VOLUME ___ OF ___ OF SUBMISSION

syngenta

Abamectin/Chlorantraniliprole

Abamectin/Chlorantraniliprole SC (A15894A) – Acute Oral Toxicity Study in Rats

Final Report

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

AUTHOR(S): Janice O. Kuhn, Ph.D., DABT

STUDY COMPLETION DATE: July 7, 2008

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

LABORATORY PROJECT ID: Report Number: 11627-08
Study Number: 11627-08
Task Number: T000603-07

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

VOLUME 1 OF 1 OF STUDY

STATEMENTS OF DATA CONFIDENTIALITY CLAIMS

1) *The following statement applies to submissions to regulatory agencies in the United States of America.*

STATEMENT OF NO DATA CONFIDENTIALITY CLAIM

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), (B), or (C).

Company: Syngenta Crop Protection, Inc.

Company Representative: Timothy E. Wilson, Ph.D.

Title: Regulatory Product Manager

Signature: Timothy E Wilson Date: Sept. 12, 2008

These data are the property of Syngenta Crop Protection, Inc. and, as such, are considered to be confidential for all purposes other than compliance with the regulations implementing FIFRA Section 10.

Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality which may exist under any other provision of common law or statute or in any other country.

2) *The following statement applies to submissions to regulatory agencies other than in the United States of America.*

THIS DOCUMENT CONTAINS INFORMATION CONFIDENTIAL AND TRADE SECRET TO SYNGENTA LIMITED.

It should not be disclosed in any form to an outside party, nor should information contained herein be used by a registration authority to support registration of this product or any other product without the written permission of Syngenta Limited.

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.

07 Jul 08
Date

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

Merrill Tisdel, B.S.
Representative of Submitter/Sponsor

SEPTEMBER 15 2008
Date

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

QUALITY ASSURANCE STATEMENT

Test Substance: Abamectin/Chlorantraniliprole SC (022.5/090)
Study Title: Abamectin/Chlorantraniliprole SC (A15894A): 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 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	13 Feb 08	13 Feb 08	13 Feb 08
Dosing	27 Feb 08	27 Feb 08	27 Feb 08
Observations/Body Wt/Necropsy	18 Mar 08	18 Mar 08	18 Mar 08
Report/Data Audit	9 May 08	9 May 08	9 May 08

Richard L. Martin

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

07 Jul 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
	Nancy Casajuana, L.A.T.	
Data Services:	Connie Pavatte, Report Preparation	

Study dates

Study initiation date: 25 Feb 08
Experimental start date: 26 Feb 08
Experimental termination date: 8 Apr 08

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

The test substance, Abamectin/Chlorantraniliprole SC (022.5/090) (A15894A), 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 and 1750 mg/kg. The study was terminated following the stopping rules of this procedure. No mortality or clinical signs occurred at the 175 mg/kg level. Clinical signs in one of two survivors at the 550 mg/kg level included activity decrease, body tremors, hunched posture and piloerection, which were no longer evident by Day 7. Convulsions, lateral recumbency, nasal/ocular discharge and sensitivity to touch/sound were observed only in animals that died on test. There was no effect on body weight gain in survivors. Abnormal necropsy findings occurred only in the animals dying on test, and pertained to fur, eyes, tongue, lungs, liver and contents of the gastrointestinal tract. The acute oral LD_{50} was estimated to be 550 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 25 Feb 08, the pre-dose experimental portion began on 25 Feb 08, and the animals were treated as follows:

Dose Level (mg/kg)	Treatment		Animal Number	In-life Termination Date
	Date	Time		
5000	26 Feb 08	1017	231	27 Feb 08
175	27 Feb 08	1040	232	12 Mar 08
550	4 Mar 08	0941	233	18 Mar 08
1750	5 Mar 08	0951	234	6 Mar 08
550	7 Mar 08	1040	235	13 Mar 08
1750	10 Mar 08	1001	236	12 Mar 08
550	12 Mar 08	1000	237	16 Mar 08
175	17 Mar 08	0930	238	31 Mar 08
550	19 Mar 08	0916	239	2 Apr 08
1750	4 Apr 08	0930	240	8 Apr 08

