RCC Study Number B25290

Syngenta Task Number: T020509-04

CGA64250/SAN619/azoxystrobin (125/030/100) EC (A13775A):

Acute Oral Toxicity Study in the Rat
(Up and Down Procedure)

Report

Author: G. Arcelin

Sponsor: Syngenta Ltd
Alderley Park
Macclesfield
Cheshire, SK10 4TJ
United Kingdom

TABLE OF CONTENTS

1 PREFACE

1.1 GENERAL

Title	CGA64250/SAN619/azoxystrobin (125/030/100) EC (A13775A): Acute Oral Toxicity Study in the Rat (Up and Down Procedure)
Sponsor	Syngenta Ltd Alderley Park Macclesfield Cheshire, SK10 4TJ United Kingdom
Monitoring Scientist	Mr. Dave Lees
Test Facility	RCC Ltd Wölferstrasse 4 4414 Füllinsdorf / Switzerland

1.2 RESPONSIBILITIES

Study Director	G. Arcelin
Deputy for Study Director	Dr. C. Simon
Technical Coordinators	F. Frickert / M. Bernstein
Head of RCC Quality Assurance	I. Wüthrich

1.3 SCHEDULE

Experimental Starting Date	06-MAR-2007
Experimental Completion Date	24-MAY-2007
Delivery of Animals	06-MAR-2007 (female no. 1) 08-MAR-2007 (female no. 2) 13-MAR-2007 (female no. 3) 14-MAR-2007 (female no. 4) 20-MAR-2007 (female no. 5) 15-MAR-2007 (female no. 6) 29-MAR-2007 (female no. 7) 03-APR-2007 (female no. 8) 13-APR-2007 (female no. 9) 17-APR-2007 (female no. 10) 20-APR-2007 (female no. 11) 03-MAY-2007 (female no. 14) 11-MAY-2007 (female no. 15)
Acclimatization	06-MAR-2007 to 12-MAR-2007 (female no. 1) 08-MAR-2007 to 14-MAR-2007 (female no. 2) 13-MAR-2007 to 19-MAR-2007 (female no. 3)

	14-MAR-2007 to 21-MAR-2007 (female no. 4) 20-MAR-2007 to 26-MAR-2007 (female no. 5) 15-MAR-2007 to 28-MAR-2007 (female no. 6) 29-MAR-2007 to 04-APR-2007 (female no. 7) 03-APR-2007 to 09-APR-2007 (female no. 8) 13-APR-2007 to 19-APR-2007 (female no. 9) 17-APR-2007 to 23-APR-2007 (female no. 10) 20-APR-2007 to 26-APR-2007 (female no. 11) 03-MAY-2007 to 09-MAY-2007 (female no. 14) 11-MAY-2007 to 17-MAY-2007 (female no. 15)
Treatment	13-MAR-2007 (female no. 1) 15-MAR-2007 (female no. 2) 20-MAR-2007 (female no. 3) 22-MAR-2007 (female no. 4) 27-MAR-2007 (female no. 5) 29-MAR-2007 (female no. 6) 05-APR-2007 (female no. 7) 10-APR-2007 (female no. 8) 20-APR-2007 (female no. 9) 24-APR-2007 (female no. 10) 27-APR-2007 (female no. 11) 10-MAY-2007 (female no. 14) 18-MAY-2007 (female no. 15)
Observation	06-MAR-2007 to 13-MAR-2007 (female no. 1) 08-MAR-2007 to 29-MAR-2007 (female no. 2) 13-MAR-2007 to 03-APR-2007 (female no. 3) 14-MAR-2007 to 05-APR-2007 (female no. 4) 20-MAR-2007 to 10-APR-2007 (female no. 5) 15-MAR-2007 to 29-MAR-2007 (female no. 6) 29-MAR-2007 to 19-APR-2007 (female no. 7) 03-APR-2007 to 24-APR-2007 (female no. 8) 13-APR-2007 to 20-APR-2007 (female no. 9) 17-APR-2007 to 08-MAY-2007 (female no. 10) 20-APR-2007 to 27-APR-2007 (female no. 11) 03-MAY-2007 to 24-MAY-2007 (female no. 14) 11-MAY-2007 to 18-MAY-2007 (female no. 15)

1.4 ARCHIVING

RCC Ltd (CH-4452 Itingen / Switzerland) will retain the study plan, study plan amendment, raw data, sample of test item(s) and the final report of the present study for a minimum of five years. Thereafter, all items described above must be archived for at least a further five years. In agreement with the Sponsor, this may be at RCC Ltd or at another GLP compliant archive facility. A report amendment need only be written if the archived items are transferred to another facility.

