NOA449280
NOA449280 SL (A16003E) - Acute Oral Toxicity Study in the Rat (Up and Down Procedure)

Final Report

DATA REQUIREMENT(S): OECD [Test Guideline, Number 425]
EPA [OPPTS 870.1100]
Japanese MAFF [12 Nohsan No. 8147]

AUTHOR(S): G. Arcelin

STUDY COMPLETION DATE: 25-Aug-2009

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

LABORATORY PROJECT ID: Report Number: C26644
Study Number: C26644
Task Number: T002525-07

SPONSOR: Syngenta Ltd
Jealott's Hill International Research Centre
Bracknell, Berkshire, RG42 6EY, United Kingdom

STATEMENTS OF DATA CONFIDENTIALITY CLAIMS

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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].

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

G. Arcelin
Study Director
Acute Toxicology

25 - Aug - 2009
Date

Performing Laboratory:

Harlan Laboratories Ltd.,
Wölferstrasse 4
4414 Füllinsdorf / Switzerland

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

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

Harlan Laboratories Study:	C26644
Syngenta Task Number:	T002525-07
Test Item:	NOA449280 SL (A16003E)
Study Director:	G. Arcelin
Study Title:	NOA449280 SL (A16003E) - Acute Oral Toxicity Study in the Rat (Up and Down Procedure)

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**
08-Jan-2009	Study Plan	08-Jan-2009
21-Jan-2009	Process based (Test System, Test Item, Raw Data, Dose Preparation, Treatment)	21-Jan-2009
25-Jun-2009	Report	25-Jun-2009

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

Quality Assurance: for S. van Dongen

Date: 21 - Aug - 2009

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function
Dr. C. Simon	Study Director until 08-Jul-2009
G. Arcelin	Study Director from 09-Jul-2009
G. Arcelin	Deputy Study Director until 08-Jul-2009
E. Rached	Deputy Study Director from 09-Jul-2009
T. Fink	Head of Harlan Laboratories Quality Assurance
R. Doran	Syngenta Study Manager

Study dates

Experimental starting date:	04-Mar-2009
Experimental completion date:	31-Mar-2009
Delivery of animals:	04-Mar-2009 (female no. 1) 04-Mar-2009 (female no. 2) 11-Mar-2009 (female no. 3)
Acclimatization:	04-Mar-2009 to 09-Mar-2009 (female no. 1) 04-Mar-2009 to 11-Mar-2009 (female no. 2) 11-Mar-2009 to 16-Mar-2009 (female no. 3)
Treatment:	10-Mar-2009 (female no. 1) 12-Mar-2009 (female no. 2) 17-Mar-2009 (female no. 3)
Observation:	04-Mar-2009 to 24-Mar-2009 (female no. 1) 04-Mar-2009 to 26-Mar-2009 (female no. 2) 11-Mar-2009 to 31-Mar-2009 (female no. 3)
Termination:	24-Mar-2009 (female no. 1) 26-Mar-2009 (female no. 2) 31-Mar-2009 (female no. 3)

Deviations from the guidelines

None

Retention of samples

See below under Other.

Performing laboratory test substance reference number

216594/A

Other

Harlan Laboratories Ltd. (4452 Itingen / Switzerland) will retain the study plan, study plan amendment, raw data, a sample of test item and the original 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 limit test with 3 animals (female HanRcc:WIST (SPF) rat) was conducted. These animals were treated with NOA449280 SL (A16003E) by gavage at the limit dose 5000 mg/kg body weight. The test item was administered undiluted at a volume of 4.63 mL/kg.

Dosing scheme for the limit test

Animal Number	Dosage [mg/kg body weight]	Volume [mL/kg body weight]
1	5000	4.63
2	5000	4.63
3	5000	4.63

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

1.2 Results

No deaths occurred during the study.

Slightly ruffled fur was noted in all three animals starting from 2 hours after test item administration up to test day 4 at the latest. Thereafter, the females were free of any clinical signs up to test day 15, the end of observation period.

The body weight of the animals was within the range commonly recorded for this strain and age.

No macroscopic findings were recorded at necropsy.