3.0 MATERIALS AND METHODS

3.1 Test Substance

Reference Name:	Abamectin/Chlorantraniliprole SC (022.5/090)
Label Identification:	MK936/SYN545170 SC (022.5/090) ID 523891 A15894A
Date & Quantity Received:	9 Jan 08; 4417 g (Gr.Wt.)
Physical Description:	White liquid
Storage:	Room temperature
Density:	1.0526 g/mL
Purity (w/w):	2.22% Abamectin; 8.44% Chlorantraniliprole
Stability:	Reassay: Jan 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 use in an acute oral study.
Source:	Texas Animal Specialties, Humble, TX
Date Born/Date Received:	24, 31 Dec 07 & 21 Jan 08 / 14, 21 Feb & 13 Mar 08
Quarantine Period:	5 days
Quantity & Sex:	10 females (nulliparous and non-pregnant)
Animal Identification:	Ear punch
Day -1 Wt/Day 0 (fasted) Wt:	195-246 g / 179-228 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:	20-25° C / 27-92% 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 0.166 mL/kg at the 175 mg/kg level to 4.75 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 Post-mortem 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. One animal (#235) was humanely sacrificed on Day 6 following observations; this animal is considered as “died on test”for result and calculation purposes. 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	232	175	O	6	237	550	X
2	233	550	O	7	238	175	O
3	234	1750	X	8	239	550	O
4	235	550	X	9	240	1750	X
5	236	1750	X				

X = died; O = survived; Note: Animal 231 dosed for limit test (5000 mg/kg) died.

The acute oral LD_{50} for female rats was estimated to be 550 mg/kg, with 95% confidence interval of 216 - 1140 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.

4.3 Clinical Signs

Clinical signs are presented in Table 2. Clinical signs in one of four survivors included activity decrease, body tremors, hunched posture and piloerection, which were no longer evident by Day 7. Convulsions, lateral recumbency, nasal/ocular discharge and sensitivity to touch/sound were observed only in animals that died on test.

4.4 Necropsy Findings

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

5.0 CONCLUSIONS

The test substance, Abamectin/Chlorantraniliprole SC (022.5/090) (A15894A), 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 550 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: Abamectin/Chlorantraniliprole SC (022.5/090)

Dose Level: 175 mg/kg (0.166 mL/kg)

Animal Number	Dose Amt (mL)	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
			Day 0	Day 7	Final		
232	0.032	27 Feb 08	195	229	238	Day 14	NOA
238	0.034	17 Mar 08	203	233	235	Day 14	NOA

Dose Level: 550 mg/kg (0.523 mL/kg)

Animal Number	Dose Amt (mL)	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
			Day 0	Day 7	Final		
233	0.094	4 Mar 08	179	206	213	Day 14	NOA
235	0.105	7 Mar 08	201	---	128	Day 6	Emaciated; red crust on muzzle; brown crust under tail; liver black; stomach & sm intestine empty; lg intestine full of green pellets.
237	0.117	12 Mar 08	224	---	164	Day 4	Brown nasal discharge; lungs bright red.
239	0.119	19 Mar 08	228	236	254	Day 14	NOA

Dose Level: 1750 mg/kg (1.66 mL/kg)

Animal Number	Dose Amt (mL)	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
			Day 0	Day 7	Final		
234	0.333	5 Mar 08	200	---	198	Day 1	Muzzle fur matted w/white discharge; brown liquid in intestines.
236	0.314	10 Mar 08	189	---	160	Day 2	Swelling around eyes; muzzle stained red; tongue protruding; stomach full of green paste; sm intestine empty; lg intestine full of green pellets.
240	0.376	4 Apr 08	226	---	189	Day 4	NOA

Dose Level: 5000 mg/kg (4.75 mL/kg)

Animal Number	Dose Amt (mL)	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
			Day 0	Day 7	Final		
231	0.964	26 Feb 08	203	---	195	Day 1	Red crust on muzzle; yellow crust on abdomen; lungs red; stomach & sm intestine full of yellow paste; lg intestine full of green paste.

