Pinoxaden/Cloquintocet-Mexyl

Pinoxaden/Cloquintocet-Mexyl EC (A13617AV) - Acute Dermal Toxicity Study in Rats

Final Report

DATA REQUIREMENT(S): OECD [Section 4, Number 402]
EPA [OPPTS 870.1200]
Commission Regulation (EC) No 440/2008

AUTHOR(S): Dr. M. Mallaun

STUDY COMPLETION DATE: 06-Oct-2010

PERFORMING LABORATORY: Harlan Laboratories Ltd.
Wölferstrasse 4
4414 Füllinsdorf / Switzerland

LABORATORY PROJECT ID: Report Number: C97193
Study Number: C97193
Task Number: TK0028295

SPONSOR(S): Syngenta Ltd.
Jealott's Hill International Research Centre
Bracknell, Berkshire, RG42 6EY / United Kingdom

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

This page is intentionally left blank.

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study has been performed in compliance with the Swiss Ordinance relating to Good Laboratory Practice, adopted May 18, 2005 [SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted November 26, 1997 by decision of the OECD Council [C(97)186/Final].

These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), and Japan (MHLW, MAFF and METI).

There were no circumstances that may have affected the quality or integrity of the data.

Dr. M. Mallaun
Study Director
Acute Toxicology

06-Oct-2010
Date

Performing Laboratory:

Harlan Laboratories Ltd.,
Wölferstrasse 4
4414 Füllinsdorf / Switzerland

FLAGGING STATEMENT

This page is intentionally left blank.

QUALITY ASSURANCE STATEMENT

Harlan Laboratories Ltd., Zelgliweg 1, 4452 Itingen / Switzerland

Harlan Laboratories Study:	C97193
Syngenta Task No:	TK0028295
Test Item:	Pinoxaden/Cloquintocet-Mexyl EC (A13617AV)
Study Director:	Dr. M. Mallaun
Study Title:	Pinoxaden/Cloquintocet-Mexyl EC (A13617AV) - Acute Dermal Toxicity Study in Rats

The general facilities and activities are inspected at least once a year and the results are reported to the responsible person and the management.

Study procedures were periodically audited. The study plan and this report were audited by the Quality Assurance. The dates are given below.

Dates and Types of QA Inspections		**Dates of Reports to the Study Director and Test Facility Management**
27-Jul-2010	Study Plan	27-Jul-2010
03-Aug-2010	Process based (Test System, Test Item, Treatment)	03-Aug-2010
02-Sep-2010	Report	02-Sep-2010

This statement also confirms that this final report reflects the raw data.

Quality Assurance: for K. Bezares

.....

Date: 06-Oct-2010

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function
Dr. M. Mallaun	Study Director
G. Arcelin	Deputy Study Director
T. Fink	Manager Quality Assurance
E. Yau	Syngenta Study Manager

Study dates

Experimental starting date:	29 July 2010
Experimental completion date:	19 August 2010
Delivery of animals:	06 July 2010 (5 males) 29 July 2010 (5 females)
Acclimatization:	29 July 2010 to 02 August 2010 (one male, one female) 29 July 2010 to 04 August 2010 (four males, four females)
Treatment:	03 August 2010 (one male, one female) 05 August 2010 (four males, four females)
Observation after Treatment:	03 August 2010 to 17 August 2010 (one male, one female) 05 August 2010 to 19 August 2010 (four males, four females)

Deviations from Study Plan

The body weights of all the males rats were higher than the study plan stated (200g ± 20%).

Since the test item was dosed with respect to the body weight, this had no impact on the outcome of the study.

Retention of samples

See below under Other.

