Azoxystrobin/Propiconazole

Azoxystrobin/Propiconazole GR (A17869A) - Acute Oral Toxicity Up-and-Down Procedure in Rats

Final Report

DATA REQUIREMENT(S): OECD 425
EPA OPPTS 870.1100

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STUDY COMPLETION DATE: January 21, 2010

PERFORMING LABORATORY: Eurofins | Product Safety Laboratories
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LABORATORY PROJECT ID: Report Number: 28353
Study Number: 28353
Task Number: TK0001743

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

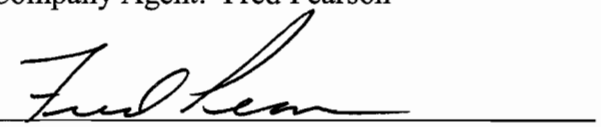
STATEMENT OF DATA CONFIDENTIALITY CLAIMS

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: Fred Pearson



U. S. Product Registration Manager

Mar 2 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 meets the requirements of 40 CFR Part 160: U.S. EPA (FIFRA) 1989, OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM (98)17, OECD, Paris, 1998 and 11-Nousan-No. 6283, 1 October, 1999: JMAFF. Specific information related to the characterization of the test substance as received and tested is the responsibility of the study Sponsor (see Test Substance section).

I, the undersigned, declare that the methods, results and data contained in this report faithfully reflect the procedures used and raw data collected during the study.

Jennifer Durando, B.S.
Study Director, Eurofins | Product Safety Laboratories

Date: 1/21/10

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Date: 3/2/10

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QUALITY ASSURANCE STATEMENT

The Eurofins | Product Safety Laboratories' Quality Assurance Unit has reviewed this final study report to assure the report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the study.

QA activities for this study:

QA Activity	Date Conducted	Date Findings Reported To Study Director And Management
Protocol review	Sept 11, 2008[1]; Jan 5, 2010	Sept 11, 2008; Jan 5, 2010
In-process inspections; *Day 2 in-life observations for Animal # 3101*	Oct 15, 2009	Jan 5, 2010
Raw data audit	Jan 5, 2010	Jan 5, 2010
Draft report review	Jan 5, 2010	Jan 5, 2010

Ilya Stolyar
Quality Assurance Auditor
Eurofins | Product Safety Laboratories

1/20/10
Date

[1] The protocol used for this study was reviewed by Quality Assurance on this date.

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Jennifer Durando, B.S.
Study Director

Study dates

Study initiation date: October 2, 2009
Experimental start date: October 13, 2009
Experimental termination date: October 28, 2009

Deviations from the Guidelines

None

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1.0 EXECUTIVE SUMMARY

An acute oral toxicity test (Up and Down Procedure) was conducted with rats to determine the potential for Azoxystrobin/Propiconazole GR (.31/.75) (A17869A) to produce toxicity from a single dose via the oral route. Under the conditions of this study, the acute oral LD_{50} of the test substance is greater than 5,000 mg/kg of body weight in female rats.

An initial limit dose of 5,000 mg/kg was administered to one healthy female rat by oral gavage. Due to the absence of mortality in this animal, two additional females were dosed simultaneously at the same dose level. Females were selected for the test because they are frequently more sensitive to the toxicity of test compounds than males. All animals were observed for mortality, signs of gross toxicity, and behavioral changes at least once daily for 14 days after dosing. Body weights were recorded prior to administration and again on Days 7 and 14 (termination) following dosing. Necropsies were performed on all animals at terminal sacrifice.

All animals survived and gained body weight during the study. Apart from ano-genital staining noted in one rat on Day 1, all animals appeared active and healthy over the observation period. There were no other signs of gross toxicity, adverse pharmacologic effects, or abnormal behavior. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

2.0 INTRODUCTION

To provide information on health hazards likely to arise from a short-term exposure to Azoxystrobin/Propiconazole GR (.31/.75) (A17869A) by the oral route.

3.0 MATERIALS AND METHODS

3.1 Test Substance

The test substance was identified as: Azoxystrobin/Propiconazole GR (.31/.75)
A17869A
Batch ID 574547

It was received on September 29, 2009 and was further identified with EPSL Reference Number 090929-5H. The test substance was stored at room temperature. Prior to use the test substance was ground in a coffee mill (Cuisinart, Model DCG #20). The ground sample was administered as a 45% w/w mixture in distilled water and kept stirring during administration. Preliminary solubility testing conducted by EPSL indicated that mixtures in excess of 45% (i.e., 50% or 60%) were too viscous to be administered properly. Documentation of the methods of synthesis, fabrication, or derivation of the test substance is retained by the Sponsor.

