VOLUME 3 OF 8 OF SUBMISSION

CGA-64250 (PROPICONAZOLE)/ASF819 (AZOXYSTROBIN) 200 SE (A13705H): FINAL REPORT

TITLE

Acute Oral Toxicity Study in Rats

DATA REQUIREMENT

OPPTS 870.1100

AUTHOR

Janice O. Kuhn, Ph. D., D.A.B.T.

COMPLETION DATE

March 7, 2003

PERFORMING LABORATORY

STILLMEADOW, Inc.
12852 Park One Drive
Sugar Land, Texas 77478

LABORATORY STUDY IDENTIFICATION

STILLMEADOW Number 7328-02
Syngenta Number 1832-02

SUBMITTER/SPONSOR

Syngenta Crop Protection, Inc.
410 Swing Road
Post Office Box 18300
Greensboro, NC 27419

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: Michele Schulz

Title: NAFTA Fungicide Team Leader

Signature: _____ Date: April 3, 2003

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

Janice O. Kuhn, Ph.D., D.A.B.T.
Study Director, STILLMEADOW, Inc.

07 Mar 03
Date

Merrill Tisdel
Representative of Submitter/Sponsor

APRIL 3 2003
Date

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QUALITY ASSURANCE STATEMENT

Test Substance: CGA-64250/Azoxystrobin 200 SE-H
Study Title: Acute Oral Toxicity Study in Rats

The study report and data have been audited in accordance with STILLMEADOW, Inc. Standard Operating Procedures (SOPs). The final report accurately reflects the study data. The findings from the inspection and audit were reported to the Study Director and Management as follows:

Study Phase Inspected	Inspection Type	Date Inspected	Reported to Study Director	Reported to Management
Protocol Review	Study-based	19 Nov 02	19 Nov 02	19 Nov 02
Necropsy	Study-based	27 Nov 02	27 Nov 02	27 Nov 02
Necropsy		17 Dec 02	17 Dec 02	17 Dec 02
Body wts & necropsy		26 Dec 02	26 Dec 02	26 Dec 02
Observations		30 Dec 02	30 Dec 02	30 Dec 02
Report/Data Audit	Study-based	3 Feb 03	4 Feb 03	4 Feb 03

B. Lynn Murphy

B. Lynn Murphy, B.S.
Quality Assurance Director, STILLMEADOW, Inc.

07Mar03
Date

SUMMARY

The test substance, CGA-64250/Azoxystrobin 200 SE-H (FL-021841), was evaluated for its acute oral toxicity potential in albino rats when administered as a gavage dose at a level of 5050 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. No mortality occurred at the 175 and 550 mg/kg levels. There were no clinical signs of toxicity in any survivors during the study. There was no effect on body weight gain in survivors. Most abnormal necropsy findings occurred only in the animals dying on test; findings pertained to fur, lungs, kidneys and contents of the gastrointestinal tract. The acute oral LD_{50} was estimated to be 1750 mg/kg.

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 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 26 November 2002, and the animals were treated as follows:

Dose (mg/kg)	Treatment		Animal Number	In-life Termination Date
	Date	Time		
5050	27 Nov 02	1018	291	27 Nov 02
175	28 Nov 02	1210	292	12 Dec 02
550	2 Dec 02	0945	293	16 Dec 02
1750	3 Dec 02	0824	294	17 Dec 02
5000	4 Dec 02	1110	295	4 Dec 02
1750	5 Dec 02	1159	3	5 Dec 02
550	11 Dec 02	0850	4	25 Dec 02
1750	12 Dec 02	0926	5	26 Dec 02
5000	13 Dec 02	0818	6	15 Dec 02
1750	16 Dec 02	0847	7	30 Dec 02
5000	18 Dec 02	0806	8	18 Dec 02

TEST SUBSTANCE

Identification:	CGA-64250/Azoxystrobin 200 SE-H FL-021841 A13705H
Date & Quantity Received:	15 Nov 02; 150 mL
Physical Description:	Cream-color liquid
Storage:	Room temperature
Density:	1.0289 g/mL
Purity:	12.0% CGA-64250; 7.16% ASF819
Stability:	Reassay: 30 Nov 03

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.

TEST SYSTEM

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 Received:	21 Nov & 5 Dec 02
Quarantine Period:	5 days
Quantity & Sex:	11 females (nulliparous and non-pregnant) were selected for testing
Group/Animal ID:	Cage cards/Ear punch
Fasted Wt on Dosing Day:	163-210 g
Date of Birth:	1 & 15 Oct 02

Animal Husbandry

Cage Type:	Suspended, wire bottom, stainless steel
Housing:	1 per cage
Environmental Controls Set to Maintain:	·Temperature Range 22°C±3° ·Humidity Range 30-70% ·12-hour light/dark cycle ·10-12 air changes/hour
Food:	PMI Feeds Inc.™ Formulab #5008; available *ad libitum* except for approximately 16 hours before dosing
Water:	Municipal water supply analyzed by TNRCC Water Utilities Division; available *ad libitum* from automatic water system.

Animal husbandry and housing at STILLMEADOW, Inc. comply with Animal Welfare Act Regulations. No contaminants were expected to have been present in the feed or water which would have interfered with or affected the results of the study.

PROCEDURES

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. 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.

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.

