VOLUME ___ OF ___ OF SUBMISSION

CYROMAZINE TECHNICAL (CGA72662) : FINAL REPORT

TITLE

Acute Oral Toxicity Up And Down Procedure In Rats with Cyromazine Technical (CGA72662)

DATA REQUIREMENT

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

AUTHOR

Daniel J. Merkel, B.S.

COMPLETION DATE

November 29, 2004

PERFORMING LABORATORY

Product Safety Laboratories
2394 Highway 130
Dayton, NJ 08810

LABORATORY STUDY IDENTIFICATION

PSL Study Number 15876
Syngenta Number T005341-03

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: John Hott, Ph.D.

Title: Senior Regulatory Product Manager

Signature: DAN CAMPBELL FOR JOHN HOTT Date: 12/10/04

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 STATEMENT

Cyromazine Technical

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 59 NohSan No. 3850, August 10, 1984: 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.

Study Director:

Daniel J. Merkel, B.S.
Product Safety Laboratories

11/29/04
Date

Submitter/Sponsor:

Merrill Tisdel
Submitter/Sponsor Representative
Syngenta Crop Protection, Inc.
410 Swing Road
Post Office Box 18300
Greensboro, NC 27419

DEC 1 2004
Date

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	1/26/04[1]; 10/26/04	1/26/04; 10/26/04
In-process inspection; *Day 2 in-life observations*	9/10/04	10/26/04
Raw data audit	10/26/04	10/26/04
Draft report review	10/26/04	10/26/04
Final report review	11/23/04	11/23/04

Louise N. Caruso, B.S.
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.

SIGNATURES

Cyromazine Technical

We, 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.

Daniel J. Merkel, B.S.
Study Director
Product Safety Laboratories

Date 11/29/04

Gary Wnorowski, B.A., M.B.A.
President
Product Safety Laboratories

Date 11/23/04

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ACUTE ORAL TOXICITY UP AND DOWN PROCEDURE IN RATS

PROTOCOL NO.:	P320.UDP
AGENCY:	EPA (FIFRA), OECD and JMAFF
STUDY NUMBER:	15876
SPONSOR:	SYNGENTA CROP PROTECTION, INC. 410 Swing Road Greensboro, NC 27419
TEST SUBSTANCE IDENTIFICATION:	Cyromazine Technical (CGA72662) FL-041054 SCW4C17109
TEST SUBSTANCE DESCRIPTION:	White to light beige crystalline powder
DATE RECEIVED:	August 19, 2004
PSL REFERENCE NO.:	040819-3H
STUDY INITIATION DATE:	August 23, 2004
DATES OF TEST:	September 2-24, 2004
NOTEBOOK NO.:	04-61: pages 137-148

1.0 PURPOSE

To provide information on health hazards likely to arise from a short-term exposure to Cyromazine Technical (CGA72662) by the oral route.

2.0 SUMMARY

An acute oral toxicity test (Up and Down Procedure) was conducted with rats to determine the potential for Cyromazine 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 greater than 2,000 milligrams per kilogram of body weight in female rats.

An initial limit dose of two thousand milligrams of the test substance per kilogram of body weight was administered to one healthy female rat by oral gavage. Due to the absence of mortality in this animal, four additional females were dosed in sequence 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 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.

One animal died following test substance administration. Toxic signs noted prior to death included hypoactivity and ano-genital staining. Apart from ano-genital staining and soft feces noted for one surviving animal on Day 1, all survivors appeared active and healthy during the study and gained body weight over the 14-day observation period. Gross necropsy of the decedent revealed discoloration of the intestines. No gross abnormalities were noted for the euthanized animals necropsied at the conclusion of the 14-day observation period.

3.0 MATERIALS

3.1 Test Substance

The test substance was identified as: Cyromazine Technical (CGA72662)
FL-041054
SCW4C17109

It was received on August 19, 2004 and was further identified with PSL Reference Number 040819-3H. The test substance was a white to light beige crystalline powder and was stored at room temperature. The sample was administered as a 40% w/w suspension in a 1% w/w solution of carboxymethylcellulose (CMC) in distilled water mixed throughly with a homogenizer (Biospec Product Inc., Model 985370). Preliminary solubility tesing conducted by PSL indicated that the sample was not soluble in distilled water and suspensions in CMC in excess of 40% (i.e. 45% or 50%) 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 Product Safety Laboratories by the Sponsor was:

Purity: Cyromazine Technical – 97.2% (wt/wt)

Solubility: Soluble in water

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

Re-Assay Date: July, 2007

3.2 Animals

1. Number of Animals: 5
2. Sex: Females, nulliparous and non-pregnant.
3. Species/Strain: Rat/Sprague-Dawley derived, albino.