The report with original signatures which will be archived at RCC is the reference document. No data will be discarded without the Sponsor’s written consent.

1.5 SIGNATURE PAGE

Study Director: G. Arcelin

date: 27-SEP-2007

Management: (fw) Dr. H. Fankhauser

date: 27-SEP-2007

1.6 QUALITY ASSURANCE GLP TOXICOLOGY

RCC Ltd, Toxicology, CH-4452 Itingen / Switzerland

STATEMENT

RCC STUDY NUMBER	:	B25290
TEST ITEM		CGA64250/SAN619/azoxystrobin (125/030/100) EC (A13775A)
STUDY DIRECTOR	:	G. Arcelin
TITLE		CGA64250/SAN619/azoxystrobin (125/030/100) EC (A13775A): Acute Oral Toxicity Study in the Rat (Up and Down Procedure)

The general facilities and activities are inspected periodically 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
01-MAR-2007 Study Plan	01-MAR-2007
13-MAR-2007 Process Based (Test System, Test Item, Raw Data, Dose Preparation, Treatment)	13-MAR-2007
21-SEP-2007 Report	21-SEP-2007

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

Quality Assurance: S. van Dongen

S. van Dongen

date: 27-Sep-2007

GOOD LABORATORY PRACTICE

1.7 STATEMENT OF COMPLIANCE

RCC STUDY NUMBER	:	B25290
TEST ITEM		CGA64250/SAN619/azoxystrobin (125/030/100) EC (A13775A)
STUDY DIRECTOR	:	G. Arcelin
TITLE		CGA64250/SAN619/azoxystrobin (125/030/100) EC (A13775A): Acute Oral Toxicity Study in the Rat (Up and Down Procedure)

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

Study Director:

G. Arcelin

.....

date: 27-SEP-2007

1.8 TEST GUIDELINES

The study procedures described in this report meet or exceed the requirements of the following guidelines:

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

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)].

EPA Health Effects Test Guidelines, OPPTS 870.1100 Acute Oral Toxicity EPA 712-C-03-190, December 2002.

1.9 ANIMAL WELFARE

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

1.10 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).

1.11 SUMMARY OF STUDY PLAN AMENDMENT

Study Plan Amendment No. 1:

Change of study director and deputy.

2 SUMMARY

A main test with 12 female HanRcc:WIST (SPF) rats (animal nos. 2 to 11 and 14 to 15) was conducted. These animals were treated with CGA64250/SAN619/azoxystrobin (125/030/100) EC (A13775A) by gavage up to the dosage of 2000 mg/kg body weight. The test item was applied undiluted. A limit-test first started with a wistar rat (animal No. 1) dosed at 2000 mg/kg which died shortly after treatment.

Table 1: Application scheme for test

Animal Number	Dosage [mg/kg body weight]	Volume [mL/kg body weight]	Viability/mortability
1	2000	1.96	Died
2	175	0.17	Survived
3	550	0.53	Survived
4	2000	1.96	Survived
5	2000	1.96	Survived
6	2000	1.96	Died
7	550	0.53	Survived
8	2000	1.96	Survived
9	2000	1.96	Died
10	550	0.53	Survived
11	2000	1.96	Killed
(12	550*	1.53*)	Died
(13	175	0.17*)	Survived
14	550	0.53	Survived
15	2000	1.96	Died

* wrong application volume of 1.53 mL/kg instead of 0.53 mL/kg. Therefore, the planed dose of 550 mg/kg was really a dose of 1560 mg/kg, which explained the death of the animal. Consequently, the animal nos. 12 and 13 were not taken into consideration for reporting.

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 necropsied and examined macroscopically.

Death occurred in animals No. 1, 6, 9, 11 and 15. Animal No. 1 and 6 died shortly after treatment. The animal No. 11 had to be killed approximately 15 minutes after treatment. The animal Nos. 9 and 15 died approximately 3.5 or 5 hours after treatment, respectively.

Animal No. 1 (2000 mg/kg) was observed with lateral recumbency, slight salivation and rhinorrhea shortly after treatment. No reaction to pinching. The animal died approximately 20 minutes after treatment.

Animal No. 2 (175 mg/kg) showed a slightly ruffled fur from the first 30 minutes to test day 4. A slight sedation was recorded at the 2 and 3 hours post-dose.The animal was free of clinical signs from test day 5 to the end of the observation (test day 15).

Animal No. 3 (550 mg/kg) was observed with a slightly ruffled fur from the 1 hour post-dose to test day 6. A slight sedation was seen from the 2 hours post-dose to test day 2. Hunched posture was recorded from the 3 to 5 hours post-dose and on test day 2. The animal was free of clinical signs from test day 7 to 15.