* - Indicates time of discovery after death (Day of dosing is Day 0; Hr is after Day 0 dosing; 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: Abamectin/Chlorantraniliprole SC (022.5/090)

		Time After Treatment																
Dose Level: 175 mg/kg (0.166 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
232	Appeared normal at each observation.																	
238	Appeared normal at each observation.																	
Dose Level: 550 mg/kg (0.523 mL/kg)																		
233	Appeared normal at each observation.																	
235	Body tremors	-	-	m	m	e	e	e	m	e								
	Activity decrease	-	-	-	m	e	-	e	m	e								
	Piloerection	-	-	-	-	s	s	m	m	-								
	Red ocular discharge	-	-	-	-	p	p	-	-	-								
	Red nasal discharge	-	-	-	-	-	p	-	-	e								
	Emaciation	-	-	-	-	-	-	-	p	p								
	Right eye closed	-	-	-	-	-	-	-	p	-								
	Death	-	-	-	-	-	-	-	-	D*								
237	Body tremors	-	e	e	e	m	m											
	Activity decrease	-	m	m	e	m	m											
	Death	-	-	-	-	-	-	D										
239	Activity decrease	-	s	m	-	-	s	m	-	-	-	-	-	-	-	-	-	-
	Body tremors	-	-	m	m	m	m	m	-	-	-	-	-	-	-	-	-	-
	Hunched posture	-	-	-	p	p	p	-	-	-	-	-	-	-	-	-	-	-
	Piloerection	-	-	-	-	-	-	-	s	s	-	-	-	-	-	-	-	-

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

TABLE 2 Pharmacologic and/or Toxicologic Signs (Continued)

ACUTE ORAL TOXICITY: UP & DOWN PROCEDURE (UDP) IN RATS
Test Substance: Abamectin/Chlorantraniliprole SC (022.5/090)

		Time After Treatment																
Dose Level: 1750 mg/kg (1.66 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
234	Lateral recumbency	-	p	p														
	Convulsions	-	p	p														
	Activity decrease	-	e	-														
	Death	-	-	-	D													
236	Body tremors	-	-	m	m													
	Piloerection	-	-	-	m													
	Activity decrease	-	-	-	e													
	Death	-	-	-	-	D												
240	Body tremors	-	p	p	p	p	p											
	Sensitive to touch	-	p	p	p	-	-											
	Sensitive to sound	-	-	-	p	-	-											
	Piloerection	-	-	-	s	s	m											
	Activity decrease	-	-	-	-	m	e											
	Death	-	-	-	-	-	-	D										
Dose Level: 5000 mg/kg (4.75 mL/kg)																		
231	Sensitive to touch/sound	-	p	p														
	Body tremors	-	p	p														
	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: Abamectin/Chlorantraniliprole SC (022.5/090)

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

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

Test Sequence	Animal Number	Dose (mg/kg)	Short Term Results*	Long Term Results
1	232	175	O	O
2	233	550	O	O
3	234	1750	X	X
4	235	550	O	X
5	236	1750	X	X
6	237	550	X	X
7	238	175	O	O
8	239	550	O	O
9	240	1750	X	X

X = died; O = survived

Dose Recommendation: Main Test Complete

Stopping Criteria Met: LR criterion

Summary of Results

Dose	O	X	Total
175	2	0	2
550	2	2	4
1750	0	3	3
All Doses:	4	5	9

Estimated LD_{50} = 550 mg/kg with 95% confidence interval of 216 – 1140 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.

APPENDICES SECTION

APPENDIX 1 Analytical Report

syngenta

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

Certificate of Analysis

A15894A
523891 (GP-071024)

Batch Identification	523891
Product Design Code	A15894A
Product Denomination	MK936/SYN545170 SC (022.5/090)
Product by Common Name	Abamectin/Chlorantraniliprole SC (022.5/090)
Other Product Code(s)	GP-071024
Source	Technology & Projects, Syngenta Crop Protection, Inc.
Chemical Analysis (Active Ingredient Content)	
Identity of the Active Ingredient(s)*	Confirmed
Content of Abamectin*	2.22 % (wt/wt) or 23.6 g/L
Content of Chlorantraniliprole*	8.44 % (wt/wt) or 89.9 g/L
Methodology Used for Characterization	HPLC
The Active Ingredient(s) content is within the FAO limits.	
Physical Analysis	
Appearance*	white liquid
Density*	1065 g/L
Stability:	
Storage Temperature	< 30°C
Expiration date	January 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:

Donna Davis
Sr Chemist
Analytical & Product Chemistry Department

December 18, 2007
Date