syngenta

S-Metolachlor

S-Metolachlor EC (915) (A9558G) – Acute Oral Toxicity Study in Rats

Final Report

DATA REQUIREMENTS: EPA Health Effects Test Guidelines,
OPPTS 870.1100
OECD Guidelines for Testing of Chemicals,
Procedure 425

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STUDY COMPLETION DATE: February 15, 2008

PERFORMING LABORATORY: STILLMEADOW, Inc.
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LABORATORY PROJECT ID: Report Number: 11283-07
Study Number: 11283-07
Task Number: T001201-07

SPONSOR: Syngenta Crop Protection, Inc.
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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.

15 Feb 08
Date

Performing Laboratory: STILLMEADOW, Inc.
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QUALITY ASSURANCE STATEMENT

Test Substance: S-Metolachlor EC (915)
Study Title: S-Metolachlor EC (915) (A9558G): 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 8 Nov 07. 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	15 Oct 07	15 Oct 07	15 Oct 07
Observations/Body Wt	8 Nov 07	8 Nov 07	8 Nov 07
Observations/Body Wt/Necropsy	5 Dec 07	5 Dec 07	5 Dec 07
Report/Data Audit	4 Jan 08	4 Jan 08	4 Jan 08

Richard L. Martin

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Quality Assurance, STILLMEADOW, Inc.

15 Feb 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: 29 Oct 07
Experimental start date: 30 Oct 07
Experimental termination date: 5 Dec 07

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1.0 EXECUTIVE SUMMARY

The test substance, S-Metolachlor EC (915) (A9558G), 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. Since the test substance failed the limit test, the main test was conducted following the up-and-down procedure (UDP) at 175, 550, 1750 and 5000 mg/kg. The study was terminated following the stopping rules of this procedure. Mortality occurred only at the 5000 mg/kg level. There were no clinical signs of toxicity in survivors during the study; signs in animals that died on test included activity decrease, ataxia, body/muscle tremors, piloerection, polyuria, salivation and sensitivity to touch. There was no effect on body weight gain in survivors, with the exception of one animal that lost weight during the second week. Abnormal necropsy findings occurred only in the animals dying on test, and pertained to fur, lungs, liver and contents of the stomach/intestines. The acute oral LD_{50} was estimated to be 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 29 Oct 07, the pre-dose experimental portion began on 29 Oct 07, and the animals were treated as follows:

Dose Level (mg/kg)	Treatment		Animal Number	In-life Termination Date
	Date	Time		
5000	30 Oct 07	1045	281	31 Oct 07
175	1 Nov 07	1040	282	15 Nov 07
550	5 Nov 07	1113	283	19 Nov 07
1750	9 Nov 07	0932	284	23 Nov 07
5000	12 Nov 07	0920	285	26 Nov 07
5000	14 Nov 07	0842	286	15 Nov 07
1750	16 Nov 07	1002	287	30 Nov 07
5000	19 Nov 07	1000	288	20 Nov 07
1750	21 Nov 07	1034	289	5 Dec 07
5000	4 Dec 07	0951	290	5 Dec 07

3.0 MATERIALS AND METHODS

3.1 Test Substance

Reference Name:	S-Metolachlor EC (915)
Label Identification:	CGA77102 EC (915) & S:CGA154281 (045) ID 518570 A9558G
Date & Quantity Received:	23 Oct 07; 4689 g (Gr.Wt.)
Physical Description:	Dark brown liquid
Storage:	Room temperature
Density:	1.1004 g/mL
Purity (w/w):	81.9% S-Metolachlor; 4.24% Benoxacor
Stability:	Reassay: Oct 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:	3 & 24 Sep 07 / 25 Oct, 15 & 20 Nov 07
Quarantine Period:	5 days
Quantity & Sex:	10 females (nulliparous and non-pregnant)
Animal Identification:	Ear punch
Day -1 Wt/Day 0 (fasted) Wt:	186-229 g / 172-210 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:	18-25° C / 33-92% 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 ranging from 0.159 mL/kg at the 175 mg/kg level to 4.54 mL/kg at the 5000 mg/kg level. 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, or at the time of discovery after death.

3.6 Postmortem Observations

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

3.7 Statistical Analysis

The LD_{50} value with 95% confidence interval was calculated using the AOT425 Stat Program supplied by the EPA.

4.0 RESULTS AND DISCUSSION

4.1 Mortality/Estimated Lethality Values

Individual mortality data, including time of death, are presented in Table 1. A summary of the mortality/survival incidence is presented below.

Main Test Sequence	Animal Number	Dose (mg/kg)	Results	Main Test Sequence	Animal Number	Dose (mg/kg)	Results
1	282	175	O	6	287	1750	O
2	283	550	O	7	288	5000	X
3	284	1750	O	8	289	1750	O
4	285	5000	O	9	290	5000	X
5	286	5000	X				

X = died; O = survived; Note: Animal 281 dosed for limit test (5000 mg/kg) died.

The acute oral LD_{50} for female rats was estimated to be 5000 mg/kg, with 95% confidence interval of 2016 - 9810 mg/kg.

4.2 Body Weights

Individual body weights are presented in Table 1. Body weight gain in surviving animals was unaffected by the administration of the test substance, with the exception of one animal that lost weight between Days 7 and 14.

