned to their cages immediately after dosing.

3.5 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.

3.6 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 Lethality Values

There was no mortality during the study. The estimated acute oral LD_{50}, as indicated by the data, was determined to be greater than 5000 mg/kg.

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

Clinical signs are presented in Table 2. Clinical signs were observed in only one animal, and included crusted muzzle on day of dosing, piloerection on Days 0-2, and alopecia around eye on Day 13.

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, Ametryn/NOA449280 SC (428.57/57.14) (A16361B), was evaluated for its acute oral toxicity potential when administered to albino rats. The acute oral LD_{50}, as indicated by the data, is estimated to be greater than 5000 mg/kg in females.

TABLES SECTION

TABLE 1 Body Weights, Time of Death and Gross Necropsy

ACUTE ORAL TOXICITY: UP & DOWN PROCEDURE (UDP) IN RATS
Test Substance: Ametryn/NOA449280 SC (428.57/57.14)

Dose Level: 5000 mg/kg (4.56 mL/kg)

Animal Number	Dose Amt (mL)	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
			Day 0	Day 7	Final		
191	0.729	24 Mar 09	160	189	204	Day 14	NOA
192	0.793	26 Mar 09	174	206	220	Day 14	NOA
193	0.848	26 Mar 09	186	208	213	Day 14	NOA

* - Day of dosing is Day 0; Day 14 is terminal sacrifice.
NOA - No Observable Abnormalities

TABLE 2 Pharmacologic and/or Toxicologic Signs

ACUTE ORAL TOXICITY: UP & DOWN PROCEDURE (UDP) IN RATS
Test Substance: Ametryn/NOA449280 SC (428.57/57.14)

Dose Level: 5000 mg/kg (4.56 mL/kg)

		Time After Treatment																
		DAY 0			DAYS													
Animal No.	Reaction and Severity	1st	2nd	3rd	1	2	3	4	5	6	7	8	9	10	11	12	13	14
191	Red crust on muzzle	p	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Piloerection	-	-	s	s	p	-	-	-	-	-	-	-	-	-	-	-	-
	Alopecia around eye	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	p	-
192	Appeared normal at each observation.																	
193	Appeared normal at each observation.																	

v = very slight; s = slight; m = moderate; e = extreme; p = present; - = observation not present; D = death

APPENDICES SECTION

APPENDIX 1 Analytical Report

syngenta

Syngenta Crop Protection, Inc.
Technology & Projects
Analytical & Product Chemistry
Greensboro, NC 27409

Certificate of Analysis

A16361B
555418 (GP-090113)

Batch Identification	555418
Product Design Code	A16361B
Product Denomination	G34162/NOA449280 SC (428.57/057.14)
Product by Common Name	Ametryn/NOA449280 SC (428.57/057.14)
Other Product Code(s)	GP-090113
Source	Technology & Projects, Syngenta Crop Protection, Inc.
Chemical Analysis (Active Ingredient Content)	
Identity of the Active Ingredient(s)*	Confirmed
Content of Ametryn*	38.2 (%wt/wt) or 427 g/L
Content of NOA449280*	5.30 (%wt/wt) or 59.3 g/L
Methodology Used for Characterization	HPLC
The Active Ingredient(s) content is within the FAO limits.	
Physical Analysis	
Appearance*	Tan liquid
Density*	1118 g/L
Stability:	
Storage Temperature	< 30°C
Expiration date	May 2010

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:

David Stubbs
Group Leader 1
Analytical & Product Chemistry Department

Febrary 5, 2019
Date