Performing laboratory test substance reference number

234351/A

Other

Harlan Laboratories Ltd. (4452 Itingen / Switzerland) will retain the study plan, all raw data, a sample of the test item and the final report of the present study for at least ten years. No data will be discarded without the Sponsor's written consent.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

1.1 Study Design

A group of one male and one female and a second group of four male and four female RccHan:WIST (SPF) rats were treated with Pinoxaden/Cloquintocet-Mexyl EC (A13617AV) at 2000 mg/kg by dermal application. The test item was applied as delivered by the Sponsor. The application period was 24 hours.

The animals were examined daily during the acclimatization period and mortality, viability and clinical signs were recorded. All animals were examined for clinical signs prior to treatment, once during the first 30 minutes after application and at approximately 1, 2, 3 and 5 hours after treatment on day 1 and once daily during test days 2 to 15. Local signs were noted once daily from test day 2 to 15. Mortality/viability was recorded prior to treatment, once during the first 30 minutes after application and at approximately 1, 2, 3 and 5 hours after administration on test day 1 (with the clinical signs) and twice daily during days 2 to 15. Body weights were recorded on day 1 (prior to administration) and on days 8 and 15. All animals were examined macroscopically at the end of the study.

1.2 Results

No deaths occurred during the course of the study.

Slight to moderate erythema was observed on the treated skin of all animals on test day 2 or 3 until test day 5 or 7. Slight to moderate desquamation was also observed on all animals from test day 3, 6 or 7 until either test day 14 or 15. No other dermal or clinical signs were recorded throughout the observation period.

The body weights were within the range commonly recorded for this strain and age.

No macroscopic findings were observed at necropsy.

1.3 Conclusion

The median lethal dose, LD_{50}, of Pinoxaden/Cloquintocet-Mexyl EC (A13617AV) after single dermal administration to rats of both sexes, observed over a period of 14 days, is:

LD_{50} (rat): greater than 2000 mg/kg body weight

2.0 INTRODUCTION

2.1 Purpose

The purpose of this study was to assess the acute dermal toxicity of Pinoxaden/Cloquintocet-Mexyl EC (A13617AV) when administered to rats by a single semi-occlusive dermal application, followed by an observation period of 14 days.

This study should provide a rational basis for hazard classification.

2.2 Guidelines

The study was done according to the following guidelines:

OECD Guidelines for Testing of Chemicals, Section 4, Number 402 "Acute Dermal Toxicity", adopted February 24, 1987.

United States Environmental Protection Agency, Health Effects Test Guidelines, OPPTS 870.1200 Acute Dermal Toxicity EPA 712-C-98-192, August 1998.

Commission Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), B.3. Acute toxicity (dermal) (Official Journal No L 142, 31/05/2008 p. 0178-0181).

2.3 Test Facility

This study was performed in an AAALAC-accredited laboratory in accordance with the Swiss Animal Protection Law under license no. 31.

3.0 MATERIALS AND METHODS

3.1 Test Substance

The following information was provided by the Sponsor:

Identification:	Pinoxaden/Cloquintocet-Mexyl EC (A13617AV)
Description:	Light yellow liquid
Batch Number:	SMU0EP001
Purity:	Content of pinoxaden: 5.14 % w/w corresponding to 49.7 g/L Content of cloquintocet-mexyl: 1.34 % w/w corresponding to 13.0 g/L Content of water: 0.24 % w/w
Density:	967 kg/m^3
Stability of Test Item:	Stable under specified storage conditions.
Reanalysis Date:	30-Nov-2012
Storage Conditions (as stated by the Sponsor):	At a temperature < 30°C, light protected.
Storage Conditions (as handled by Harlan Laboratories):	At room temperature (range of 20 ± 5 °C, provided by Harlan Laboratories Ltd.), light protected.
Safety Precautions:	Routine hygienic procedures were used to ensure the health and safety of the personnel.

The certificate of analysis is attached in Appendix 1.

3.2 Experimental Design

One day before treatment, the backs of the animals were clipped with an electric clipper, exposing an area of approximately 10% of the total body surface.

Only those animals without injury or irritation on the skin were used in the test.