4.3 Clinical Signs

Clinical signs are presented in Table 2. All surviving animals appeared normal for the duration of the study. Signs in animals that died on test included activity decrease, ataxia, body/muscle tremors, piloerection, polyuria, salivation and sensitivity to touch.

4.4 Necropsy Findings

Individual necropsy findings are presented in Table 1. The gross necropsy on animals that died on test revealed crusted/stained fur; discolored lungs, liver and contents of the stomach/large intestine; and empty gastrointestinal tract. The gross necropsy on animals surviving to termination of the study revealed no observable abnormalities.

5.0 CONCLUSIONS

The test substance, S-Metolachlor EC (915) (A9558G), 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 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: S-Metolachlor EC (915)

Dose Level: 175 mg/kg (0.159 mL/kg)

Animal Number	Dose Amt (mL)	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
			Day 0	Day 7	Final		
282	0.030	1 Nov 07	187	224	233	Day 14	NOA

Dose Level: 550 mg/kg (0.500 mL/kg)

Animal Number	Dose Amt (mL)	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
			Day 0	Day 7	Final		
283	0.099	5 Nov 07	198	227	252	Day 14	NOA

Dose Level: 1750 mg/kg (1.59 mL/kg)

Animal Number	Dose Amt (mL)	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
			Day 0	Day 7	Final		
284	0.313	9 Nov 07	197	233	228	Day 14	NOA
287	0.315	16 Nov 07	198	238	248	Day 14	NOA
289	0.274	21 Nov 07	172	214	236	Day 14	NOA

Dose Level: 5000 mg/kg (4.54 mL/kg)

Animal Number	Dose Amt (mL)	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
			Day 0	Day 7	Final		
281	0.781	30 Oct 07	172	---	166	Day 1	Liver dark red; stomach full of light yellow creamy matter.
285	0.913	12 Nov 07	201	226	245	Day 14	NOA
286	0.850	14 Nov 07	187	---	178	Day 2	Crust on muzzle; abdomen stained yellow; stomach & intestines empty.
288	0.859	19 Nov 07	189	---	184	Day 1	NOA
290	0.954	4 Dec 07	210	---	202	Day 1	Crust on muzzle; lungs bright red; stomach full of creamy liquid; sm intestine empty; lg intestine full of green paste.

* - Indicates time of discovery after death (Day of dosing is Day 0; Day 14 is terminal sacrifice). If discovery was between scheduled observations, the time of death was recorded under the next scheduled observation.
NOA - No Observable Abnormalities

TABLE 2 Pharmacologic and/or Toxicologic Signs

ACUTE ORAL TOXICITY: UP & DOWN PROCEDURE (UDP) IN RATS
Test Substance: S-Metolachlor EC (915)

		Time After Treatment																
Dose Level: 175 mg/kg (0.159 mL/kg)		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
282	Appeared normal at each observation.																	
Dose Level: 550 mg/kg (0.500 mL/kg)																		
283	Appeared normal at each observation.																	
Dose Level: 1750 mg/kg (1.59 mL/kg)																		
284	Appeared normal at each observation.																	
287	Appeared normal at each observation.																	
289	Appeared normal at each observation.																	
Dose Level: 5000 mg/kg (4.54 mL/kg)																		
281	Body tremors	-	p	-														
	Salivation	-	v	v														
	Activity decrease	-	s	s														
	Piloerection	-	-	s														
	Death	-	-	-	D													
285	Appeared normal at each observation.																	
286	Salivation	-	s	v	v													
	Piloerection	-	s	s	s													
	Polyuria	-	-	s	s													
	Activity decrease	-	-	s	s													
	Death	-	-	-	-	D												
288	Piloerection	-	m	m														
	Activity decrease	-	m	m														
	Ataxia	-	-	p														
	Muscle tremors	-	-	p														
	Sensitive to touch	-	-	p														
	Death	-	-	-	D													
290	Activity decrease	s	s	s														
	Piloerection	-	-	s														
	Death	-	-	-	D													

v = very slight; s = slight; m = moderate; e = extreme; p = present; - = observation not present; D = death
Note: Time of death indicates time of discovery after death. If discovery was between scheduled observations, death is presented under next observation time.

TABLE 3 LD_{50} Analysis

ACUTE ORAL TOXICITY: UP & DOWN PROCEDURE (UDP) IN RATS
Test Substance: S-Metolachlor EC (915)

Test Type: Main Test — Limit Dose: 5000 mg/kg
Assumed LD_{50}: Default — Assumed sigma: 0.5 mg/kg

Recommended dose progression (mg/kg): 5000, 1750, 550 and 175

Test Sequence	Animal Number	Dose (mg/kg)	Short Term Results*	Long Term Results
1	282	175	O	O
2	283	550	O	O
3	284	1750	O	O
4	285	5000	O	O
5	286	5000	X	X
6	287	1750	O	O
7	288	5000	X	X
8	289	1750	O	O
9	290	5000	X	X

X = died; O = survived

Dose Recommendation: Main Test Complete

Stopping Criteria Met: LR criterion

Summary of Results

Dose	O	X	Total
175	1	0	1
550	1	0	1
1750	3	0	3
5000	1	3	4
All Doses:	6	3	9

Estimated LD_{50} = 5000 mg/kg with 95% confidence interval of 2016 – 9810 mg/kg.

Based on AOT425statpgm (Version 1.0) Test Results and Recommendations Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program
* - At ~24-48 hrs after dosing that animal or when next dose is selected.