Characterization of the test substance was provided to Eurofins | Product Safety Laboratories by the Sponsor:

Composition (see Appendix 1): Content of Azoxystrobin 0.31 (%wt/wt)
Content of Propiconazole 0.74 (%wt/wt)

Physical Description: Brown granules

Solubility: Not provided

Stability: Test substance was expected to be stable for the duration of testing

Expiration Date: September 2012

3.2 Animals

Number of Animals: 3

Sex: Female, nulliparous and non-pregnant
.
Species/Strain: Rat/Sprague-Dawley derived, albino.

Age/Body weight: Young adult (10 weeks)/171-182 grams at experimental start.

Source: Received from Ace Animals, Inc., Boyertown, PA on September 29, 2009.

Justification of Test System and Route of Exposure: The rat was the system of choice because, historically, it has been the preferred and most commonly used species for acute oral toxicity tests. The oral route of administration was used because human exposure may occur via this route.

3.3 Husbandry

Housing: The animals were singly housed in suspended stainless steel caging with mesh floors which conform to the size recommendations in the most recent *Guide for the Care and Use of Laboratory Animals DHEW (NIH).* Litter paper was placed beneath the cage and was changed at least three times per week.

Animal Room Temperature and Relative Humidity Ranges: 19-22ºC and 34-69%, respectively.

Photoperiod: 12-hour light/dark cycle

Acclimation Period: 14 or 15 days

Food: Purina Rodent Chow #5012 was supplied *ad libitum.*

Water: Filtered tap water was supplied *ad libitum* by an automatic water dispensing system.

Contaminants: There were no known contaminants reasonably expected to be found in the food or water at levels which would have interfered with the results of this study. Analyses of the food and water are conducted regularly and the records are kept on file at Eurofins | Product Safety Laboratories.

3.4 Identification

Cage: Each cage was identified with a cage card indicating at least the study number and identification and sex of the animal.

Animal: A number was allocated to each rat on receipt and a stainless steel ear tag bearing this number was attached to the rat. This number, together with a sequential animal number assigned to study number 28353, constituted unique identification.

3.5 Selection of Animals

Prior to each dosing, experimentally naive rats were fasted overnight by removing the feed from their cages. During the fasting period, the rats were examined for health and weighed. Three healthy naive female rats (not previously tested) were selected for test.

3.6 Dose Calculations

Individual doses were calculated based on the initial body weights, taking into account the specific gravity (determined by EPSL) and concentration of the test mixture.

3.7 Dosing

The ground test substance was administered as a 45% w/w mixture in distilled water to the stomach using a stainless steel ball-tipped gavage needle attached to an appropriate syringe. Following administration, each animal was returned to its designated cage. Feed was replaced approximately 3-4 hours after test substance administration.

Individual animals were dosed as follows:

Limit Test

Dosing Sequence	Animal No.	Dose Level (mg/kg)	Short-Term Outcome	Long-Term Outcome
1	3101	5,000	S	S
2	3102		S	S
3	3103		S	S

S – Survival

3.8 Body Weights

Individual body weights of the animals were recorded prior to test substance administration (initial-Day 0) and again on Days 7 and 14 (termination) following dosing.

3.9 Cage-Side Observations

The animals were observed for mortality, signs of gross toxicity, and behavioral changes within the first several hours post-dosing and at least once daily thereafter for up to 14 days after dosing. Observations included gross evaluation of skin and fur, eyes and mucous membranes, respiratory, circulatory, autonomic and central nervous systems, somatomotor activity and behavior pattern. Particular attention was directed to observation of tremors, convulsions, salivation, diarrhea and coma.

3.10 Necropsy

All rats were euthanized via CO_2 inhalation at the end of the 14-day observation period. Gross necropsies were performed all animals. Tissues and organs of the thoracic and abdominal cavities were examined.