The test item was administered undiluted, with respect to the density.
The application volume was 2.068 mL/kg (x 967 mg/mL = 2000 mg/kg).

On test day 1, the amount of test item was calculated for each animal on the basis of its body weight. The appropriate amount was weighed on a suitable precision balance into a plastic weighing boat. The test item was put on a surgical gauze patch. This gauze patch was applied to the intact skin of the clipped area. The patch was covered with a semi-occlusive dressing. The dressing was wrapped around the abdomen and anchored with tape.

Twenty-four hours after the application the dressing was removed and the skin was flushed with lukewarm tap water and dried with disposable paper towels. Thereafter, the reaction sites were assessed.

A single animal of each sex was treated first. Since no deaths, no severe local effects and no severe systemic symptoms were observed after the 24-hour exposure, the test was completed using the remaining four male and four female animals for an exposure period of 24 hours.

Rationale: Dermal administration was used as this is one possible route of human exposure during manufacture, handling and use of the test item.

Viability/mortality was recorded daily during the acclimatization period, prior to treatment, during the first 30 minutes and at approximately 1, 2, 3 and 5 hours after administration on test day 1 (with the clinical signs) and twice daily during days 2 to15.

Clinical signs were recorded daily during the acclimatization period, prior to treatment, during the first 30 minutes and at approximately 1, 2, 3 and 5 hours after administration on test day 1. Once daily during days 2 to15. All abnormalities were recorded.

Local dermal signs were recorded once daily from test days 2 to 15. The skin reactions were assessed according to the numerical scoring system listed in the Commission Regulation (EC) No 440/2008 B.4 (see Appendix 3).

The body weights were recorded on test days 1 (prior to administration), 8 and 15.

3.2.1 Animals

Animal Species and Strain:	Rat, RccHan:WIST (SPF)
Rationale:	Recognized by international guidelines as a recommended test system.
Breeder/Supplier:	Harlan Laboratories B.V. Kreuzelweg 53 5961 NM Horst / The Netherlands
Number of Animals per Group:	Group 1: 1 male and 1 female Group 2: 4 males and 4 females
Total Number of Animals:	5 males and 5 females (nulliparous and non-pregnant)
Age (when treated):	Males: 10 weeks Females: 10 weeks
Body Weight Range (when treated):	Males: 272.8 g – 300.8 g Females: 174.6 g – 199.8 g
Identification:	Unique cage number and corresponding color-coded spots on the tail. The animals were marked at acclimatization start.

Randomization:	Randomly selected by hand at time of delivery.
Acclimatization:	Under laboratory conditions. 5 days (one male and one female) or 7 days (four males and four females), after health examination. Only animals without any visible signs of illness were used for the study.

3.2.2 Husbandry

Room Number:	0105 / Harlan Laboratories Ltd., Füllinsdorf
Conditions:	Standard Laboratory Conditions. Air-conditioned with 10-15 air changes per hour, and continuously monitored environment with a room temperature of 22 ± 3 °C and a relative humidity between 30-70%, automatically controlled light cycle of 12 hours light and 12 hours dark and music played during the daytime light period.
Accommodation:	During acclimatization in groups of five per sex in Makrolon type-4 cages with standard softwood bedding. Individually in Makrolon type-3 cages with standard softwood bedding ('Lignocel' J. Rettenmaier&Söhne GmbH&CoKG, 73494 Rosenberg / Germany, imported by Provimi Kliba AG, 4303 Kaiseraugst / Switzerland) during treatment and observation. Accomodation included paper enrichment (batch no. -67, Enviro-dri from Lillico, Biotechnology, Surrey, UK).
Diet:	Pelleted Teklad Rat-Mouse Diet 2914C diet, batch no. 30/10 (provided by Provimi Kliba AG, 4303 Kaiseraugst / Switzerland) *ad libitum*. Results of analyses for contaminants are archived at Harlan Laboratories Ltd.
Water:	Community tap water from Füllinsdorf *ad libitum*. Results of bacteriological, chemical and contaminant analyses are archived at Harlan Laboratories Ltd.

