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PROFENOFOS TECHNICAL: ACUTE ORAL TOXICITY UP AND DOWN PROCEDURE IN RATS

FINAL REPORT

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

AUTHOR: Jennifer Durando, B.S.

STUDY COMPLETION DATE: November 30, 2005

PERFORMING LABORATORY: Product Safety Laboratories
2394 Highway 130
Dayton, NJ 08810

LABORATORY PROJECT ID: PSL Study Number 18537
Syngenta Number T018339-04

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

STATEMENTS OF DATA CONFIDENTIALITY CLAIM

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: Carolyn Brinkley

Title: Senior Regulatory Product Manager

Signature: Carolyn Brinkley Date: Dec. 9, 2005

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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.*

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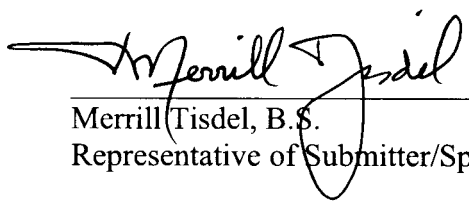
GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

The Good Laboratory Practice Compliance Statement as defined by 40 CFR Part 160, found on page 5 of this volume and signed by the Study Director, is truthful and accurate.



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

DECEMBER 9 2005
Date

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study meets the requirements of 40 CFR Part 160: U.S. EPA (FIFRA), 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 with the following exception: The stability, characterization, identity and verification of the test substance concentration as received and tested are the responsibility of the study Sponsor.

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 11/30/03

Jennifer Durando, B.S. Date
Study Director, Product Safety Laboratories

Performing Laboratory: Product Safety Laboratories
2394 Highway 130
Dayton, NJ 08810

QUALITY ASSURANCE STATEMENT

The Product Safety Laboratories' Quality Assurance Unit reviewed this study for adherence to PSL's Standard Operating Procedures, the study protocol, and all applicable GLP standards. This final report was found to be an accurate representation of the work conducted. Records of QA findings are kept on file. The summary below provides verification of statements made in the final report section that addresses Quality Assurance audits.

QA activities for this study:

QA Activity	Date Conducted	Date Findings Reported To Study Director And Management
Protocol review	9/27/05[1]; 11/23/05	9/27/05; 11/23/05
In-process inspection; *One hour in-life observations for Animal #6108*	10/28/05	11/23/05
Raw data audit	11/23/05	11/23/05
Draft report review	11/23/05	11/23/05
Final report review	11/30/05	11/30/05

Annamarie LaPorte
Quality Assurance Auditor
Product Safety Laboratories

[1] PSL's "generic" protocol used for this study was reviewed by the Quality Assurance group 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 26, 2005
Experimental start date: October 27, 2005
Experimental termination date: November 18, 2005

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 Profenofos Technical 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 estimated to be 620.5 mg/kg of body weight in female rats with an approximate 95% Confidence Interval of 350 mg/kg (lower) to 1,100 mg/kg (upper).

Based on an estimate of the LD_{50} supplied by the Sponsor (1,100 mg/kg), an initial dose of 350 mg/kg was administered to one healthy female rat by oral gavage. Following the Up and Down procedure, five additional females were tested at levels of 350 or 1,100 mg/kg. 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 or until death occurred. Body weights were recorded prior to administration and again on Days 7 and 14 (termination) following dosing or after death. Necropsies were performed on all animals.

2.0 INTRODUCTION

To provide information on health hazards likely to arise from a short-term exposure to Profenofos Technical by the oral route.

3.0 MATERIALS AND METHODS

3.1 Test substance

The test substance was identified as: Profenofos Technical
Batch ID PO3

It was received on October 18, 2005 and was further identified with PSL Reference Number 051018-4H. The test substance was a light brown liquid and was stored refrigerated. The sample was administered as received. Documentation of the methods of synthesis, fabrication, or derivation of the test substance is retained by the Sponsor.

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

Purity: Chlorobenzene (<= 2%)
Profenofos (89.0%)

pH: 4.2 (in deionized H_2O @ 68ºF)

Solubility: Completely miscible in water, methanol, ethanol and acetone

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

Re-Assay Date: September 2007

3.2 Animals

Number of Animals: 6

Sex: Female, nulliparous and non-pregnant.

Species/Strain: Rat/Sprague-Dawley derived, albino.

Age/Body weight: Young adult (10-12 weeks)/185-225 grams at experimental start.

Source: Received from Ace Animals, Inc., Boyertown, PA on October 11, 2005.

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 Range: 19-21ºC

Photoperiod: 12-hour light/dark cycle

Acclimation Period: 16-27 days

Food: Purina Rodent Chow #5012

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 at least once a year and the records are kept on file at 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 18537, 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. Six healthy female rats 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 PSL) of the test substance.