3.11 Study Conduct

This study was conducted at Eurofins | Product Safety Laboratories, 725 Cranbury Road, East Brunswick, NJ 08816. The study director for this study was Jennifer Durando, B.S. The primary scientist for this study was Jacek Ochalski, D.V.M., with contributions by Alicia Adamiec and Jessica Beyenhof. This study was conducted to comply with the Good Laboratory Practice (GLP) regulations as defined in:

- OECD Principles of GLP (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998
- 40 CFR 160: United States Environmental Protection Agency GLP Standards: Pesticide Programs (FIFRA) 1989
- 11-Nousan-No. 6283, 1 October, 1999: JMAFF GLP Standards

and based on the following testing guidelines:

- OECD Guidelines for Testing of Chemicals, Test No. 425
- United States Environmental Protection Agency Health Effects Test Guidelines, OPPTS 870.1100

In the opinion of the Sponsor and the Study Director, this study did not unnecessarily duplicate any previous work.

3.12 Quality Assurance

The final report was audited for agreement with the raw data records and for compliance with the protocol, Eurofins | Product Safety Laboratories Standard Operating Procedures and appropriate Good Laboratory Practice Standards. Dates of inspections and audits performed during the study and the dates of reporting of the inspection and audit findings to the Study Director and Facility Management are presented in the Quality Assurance Statement.

3.13 Amendment to Final Protocol

For clarification, the Sponsor address on the Protocol Cover Form was changed from Syngenta Crop Protection, Inc., 410 Swing Road, Greensboro, NC 27409 to Syngenta Crop Protection, Inc., 410 Swing Road, Post Office Box 18300, Greensboro, NC 27419-8300 USA.

3.14 Deviations from Final Protocol

None

3.15 Records to be Maintained

The original signed final report and an electronic copy (pdf.) of the final report, including the signed QA and GLP Compliance pages will be sent to the Sponsor. A copy of the signed report, together with the protocol (P320.UDP SYN) and all raw data generated at Eurofins | Product Safety Laboratories, is maintained in the Eurofins | Product Safety Laboratories Archives in Notebook No. 09-198: pages 1-3, 3A-10, 10A. EPSL will maintain these records for a period of at least five years. After this time, the Sponsor will be offered the opportunity to take possession of the records or may request continued archiving by EPSL.

4.0 RESULTS AND DISCUSSION

Individual body weights/weight gains and doses are presented in Table 1. Individual cage-side and necropsy observations are presented in Tables 2 and 3, respectively.

All animals survived and gained body weight during the study. Apart from ano-genital staining noted in one rat on Day 1, all animals appeared active and healthy over the observation period. There were no other signs of gross toxicity, adverse pharmacologic effects, or abnormal behavior. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

5.0 CONCLUSIONS

Under the conditions of this study, the acute oral LD_{50} of Azoxystrobin/Propiconazole GR (A17869A) is greater than 5,000 mg/kg of body weight in female rats.

TABLES SECTION

TABLE 1 Individual Body Weights/Weight Gains and Doses

Animal No.	Sex	Dose Level (mg/kg)	Body Weight (g)					Dose[1] ml
			Day 0 Weight	Day 7 Weight	Gain*	Day 14 Weight	Gain*	
3101	F	5,000	182	210	28	250	68	1.6
3102	F		180	203	23	248	68	1.6
3103	F		171	200	29	253	82	1.5

* - Body weight gain from Day 0.

[1] The ground test substance was administered as a 45% w/w mixture in distilled water. Specific Gravity – 1.227 g/ml.

TABLE 2 Individual Cage-Side Observations

Animal Number	Findings	Day of Occurrence
3101, 3102	Active and healthy	0-14
3103	Active and healthy	0 (1-5.5 hrs), 2-14
	Ano-genital staining	1

TABLE 3 Individual Necropsy Observations

Animal Number	Tissue	Findings
3101, 3102, 3103	All tissues and organs	No gross abnormalities

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis

syngenta

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

Certificate of Analysis

A17869A
574547 (GP-090842)

Batch Identification	574547
Product Design Code	A17869A
Product Denomination	IC15504/CGA64250 GR (.31/.75)
Product by Common Name	Azoxystrobin/ Propiconazole GR (.31/.75)
Other Product Code(s)	GP-090842
Source	Technology & Projects, Syngenta Crop Protection, Inc.
Chemical Analysis (Active Ingredient Content)	
Identity of the Active Ingredient(s)*	Confirmed
Content of Azoxystrobin*	**0.31** (%wt/wt)
Content of Propiconazole*	**0.74** (%wt/wt)
Methodology Used for Characterization	HPLC
The Active Ingredient(s) content is within the FAO limits.	
Physical Analysis	
Appearance*	brown granules
Stability:	
Storage Temperature	< 30°C
Expiration date	September **2012**

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

Sept. 9, 2009
Date