3.3 *Post Mortem* Investigations

All animals were killed at the end of the observation period by carbon dioxide asphyxiation and discarded after macroscopic examinations were performed. An external examination and opening of the abdominal and thoracic cavities for examinations of major organs were performed. The appearance of any macroscopic abnormalities was recorded. No organs or tissues were retained.

3.4 Data Evaluation

Viability/mortality was recorded on data sheets.

Body weights were recorded on-line by the ToxControl Computer System.

Clinical signs, local dermal signs and macroscopic findings were compiled into the ToxControl Computer System during recording.

The ToxControl Computer System has been licensed for Harlan Laboratories and validated with respect to data acquisition, storage and retrievability.

4.0 RESULTS AND DISCUSSION

Individual viability/mortality data, clinical signs, local dermal signs, body weights and necropsy results are presented in Table 1, Table 2, Table 3, Table 4 and Table 5, respectively.

4.1 Mortality

No intercurrent deaths occurred during the course of the study.

4.2 Clinical Signs / Local Dermal Signs

Slight to moderate erythema was observed on the treated skin of all animals on test day 2 or 3 until test day 5 or 7. Slight to moderate desquamation was also observed on all animals from test day 3, 6 or 7 until either test day 14 or 15. No other dermal or clinical signs were recorded throughout the observation period.

4.3 Body Weights

The body weights were within the range commonly recorded for this strain and age.

4.4 Macroscopic Findings

No macroscopic findings were recorded at necropsy.

5.0 CONCLUSIONS

The median lethal dose, LD_{50}, of Pinoxaden/Cloquintocet-Mexyl EC (A13617AV) after single dermal administration to rats of both sexes, observed over a period of 14 days post treatment days, is:

LD_{50} (rat): greater than 2000 mg/kg body weight

6.0 REFERENCES

Literature references listed are available upon request.

External references

Commission Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), B.3. Acute toxicity (dermal) (Official Journal No L 142, 31/05/2008 p. 0178-0181).

TABLES SECTION

TABLE 1 Individual Findings – Mortality

MORTALITY DATA
ALL NECROPSIES
MALES

Group 1 (2000 mg/kg)

Acclimatization (Days 1 to 7)

No mortality data recorded

Treatment (Days 1 to 15)

ANIMAL	DEATH DATE	DAY	P	K	S	O	COMMENT
1	17-AUG-10	15	X				
		Total:	1	0	0	0	

P = PLANNED NECROPSY , K = KILLED IN EXTR. , S = SPONTAN. DEATH , O = OTHER

TABLE 1 Individual Findings – Mortality (Continued)

MORTALITY DATA
ALL NECROPSIES
MALES

Group 2 (2000 mg/kg)

Acclimatization (Days 1 to 7)

No mortality data recorded

Treatment (Days 1 to 15)

ANIMAL	DEATH DATE	DAY	P	K	S	O	COMMENT
3	19-AUG-10	15	X				
4	19-AUG-10	15	X				
5	19-AUG-10	15	X				
6	19-AUG-10	15	X				
		Total:	4	0	0	0	

P = PLANNED NECROPSY , K = KILLED IN EXTR. , S = SPONTAN. DEATH , O = OTHER

TABLE 1 Individual Findings – Mortality (Continued)

MORTALITY DATA
ALL NECROPSIES
FEMALES

Group 1 (2000 mg/kg)

Acclimatization (Days 1 to 7)

No mortality data recorded

Treatment (Days 1 to 15)

ANIMAL	DEATH DATE	DAY	P	K	S	O	COMMENT
2	17-AUG-10	15	X				
		Total:	1	0	0	0	

P = PLANNED NECROPSY , K = KILLED IN EXTR. , S = SPONTAN. DEATH , O = OTHER

TABLE 1 Individual Findings – Mortality (Continued)