4. Age/Body weight: Young adult (9-11 weeks)/176-212 grams at experimental start.
5. Source: Received from Ace Animals, Inc., Boyertown, PA on August 24, 2004.
6. 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.

4.0 METHODS

4.1 Husbandry

1. 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.
2. Animal Room: Temperature Range: 19-25ºC
3. Photoperiod: 12-hour light/dark cycle
4. Acclimation Period: 9-20 days
5. Food: Purina Rodent Chow #5012
6. Water: Filtered tap water was supplied *ad-libitum* by an automatic water dispensing system.
7. 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.

4.2 Identification:

1. Cage: Each cage was identified with a cage card indicating at least the study number and identification and sex of the animal.
2. 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 15876, constituted unique identification.

5.0 PROCEDURE

5.1 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. Five healthy female rats were selected for test.

5.2 Dose Calculations

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

5.3 Dosing

The test substance was administered as a 40% w/w suspension in a 1% w/w solution of CMC in distilled water 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:

Dosing Sequence	Animal No.	Dose Level (mg/kg)	Short-Term Outcome	Long-Term Outcome
1	6874	2,000	S	S
2	6885	2,000	S	S
3	6911	2,000	S	S
4	6997	2,000	S	S
5	7002	2,000	D	D

S – Survival D-Death

The animals were dosed in sequence as described above.

5.4 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.

5.5 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 to14 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.

5.6 Necropsy

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

6.0 STUDY CONDUCT

This study was conducted at Product Safety Laboratories, 725 Cranbury Road, East Brunswick, NJ 08816. The primary technician 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)
- OECD Principles of GLP (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998
- 59 NohSan No. 3850, August 10, 1984: 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

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

7.0 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.

8.0 AMENDMENT TO FINAL PROTOCOL

None

9.0 DEVIATIONS FROM FINAL PROTOCOL

None.

10.0 RECORDS TO BE MAINTAINED

A copy of this signed report, together with the protocol and all raw data generated at Product Safety Laboratories, is maintained in the Product Safety Laboratories Archives. 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.

11.0 RESULTS

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

One animal died following test substance administration. Toxic signs noted prior to death included hypoactivity and ano-genital staining. Apart from ano-genital staining and soft feces noted for one surviving animal on Day 1, all survivors appeared active and healthy during the study and gained body weight over the 14-day observation period. Gross necropsy of the decedent revealed discoloration of the intestines. No gross abnormalities were noted for the euthanized animals necropsied at the conclusion of the 14-day observation period.

12.0 CONCLUSION

Under the conditions of this study, the acute oral LD_{50} of Cyromazine Technical (CGA72662) is greater than 2,000 milligrams per kilogram of body weight in female rats.

13.0 TABLES

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)
6874	F	2,000	176	198	22	244	68	0.80	E	-
6885	F		189	206	17	249	60	0.86	E	-
6911	F		212	233	21	263	51	0.96	E	-
6997	F		197	221	24	252	55	0.90	E	-
7002	F		196	-	-	-	-	0.89	1	188

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

[1] Administered as a 40% w/w suspension in a 1% w/w solution of CMC in distilled water. Specific Gravity – 1.100 g/ml.

TABLE 2: INDIVIDUAL CAGE-SIDE OBSERVATIONS

Animal Number	Findings	Day of Occurrence
FEMALES		
6874, 6885, 6997	Active and healthy	0-14
6911	Active and healthy	0 (1-5 hrs), 2-14
	Ano-genital staining, soft feces	1
7002	Active and healthy	0 (1 hr)
	Ano-genital staining	0 (3-4 hrs)
	Hypoactive	0 (4 hrs)
	Dead	1

TABLE 3: INDIVIDUAL NECROPSY OBSERVATIONS

Animal Number	Tissue	Findings
FEMALES		
6874, 6885, 6911, 6997	All tissues and organs	No gross abnormalities
7002	Intestines	Red

CERTIFICATE OF ANALYSIS

syngenta

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

Certificate of Analysis

CYROMAZINE TECHNICAL

FL041054

Batch Identification	FL041054
Product Design Code	CGA72662
Product Common Name	Cyromazine
Source	Specialtychem Products Marinette, WI
Other ID	SCW4C17109

Chemical Analysis
(Active Ingredient Content)

Identity of the Active Ingredient(s)	confirmed
Content of Cyromazine Technical	97.2% (wt/wt)

Methodology used for Characterization HPLC
The Active Ingredient(s) content is within the FAO limits.

Physical Analysis

- Appearance: White powder

Stability:

- Storage Temperature: <30°C
- Expiration date: July 2007

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 which originate either from a single study or from several individual studies which have 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. No GLP compliance is claimed for this certificate.

Authorization:

Rene V. Arenas — July 30, 2004

Rene Arenas
Team Leader
Analytical & Product Chemistry Department

Date