1.3 Conclusion

The median lethal dose of NOA449280 SL (A16003E) after single oral administration to female rats, observed over a period of 14 days is:

LD_{50} (female rat): greater than 5000 mg/kg body weight

2.0 INTRODUCTION

2.1 Purpose

The purpose of this study was to investigate the acute oral toxicity of the test item using the Modified Up-and-Down Procedure (ASTM, 1987).

2.2 Guidelines

The study was done according to the following guidelines:

OECD guideline reference 425 (2001): Acute Oral Toxicity - Up-and-Down Procedure.

United States Environmental Protection Agency, Health Effects Test Guidelines, OPPTS 870.1100 Acute Oral Toxicity EPA 712-C-03-190, December 2002.

Japanese MAFF Test Data for Registration of Agricultural Chemicals, Test Guidelines, Acute oral toxicity studies, 12 NohSan No. 8147, Agricultural Production Bureau, November 24, 2000 [English translation by IAI:ACIS, revised on June 26, 2001 (13 Seisan No. 1739) and December 10, 2002 (14 Seisan No. 7269)].

2.3 Animal welfare

This study was performed in an AAALAC-accredited laboratory in accordance with the Swiss Animal Protection Law under license no. 254.

3.0 MATERIALS AND METHODS

3.1 Test substance

The following information was provided by the sponsor:

Identification:	NOA449280 SL (A16003E)
Product code:	A16003E
Description:	Liquid; brown
Batch number:	J8308/145
Density:	1079 kg/m^3
Reanalysis date:	End of May 2011
Stability of test item:	Stable under specified storage conditions.
Storage conditions:	At a temperature < 30°C (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 as attached in Appendix 1.

3.2 Experimental design

The animals received a single dose of the test item by oral gavage administration after being fasted for approximately 17 ½ to 18 hours, but with free access to water. Food was presented approximately 3 to 4 hours after dosing.

The test item was applied undiluted as delivered by the sponsor.

Homogeneity of the test item in the vehicle was maintained during administration using a magnetic stirrer.

Dosing started in one female animal at a dose level of 5000 mg/kg. The dose volume was 4.63 mL/kg body weight. A total of 3 animals were treated at this dosage because no death occurred and no animals had to be killed during the course of the study.

Application scheme:

Animal Number	Dosage [mg/kg body weight]	Volume [mL/kg body weight]	Viability/Mortality
1	5000	4.63	Survived
2	5000	4.63	Survived
3	5000	4.63	Survived

Rationale:

Oral administration was considered to be an appropriate application method as it is a possible route of human exposure.

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

3.2.1 Animals

Animal species and strain:	Rat, HanRcc:WIST (SPF)
Rationale:	Recognized by international guidelines as a recommended test system.
Breeder/supplier:	Harlan Laboratories Ltd, Laboratory Animal Services Wölferstrasse 4 4414 Füllinsdorf / Switzerland
Number of animals per group:	1 female
Total number of animals:	3 females
Age (when treated):	11 weeks
Body Weight (when treated):	176.2 g - 195.5 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. No computer generated randomization program.

Acclimatization:	Under laboratory conditions, 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 ranges for room temperature 22 ± 3 °C and for relative humidity between 30-70% (values above 70% during cleaning process possible), automatically controlled light cycle of 12 hours light and 12 hours dark, music during the daytime light period.
Accommodation:	Individually in Makrolon type-3 cages with standard softwood bedding (‘Lignocel’ Schill AG, 4132 Muttenz / Switzerland) during treatment and observation.
Diet:	Pelleted standard Provimi Kliba 3433 rat/mouse maintenance diet, batches nos. 61/08 and 76/08 (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.

No organs or tissues were retained.

3.4 Data evaluation

Body weights were recorded on-line.

Clinical signs were recorded on data sheets.

Mortality/viability were compiled into the RCC Tox Computer System during recording or recorded on data sheets.

Macroscopic findings were compiled into the RCC Tox Computer System during recording.

The RCC Tox Computer System (RCC-Tox-Lims) has been validated with respect to data collection, storage and retrievability.

Data were evaluated using the Acute Oral Toxicity (OECD Test Guidelines 425) Statistical Programme (AOT 425 Stat Pgm).