MORTALITY DATA
ALL NECROPSIES
FEMALES

Group 2 (2000 mg/kg)

Acclimatization (Days 1 to 7)

No mortality data recorded

Treatment (Days 1 to 15)

ANIMAL	DEATH DATE	DAY	P	K	S	O	COMMENT
7	19-AUG-10	15	X				
8	19-AUG-10	15	X				
9	19-AUG-10	15	X				
10	19-AUG-10	15	X				
		Total:	4	0	0	0	

P = PLANNED NECROPSY , K = KILLED IN EXTR. , S = SPONTAN. DEATH , O = OTHER

TABLE 2 Individual Findings – Clinical Signs

Clinical signs

Comments

Data excluded from Summary Report

Not Reported

Daily Observations

A	Clinical Signs
B	Within 30min After Application
C	1h After Application
D	2h After Application
E	3h After Application
F	5h After Application

Incomplete Recordings

Selection of Findings

All findings reported

TABLE 2 Individual Findings – Clinical Signs (Continued)

Clinical signs
MALES

Acclimatization

	Weeks / Days / Daily Observations (A)
	1
	1 2 3 4 5 6 7
	A A A A A A A

Group 1 (2000 mg/kg)

No abnormality recorded.

Group 2 (2000 mg/kg)

No abnormality recorded.

TABLE 2 Individual Findings – Clinical Signs (Continued)

Clinical signs
MALES

Treatment

	Weeks / Days / Daily Observations (A,B,C,D,E,F)						
	1						
	1	2	3	4	5	6	7
	ABCDEFA-----	A-----	A-----	A-----	A-----	A-----	A-----
Group 1 (2000 mg/kg)							
No abnormality recorded.							
Group 2 (2000 mg/kg)							
No abnormality recorded.							

TABLE 2 Individual Findings – Clinical Signs (Continued)

Clinical signs
MALES

Treatment

	Weeks / Days / Daily Observations (A,B,C,D,E,F)						
	2						
	1	2	3	4	5	6	7
	A	A	A	A	A	A	A

Group 1 (2000 mg/kg)

No abnormality recorded.

Group 2 (2000 mg/kg)

No abnormality recorded.

TABLE 2 Individual Findings – Clinical Signs (Continued)

Clinical signs
MALES

Treatment

	Weeks / Days / Daily Observations (A,B,C,D,E,F)
	3
	1
	A-----
Group 1 (2000 mg/kg)	
No abnormality recorded.	
Group 2 (2000 mg/kg)	
No abnormality recorded.	

TABLE 2 Individual Findings – Clinical Signs (Continued)

Clinical signs
FEMALES

Acclimatization

	Weeks / Days / Daily Observations (A)
	1
	1 2 3 4 5 6 7
	A A A A A A A

Group 1 (2000 mg/kg)

No abnormality recorded.

Group 2 (2000 mg/kg)

No abnormality recorded.

TABLE 2 Individual Findings – Clinical Signs (Continued)

Clinical signs
FEMALES

Treatment

	Weeks / Days / Daily Observations (A,B,C,D,E,F)						
	1						
	1	2	3	4	5	6	7
	ABCDEFA-----	A-----	A-----	A-----	A-----	A-----	A-----
Group 1 (2000 mg/kg)							
No abnormality recorded.							
Group 2 (2000 mg/kg)							
No abnormality recorded.							

TABLE 2 Individual Findings – Clinical Signs (Continued)

Clinical signs
FEMALES

Treatment

	Weeks / Days / Daily Observations (A,B,C,D,E,F)						
	2						
	1	2	3	4	5	6	7
	A	A	A	A	A	A	A
Group 1 (2000 mg/kg)							
No abnormality recorded.							
Group 2 (2000 mg/kg)							
No abnormality recorded.							