3.7 Dosing

The test substance was administered 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:

Main Test

Dosing Sequence	Animal No.	Dose Level (mg/kg)	Short-Term Outcome	Long-Term Outcome
1	6099	350	S	S
2	6108	1,100	D	D
3	6220	350	S	S
4	6261	1,100	D	D
5	6372	350	S	S
6	6384	1,100	D	D

S – Survival D – Death

The test substance was administered in sequence to the animals as described above. The decision to proceed with the next animal was based on the survival of the previous animal following dosing. Dose progressions and stopping criteria were determined using the statistical program described in Section 3.11.

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 or after death.

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 or until death occurred. 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

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

3.11 Statistical Analysis

The *Acute Oral Toxicity (Guideline 425) Statistical Program* (Weststat, version 1.0, May 2001) was used for all data analyses including: dose progression selections, stopping criteria determinations and/or LD_{50} and confidence limit calculations.

3.12 Study Conduct

This study was conducted at Product Safety Laboratories, 725 Cranbury Road, East Brunswick, NJ 08816. The primary scientist for this study was Jacek Ochalski, D.V.M. This study was conducted to comply with the Good Laboratory Practice (GLP) regulations as defined in:

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

and in accordance with:

- U.S. EPA Health Effects Test Guidelines, OPPTS 870.1100 (2002)
- OECD Guidelines for Testing of Chemicals, Procedure 425 (2001)

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

3.13 Quality Assurance

The final report was audited for agreement with the raw data records and for compliance with the protocol, 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.

3.14 Amendments To Final Protocol

None

3.15 Deviations From Final Protocol

None.

3.16 Records To Be Maintained

A copy of this signed report, together with the protocol (P320.UDP) and all raw data generated at Product Safety Laboratories, is maintained in the Product Safety Laboratories Archives in Notebook No. 05-100: pages 67-80. PSL 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 will be charged an archiving fee for continued archiving by PSL.

4.0 RESULTS AND DISCUSSION

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

350 mg/kg (3 animals)

All animals survived, appeared active and healthy and gained body weight over the 14-day observation period. There were no signs of gross toxicity, adverse pharmacologic effect or abnormal behavior. No gross abnormalities were noted for either animal when necropsied following the 14-day observation period.

1,100 mg/kg (3 animals)

All animals died within two days of test substance administration. Toxic signs noted prior to death included ocular discharge, hypoactivity, abnormal posture, piloerection, ano-genital staining and a reduced fecal volume. Gross necropsy of the decedents revealed discoloration of the intestines.

5.0 CONCLUSIONS

Under the conditions of this study, the acute oral LD_{50} of Profenofos Technical is estimated to be 620.5 mg/kg of body weight in female rats with an approximate 95% Confidence Interval of 350 mg/kg (lower) to 1,100 mg/kg (upper).

TABLES SECTION

TABLE 1: INDIVIDUAL BODY WEIGHTS/WEIGHT GAINS, DOSES, AND MORTALITIES

Animal No.	Sex	Dose Level (mg/kg)	Body Weight (g)					Dose[1] ml	Mortality	
			Day 0 Weight	Day 7 Weight	Gain*	Day 14 Weight	Gain*		Day	Weight (g)
6099	F	350	200	218	18	247	47	0.048	E	-
6220	F		215	227	12	249	34	0.052	E	-
6372	F		223	234	11	282	59	0.054	E	-
6108	F	1,100	185	-	-	-	-	0.14	1	176
6261	F		219	-	-	-	-	0.16	2	201
6384	F		225	-	-	-	-	0.17	1	219

* - Body weight gain from Day 0.
E - Euthanized via CO_2 inhalation after weighing on Day 14

[1] The test substance was administered as received. Specific Gravity – 1.487 g/ml.

TABLE 2: INDIVIDUAL CAGE-SIDE OBSERVATIONS

Animal Number	Findings	Day of Occurrence
350 mg/kg		
6099, 6220, 6372	Active and healthy	0-14
1,100 mg/kg		
6108	Active and healthy	0 (1 hr)
	Hypoactive	0 (3-6 hrs)
	Ocular discharge (clear), hunched posture	0 (6 hrs)
	Dead	1
6261	Active and healthy	0 (1 hr)
	Hypoactive	0 (3 hrs)-1
	Ano-genital staining, reduced fecal volume	1
	Prone posture	1
	Dead	2
6384	Active and healthy	0 (1 hr)
	Hypoactive	0 (3-7 hrs)
	Hunched posture, piloerection	0 (7 hrs)
	Dead	1

TABLE 3: INDIVIDUAL NECROPSY OBSERVATIONS

Animal Number	Tissue	Findings
350 mg/kg		
6099, 6220, 6372	All tissues and organs	No gross abnormalities
1,100 mg/kg		
6108, 6261, 6384	Intestines	Red