4.0 RESULTS AND DISCUSSION

Individual clinical observations and mortality results are presented in Table 1. Individual body weights and necropsy results are presented in Tables 2 and 3, respectively.

4.1 Mortality

No deaths occurred during the study.

4.2 Body weights

The body weight of the animals was within the range commonly recorded for rat of this strain and age.

4.3 Clinical signs

The three females treated at 5000 mg/kg showed slightly ruffled fur from 2 hours to 5 hours, test day 2 or test day 4. Thereafter, all animals were free of clinical signs up to test day 15, the end of observation time.

4.4 Macroscopic findings

No macroscopic findings were recorded for all animals at necropsy.

5.0 CONCLUSIONS

The median lethal dose of NOA449280 SL (A16003E) after single oral administration to female rats, observed over a period of 14 days post treatment is:

LD_{50} (female rat): greater than 5000 mg/kg body weight

6.0 REFERENCES

Literature references listed are available upon request.

External references

ASTM (1987). Standard Test Method for Estimating Acute Oral Toxicity in Rats. American Society for Testing and Materials, Philadelphia, PA, E 1163 - 1187.

Acute Oral Toxicity (OECD Test Guideline 425) Statistical Programme (AOT 425 Stat Pgm). Version: 1.0, 2001. [http://www.oecd.org/pages/home/display general/0,3380,EN-document-524-nodirectorite-0-24-6775-8,FF.html).

TABLES SECTION

TABLE 1 Individual Findings – Mortality / Clinical Signs

Dose mg/kg bw	Animal No.	Sex	Signs	Test days																	
				1					2	3	4	5	6	7	8	9	10	11	12	13	14	15
				0.5*	1*	2*	3*	5*														
5000	1	F	No clinical signs	√	√				√	√	√	√	√	√	√	√	√	√	√	√	√	√
			Ruffled fur			1	1	1														
5000	2	F	No clinical signs	√	√							√	√	√	√	√	√	√	√	√	√	√
			Ruffled fur			1	1	1	1	1	1											
5000	3	F	No clinical signs	√	√					√	√	√	√	√	√	√	√	√	√	√	√	√
			Ruffled fur			1	1	1	1													

Key: √ noted, 1 slight

* Examinations were performed within the first 30 minutes and approximately 1, 2, 3 and 5 hours after treatment.

No clinical signs were evident in any animal during the acclimatization period.

TABLE 2 Body Weights

Dose mg/kg body weight	Animal No.	Sex	Day -1 (prior to removal of food)	Day 1 (prior to treatment)	Day 8	Day 15
5000	1	F	189.1	176.2	203.3	213.7
5000	2	F	191.0	188.6	204.4	213.2
5000	3	F	200.9	195.5	211.8	216.8

Body weights are presented in grams.

TABLE 3 Macroscopic Findings

Dose mg/kg body weight	Animal No.	Sex	Mode of death	Findings
5000	1	F	S	No macroscopic findings
5000	2	F	S	No macroscopic findings
5000	3	F	S	No macroscopic findings

S: scheduled necropsy

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis

syngenta

GLP Testing Facility WMU
Analytical Development &
Product Chemistry GS2131

Syngenta Crop Protection
Münchwilen AG
Breitenloh 5
CH-4333 Münchwilen

Certificate of Analysis

A16003E
NOA449280 SL (200)
J8308/145

Batch Identification	**J8308/145**
Product Code	**A16003E**
Other Product Code(s)	---

Chemical Analysis
(Active Ingredient Content)

– **Identity of the Active Ingredient(s)***	**confirmed**
– **Content of NOA449280***	**18.3 % w/w corresponding to 197 g/l**
Methodology used for Characterization	HPLC

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

Physical Analysis

– **Appearance**	**brown liquid**
– **Density ***	**1079 kg/m^3**

Stability:

– **Storage Temperature**	**< 30°C**
– **Reanalysis date**	**End of May 2011**

The stability of this test substance will be controlled by reanalysis of material held in the inventory at Syngenta Crop Protection Muenchwilen AG at the appropriate time.

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.

Characterisation: 119332 Reanalysis:

Authorisation: Andrew McIntyre 14th January 2009

Dr. A. McIntyre
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.

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