TABLE 2 Individual Findings – Clinical Signs (Continued)

Clinical signs
FEMALES

Treatment

	Weeks / Days / Daily Observations (A,B,C,D,E,F)
	3
	1
	A-----

Group 1 (2000 mg/kg)

No abnormality recorded.

Group 2 (2000 mg/kg)

No abnormality recorded.

TABLE 3 Individual Findings - Local Dermal Signs

Local dermal signs

Comments

Data excluded from Summary Report

Not Reported

Incomplete Recordings

Selection of Findings

All findings reported

TABLE 3 Individual Findings - Local Dermal Signs (Continued)

Local dermal signs
MALES

Treatment

	Weeks / Days 1 2 3 -2345671234567 1
Group 1 (2000 mg/kg)	
Animal 1	
ERYTHEMA	
-ERYTHEMA (4)	
ANTERIOR DORSUM	.11111........
GENERAL	
-DESQUAMATION (3)	
ANTERIOR DORSUM	.1111111222222
No further abnormality recorded.	
Group 2 (2000 mg/kg)	
Animal 3	
ERYTHEMA	
-ERYTHEMA (4)	
ANTERIOR DORSUM	.111..........
GENERAL	
-DESQUAMATION (3)	
ANTERIOR DORSUM	122222221
Animal 4	
ERYTHEMA	
-ERYTHEMA (4)	
ANTERIOR DORSUM	.111..........
GENERAL	
-DESQUAMATION (3)	
ANTERIOR DORSUM	122222221
Animal 5	
ERYTHEMA	
-ERYTHEMA (4)	
ANTERIOR DORSUM	.111..........

TABLE 3 Individual Findings - Local Dermal Signs (Continued)

Local dermal signs
MALES

Treatment

	Weeks / Days 1 2 3 -2345671234567 1
Group 2 (2000 mg/kg)	
Animal 5	
GENERAL	
-DESQUAMATION (3)	
ANTERIOR DORSUM	.....12222221.
Animal 6	
ERYTHEMA	
-ERYTHEMA (4)	
ANTERIOR DORSUM	.111..........
GENERAL	
-DESQUAMATION (3)	
ANTERIOR DORSUM	.....12222221.

No further abnormality recorded.

TABLE 3 Individual Findings - Local Dermal Signs (Continued)

Local dermal signs
FEMALES

Treatment

	Weeks / Days 1 2 3 -2345671234567 1
Group 1 (2000 mg/kg)	
Animal 2	
ERYTHEMA	
-ERYTHEMA (4)	111111........
GENERAL	
-DESQUAMATION (3)	
ANTERIOR DORSUM	.1111111222222
No further abnormality recorded.	
Group 2 (2000 mg/kg)	
Animal 7	
ERYTHEMA	
-ERYTHEMA (4)	
ANTERIOR DORSUM	.111..........
GENERAL	
-DESQUAMATION (3)	
ANTERIOR DORSUM	....112222221.
Animal 8	
ERYTHEMA	
-ERYTHEMA (4)	
ANTERIOR DORSUM	.111..........
GENERAL	
-DESQUAMATION (3)	
ANTERIOR DORSUM	.....12222221.
Animal 9	
ERYTHEMA	
-ERYTHEMA (4)	
ANTERIOR DORSUM	.111..........
GENERAL	
-DESQUAMATION (3)	
ANTERIOR DORSUM	.....12222221.

TABLE 3 Individual Findings - Local Dermal Signs (Continued)

Local dermal signs
FEMALES

Treatment

	Weeks / Days 1 2 3 -2345671234567 1
Group 2 (2000 mg/kg)	
Animal 10	
ERYTHEMA	
-ERYTHEMA (4)	
ANTERIOR DORSUM	.111.....
GENERAL	
-DESQUAMATION (3)	
ANTERIOR DORSUM	.....1222222 1.

No further abnormality recorded.