Animal No. 4 (2000 mg/kg) was observed with a slightly ruffled fur from the 1 hour post-dose to test day 9. A slight sedation was seen at the 2, 3 and 5 hours post-dose. Hunched posture was recorded from the first 30 minutes post-dose to test day 3. The animal was free of clinical signs from test day 10 to 15.

Animal No. 5 (2000 mg/kg) was observed with a slightly ruffled fur from the 1 hour post-dose to test day 7. A slight to moderate sedation was seen from the first 30 minutes to the 5 hours post-dose. Hunched posture was recorded from the 1 hour post-dose to test day 3. A slightly poor coordination was observed from the 1 hour to the 5 hours post-dose. The animal was free of clinical signs from test day 8 to 15.

Animal No. 6 (2000 mg/kg) was observed with lateral recumbency and convulsions approximately 20 minutes after treatment. The animal died immediately therafter.

Animal No. 7 (550 mg/kg) did not show any clinical signs during the first 2 hours post-dose. Slightly ruffled fur, hunched posture and slightly sedation were seen 3 and 5 hours after treatment. The animal was free of clinical signs from test day 2 to 15.

Animal No. 8 (2000 mg/kg) was observed with a slightly ruffled fur from the first 30 minutes post-dose to test day 5. The slight sedation was seen at the 2, 3 and 5 hours post-dose. A hunched posture was recorded during the first 30 minutes to test day 2. The animal was free of clinical signs from test day 6 to 15.

Animal No. 9 (2000 mg/kg) was observed with a slightly ruffled fur and a hunched posture from the first 30 minutes to 3 hours post-dose. A slight sedation was noted at the 2 and 3 hours post-dose. A slightly poor coordination was still recorded at the 3 hours before spontaneous death occurred shortly therafter.

Animal No. 10 (550 mg/kg) showed a slightly ruffled fur from the first 30 minutes to test day 3. No clinical signs were seen from test day 4 to 15.

Animal No. 11 (2000 mg/kg) was observed with a slightly ruffled fur, ventral recumbency, severe convulsions approximately 15 minutes following the treatment. Additionally, vocalization of the animal was noted. It was humanely sacrificed immediately therafter.

Animal No. 14 (550 mg/kg) was observed with a slightly ruffled fur from the first 30 minutes to test day 2. No clinical signs were seen from test day 3 to 15.

Animal No. 15 (2000 mg/kg) showed slightly to moderately ruffled fur and hunched posture from the first 30 minutes to 3 hours post-dose. A slight sedation was noted at the 2 and 3 hours post-dose. The animal was found dead at the 5-hour observation.

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

No macroscopic findings were observed at the scheduled and non-scheduled necropsy except in animal Nos. 1 and 11 which were observed with congestion of the lungs and liquid contents in the stomach, respectively.

3 CONCLUSION

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

Estimated LD_{50} (female rat): is 2000 mg/kg body weight
(Based on an assumed sigma of 0.5)

Approximate 95 % confidence interval is 990.7 to 9320 mg/kg body weight.

4 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).

5 MATERIALS AND METHODS

5.1 TEST SYSTEM

Test system	Rat, HanRcc:WIST (SPF)
Rationale	Recognized by the international guidelines as a recommended test system.
Source	RCC Ltd, Laboratory Animal Services CH-4414 Füllinsdorf / Switzerland
Number of animals per group	One female
Total number of animals	13 females
Age when treated	11 - 12 weeks
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, after health examination. Only animals without any visible signs of illness were used for the study.

5.2 HUSBANDRY

Room no.	0105 / RCC 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, CH-4132 Muttenz) during treatment and observation.
Diet	Pelleted standard Provimi Kliba 3433 rat/mouse maintenance diet, batch nos. 80/06 and 89/06 (Provimi Kliba AG, CH-4303 Kaiseraugst/Switzerland) *ad libitum*. Results of analyses for contaminants are archived at RCC Ltd.
Water	Community tap water from Füllinsdorf *ad libitum*. Results of bacteriological, chemical and contaminant analyses are archived at RCC Ltd.

5.3 TEST ITEM

The following information was provided by the sponsor:

Identification	CGA64250/SAN619/azoxystrobin (125/030/100) EC (A13775A)
Description	Brownish liquid
Density	1.02 g/mL
Batch number	J4907/92
Purity / Formulation (Active ingredient content)	Content of CGA64250 123 g/l corresponds to 12 % w/w Content of SAN 619 29.4 g/l corresponds to 2.87 % w/w Content of azoxystrobin 100 g/l corresponds to 9.78% w/w
Stability of test item	Stable under storage conditions.
Reanalysis date	February 2010
Storage conditions	< 30°C, protected from light and humidity.
Safety precautions	Routine hygienic procedures were used to ensure the health and safety of the personnel.