Postmortem Observations

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

Statistical Analysis

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

RESULTS AND DISCUSSION

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	292	175	O	6	4	550	O
2	293	550	O	7	5	1750	O
3	294	1750	O	8	6	5000	X
4	295	5000	X	9	7	1750	O
5	3	1750	X	10	8	5000	X

X = died; O = survived; Note: Animal 291 dosed for limit test (5050 mg/kg) died.

The acute oral LD_{50} for female rats was estimated to be 1750 mg/kg, with 95% confidence interval of 1239 - 4450 mg/kg.

RESULTS AND DISCUSSION (cont.)

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.

Clinical Signs

Clinical signs are presented in Table 2. All surviving animals appeared normal for the duration of the study.

Necropsy Findings

Individual necropsy findings are presented in Table 1. The gross necropsy on animals that died on test revealed crusted/wet muzzle; discolored lungs and contents of the stomach/large intestine; and empty small intestine. The gross necropsy on animals surviving to termination of the study revealed no observable abnormalities except pale kidneys in two animals.

CONCLUSION

The test substance, CGA-64250/Azoxystrobin 200 SE-H, 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 1750 mg/kg in females.

Study Director: Janice O. Kuhn, Ph.D., D.A.B.T. — Date: 07 Mar 03
Sr. Toxicologist, STILLMEADOW, Inc.

STUDY PERSONNEL

Technical Staff: Stephen Balestrier, B.S.; Paul Siemens, B.A.; Hector Fuentes; Carol Morris, B.A.; Richard Rao, B.S.; Robert Preston

Data Services: Connie Pavatte, Report Preparation

TABLE 1
ACUTE ORAL TOXICITY STUDY: UP & DOWN PROCEDURE (UDP) IN RATS
Body Weights, Time of Death, and Gross Necropsy
Test Substance: CGA-64250/Azoxystrobin 200 SE-H

Dose Level: 175 mg/kg

Animal Number	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
		Day 0	Day 7	Final		
292-F	28 Nov 02	176	215	238	Day 14	Right kidney pale.

Dose Level: 550 mg/kg

Animal Number	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
		Day 0	Day 7	Final		
293-F	2 Dec 02	204	228	242	Day 14	NOA
4-F	11 Dec 02	164	204	229	Day 14	Kidneys pale.

Dose Level: 1750 mg/kg

Animal Number	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
		Day 0	Day 7	Final		
294-F	3 Dec 02	183	219	230	Day 14	NOA
3-F	5 Dec 02	184	---	182	2 Hrs	Cream-color fluid in stomach; sm intestine empty; lg intestine full of green paste.
5-F	12 Dec 02	183	220	237	Day 14	NOA
7-F	16 Dec 02	191	193	202	Day 14	NOA

Dose Level: 5000 mg/kg

Animal Number	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
		Day 0	Day 7	Final		
295-F	4 Dec 02	182	---	181	1 Hr	Muzzle wet; white fluid in stomach; sm intestine empty; lg intestine full of green paste.
6-F	13 Dec 02	163	---	151	Day 2	White paste in stomach.
8-F	18 Dec 02	210	---	207	1 Hr	Stomach full of white fluid; sm intestine empty; lg intestine full of green paste.

Dose Level: 5050 mg/kg

Animal Number	Date of Dosing	Body Weights (g)			Time of Death*	Gross Necropsy Findings
		Day 0	Day 7	Final		
291-F	27 Nov 02	164	---	164	2 Hrs	Fur crusted at mouth; lungs mottled; stomach full of white fluid; sm intestine empty; lg intestine full of green paste.

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

TABLE 2
ACUTE ORAL TOXICITY STUDY: UP & DOWN PROCEDURE (UDP) IN RATS
Pharmacologic and/or Toxicologic Signs
Test Substance: CGA-64250/Azoxystrobin 200 SE-H

		Time After Treatment															
		HOURS			DAYS												
Animal No.	Reaction and Severity	1	2	4	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Dose Level: 175 mg/kg																		
292-F	Animal appeared normal for the duration of the study.																	
Dose Level: 550 mg/kg																		
293-F	Animal appeared normal for the duration of the study.																	
4-F*	Animal appeared normal for the duration of the study.																	
Dose Level: 1750 mg/kg																		
294-F	Animal appeared normal for the duration of the study.																	
3-F	Activity decrease	e																
	Death	-	D															
5-F	Animal appeared normal for the duration of the study.																	
7-F	Animal appeared normal for the duration of the study.																	
Dose Level: 5000 mg/kg																		
295-F	Death	D																
6-F	Activity decrease	s	-	-	-													
	Death	-	-	-	-	D												
8-F	Death	D																
Dose Level: 5050 mg/kg																		
291-F	Death	-	D															

F = Female; v = very slight; s = slight; m = moderate; e = extreme; p = present; - = observation not present; D = death; * - Day 3 obs. not recorded
Note: Digits indicate number of animals exhibiting reaction. 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 STUDY: UP & DOWN PROCEDURE (UDP) IN RATS
Test Substance: CGA-64250/Azoxystrobin 200 SE-H

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)	Results
1	292	175	O
2	293	550	O
3	294	1750	O
4	295	5000	X
5	3	1750	X
6	4	550	O
7	5	1750	O
8	6	5000	X
9	7	1750	O
10	8	5000	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	2	0	2
1750	3	1	4
5000	0	3	3
All Doses:	6	4	10

Estimated LD_{50} = 1750 mg/kg with 95% confidence interval of 1239 - 4450 mg/kg.

* - AOT425statpgm (Version 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program