TABLE 4 Body Weights

BODY WEIGHTS (G)
MALES

Group 1 (2000 mg/kg)

Animal		1
Treatment		
Day	1	291.8
	8	305.7
	15	333.5

TABLE 4 Body Weights (Continued)

BODY WEIGHTS (G)
MALES

Group 2 (2000 mg/kg)

Animal		3	4	5	6
Treatment					
Day	1	298.8	272.8	291.9	300.8
	8	313.8	277.5	295.9	310.1
	15	337.9	290.4	317.6	332.5

TABLE 4 Body Weights (Continued)

BODY WEIGHTS (G)
FEMALES

Group 1 (2000 mg/kg)		
Animal		2
Treatment		
Day	1	199.8
	8	204.2
	15	219.9

TABLE 4 Body Weights (Continued)

BODY WEIGHTS (G)
FEMALES

Group 2 (2000 mg/kg)

Animal		7	8	9	10
Treatment					
Day	1	190.3	174.6	184.4	191.1
	8	200.3	185.1	197.8	194.6
	15	209.7	187.5	207.5	203.0

TABLE 5 Macroscopic Findings

MACROSCOPICAL FINDINGS
Final necropsy
ALL NECROPSIES

Animals without necropsy

Animals not recorded

Animals not completed

Animals with not translated finding

Not Reported

TABLE 5 Macroscopic Findings (Continued)

MACROSCOPICAL FINDINGS
Final necropsy
ALL NECROPSIES
MALES

Group 1 (2000 mg/kg)

Animal 1 PLANNED NECROPSY , 17-AUG-2010

NO FINDINGS NOTED

TABLE 5 Macroscopic Findings (Continued)

MACROSCOPICAL FINDINGS
Final necropsy
ALL NECROPSIES
MALES

Group 2 (2000 mg/kg)

Animal 3 PLANNED NECROPSY , 19-AUG-2010

NO FINDINGS NOTED

Animal 4 PLANNED NECROPSY , 19-AUG-2010

NO FINDINGS NOTED

Animal 5 PLANNED NECROPSY , 19-AUG-2010

NO FINDINGS NOTED

Animal 6 PLANNED NECROPSY , 19-AUG-2010

NO FINDINGS NOTED

TABLE 5 Macroscopic Findings (Continued)

MACROSCOPICAL FINDINGS
Final necropsy
ALL NECROPSIES
FEMALES

Group 1 (2000 mg/kg)

Animal 2 PLANNED NECROPSY , 17-AUG-2010

NO FINDINGS NOTED

TABLE 5 Macroscopic Findings (Continued)

MACROSCOPICAL FINDINGS
Final necropsy
ALL NECROPSIES
FEMALES

Group 2 (2000 mg/kg)

Animal 7 PLANNED NECROPSY , 19-AUG-2010

NO FINDINGS NOTED

Animal 8 PLANNED NECROPSY , 19-AUG-2010

NO FINDINGS NOTED

Animal 9 PLANNED NECROPSY , 19-AUG-2010

NO FINDINGS NOTED

Animal 10 PLANNED NECROPSY , 19-AUG-2010

NO FINDINGS NOTED

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis

syngenta

GLP Testing Facility WMU
Analytical Development &
Product Chemistry GS2131

Syngenta Crop Protection
Münchwilen AG
Breitenich 5
CH-4333 Münchwilen

Certificate of Analysis

A13617AV
pinoxaden/cloquintocet-mexyl
EC (050/012.5)
SMU0EP001

Batch Identification	**SMU0EP001**
Product Code	**A13617AV**
Other Product Code(s)	pinoxaden/cloquintocet-mexyl EC (050/012.5)
Chemical Analysis (Active Ingredient Content)	
– **Identity of the Active Ingredient(s)***	**confirmed**
– **Content of pinoxaden***	**5.14 % w/w corresponding to 49.7 g/l**
– **Content of cloquintocet-mexyl***	**1.34 % w/w corresponding to 13.0 g/l**
– **Content of water***	**0.24 % w/w**

The Active Ingredient(s) content is within the FAO limits.

Methodology used for Characterization	HPLC, Karl Fischer Titration
Physical Analysis	
– **Appearance**	**light yellow liquid**
– **Density ***	**967 kg/m^3**

Stability:

– **Storage Temperature**	**< 30°C**
– **Recertification Date**	**End of November 2012**

If stored under the conditions given above, this test substance can be considered stable until the recertification date is reached.

This Certificate of Analysis summarizes data which originates either from a single study or from several individual studies. Tests marked with an asterisk (*) have been conducted in compliance with GLP. Raw data, documentation, study plans, any amendments to study plans and reports pertaining to this/these study/studies are stored under the study number(s) referenced below within the archives of the GLP Testing Facility WMU at Syngenta Crop Protection Muenchwilen AG.

Study number of batch characterization: 121383
Study number(s) of batch recertification:

Authorisation: Jul 21, 2010

S. De Benedictis
Analytical Development & Product Chemistry

APPENDIX 2 GLP Certificate

The Swiss GLP Monitoring Authorities

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Confederation

Federal Department of Home Affairs DHA
Federal Office of Public Health FOPH

Federal Department of the Environment, Transport, Energy and Communications DETEC
Federal Office for the Environment FOEN

swissmedic
Swiss Agency for Therapeutic Products

Statement of GLP Compliance

According to Article 14 paragraph 3 Ordinance on Good Laboratory Practice [OGLP, SR 813.112.1]

The notification authority for chemicals confirms that the following test facility was inspected with respect to the compliance with the Swiss Ordinance on Good Laboratory Practice, adopted on 18th May 2005 [OGLP, SR 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted on 26th November 1997 by decision of the OECD Council [C(97)186/Final].

Unequivocal name and address of the test facility:	Areas of expertise according to article 3 paragraph 1 letter d OGLP:
Harlan Laboratories Ltd. Zelgliweg 1 4452 Itingen, Switzerland.	1./ Physical-chemical testing, 2./ Toxicity studies, 4./ Environmental toxicity studies on aquatic and terrestrial organisms, 5./ Studies on behaviour in water, soil and air; bioaccumulation, 6./ Residue studies, 7./ Studies on effects on mesocosms and natural ecosystems, 8./ Analytical and clinical chemistry testing, 9./ Other studies (safety pharmacology and animal metabolism).

Inspection authority: Federal Office for the Environment (FOEN) / Federal Office of Public Health (FOPH) / Swiss Agency for Therapeutic Products (Swissmedic)

Date of inspection: 05th to 09th and 26th to 30th November 2007

Date of decision: 30th April 2008

Based on the above mentioned decision it can be confirmed that the above mentioned test facility is able to conduct studies according to the aforementioned areas of expertise in compliance with the principles of GLP. The above mentioned test facility is listed in the register and GLP list according to the Article 14 OGLP and is inspected on a regular basis according to Article 6 paragraph 2 OGLP.

Swiss Federal Office of Public Health
Consumer protection directorate
Notification authority for chemicals
CH-3003 Bern

FEDERAL OFFICE OF PUBLIC HEALTH

Bern, 12th November 2008, The Head, Dr. Dag Kappes.

The notification authority for chemicals is the coordination and decision authority for the good laboratory practice (GLP) for the FOEN, the FOPH and Swissmedic.
Swiss Federal Office of Public Health, Consumer protection directorate, Notification authority for chemicals, CH-3003 Bern.
www.glp.admin.ch, Phone: +41 (0)31 322 73 05, Fax: +41 (0)31 323 54 86

APPENDIX 3 Grading of Skin Reactions

Erythema and Eschar Formation

No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beef redness) or eschar formation (injuries in depth preventing erythema) reading	4

Oedema Formation

No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well-defined by definite raising)	2
Moderate oedema (edges raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extending beyond the area of exposure)	4