5.4 DOSE FORMULATION

The dose levels are in terms of the test item as supplied by the sponsor.

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

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

5.5 TREATMENT

The animal received a single dose of the test item by oral gavage administration after being fasted for 16 to 20 hours, but with free access to water. Food was presented approximately 3 to 4 hours after dosing.

Limit Test

A limit-test first started by dosing one animal (No.1) at 2000 mg/kg.

The application volume was 1.96 mL/kg (x 1.02 g/mL = 2000 mg/kg).

The animal died shortly after treatment. Therefore, a main test was performed as follows:

Main Test

The starting dose was 175 mg/kg. A single animal was initially dosed at this level. Further dose levels were chosen using the criteria in Appendix 1 in the study plan. A minimum of 48 hours was allowed before dosing the next animal in the sequence.

For the dose of 175 mg/kg, the application volume was 0.17 mL/kg (x 1.02 g/mL = 175 mg/kg).

An application volume of 0.53 mL/kg and 1.96 mL/kg were used for the doses of 550 and 2000 mg/kg, respectively.

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

5.6 OBSERVATIONS

Mortality / Viability	Daily during the acclimatization period, during the first 30 minutes after treatment, 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	On test day –1 (prior to removal of food), on test days 1 (prior to administration), 8 and 15
Clinical signs	Daily during the acclimatization period, during the first 30 minutes after treatment and at approximately 1, 2, 3 and 5 hours after administration on test day 1. Once daily during days 2-15. All abnormalities were recorded.

6 PATHOLOGY

6.1 NECROPSY

All animals which died spontaneously or had to be killed in extremis during the observation period were necropsied as soon as they were found died or were killed by an intraperitoneal injection of pentobarbitone at a dose of at least 2.0 mL/kg body weight.

All surviving 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.

7 STATISTICAL ANALYSIS

The 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) was used for the selection of dose levels and calculation of the LD_{50} values.

8 DATA COMPILATION

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) had been validated with respect to data collection, storage and retrievability.

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

9 RESULTS

9.1 MORTALITY

Death occurred in animals No. 1, 6, 9, 11 and 15. Animal No. 1 and 6 died shortly after treatment. The animal No. 11 had to be killed approximately 15 minutes after treatment. The animal Nos. 9 and 15 died approximately 3.5 or 5 hours after treatment, respectively.

9.2 CLINICAL SIGNS

Animal No. 1 (2000 mg/kg) was observed with lateral recumbency, slight salivation and rhinorrhea shortly after treatment. No reaction to pinching. The animal died approximately 20 minutes after treatment.

Animal No. 2 (175 mg/kg) showed a slightly ruffled fur from the first 30 minutes to test day 4. A slight sedation was recorded at the 2 and 3 hours post-dose.The animal was free of clinical signs from test day 5 to the end of the observation (test day 15).

Animal No. 3 (550 mg/kg) was observed with a slightly ruffled fur from the 1 hour post-dose to test day 6. A slight sedation was seen from the 2 hours post-dose to test day 2. Hunched posture was recorded from the 3 to 5 hours post-dose and on test day 2. The animal was free of clinical signs from test day 7 to 15.

Animal No. 4 (2000 mg/kg) was observed with a slightly ruffled fur from the1 hour post-dose to test day 9. A slight sedation was seen at the 2, 3 and 5 hours post-dose. Hunched posture was recorded from the first 30 minutes post-dose to test day 3. The animal was free of clinical signs from test day 10 to 15.

Animal No. 5 (2000 mg/kg) was observed with a slightly ruffled fur from the 1 hour post-dose to test day 7. A slight to moderate sedation was seen from the first 30 minutes to the 5 hours post-dose. Hunched posture was recorded from the 1 hour post-dose to test day 3. A slightly poor coordination was observed from the 1 hour to the 5 hours post-dose. The animal was free of clinical signs from test day 8 to 15.

Animal No. 6 (2000 mg/kg) was observed with lateral recumbency and convulsions approximately 20 minutes after treatment. The animal died immediately therafter.

Animal No. 7 (550 mg/kg) did not show any clinical signs during the first 2 hours post-dose. Slightly ruffled fur, hunched posture and slightly sedation were seen 3 and 5 hours after treatment. The animal was free of clinical signs from test day 2 to 15.

Animal No. 8 (2000 mg/kg) was observed with a slightly ruffled fur from the first 30 minutes post-dose to test day 5. The slight sedation was seen at the 2, 3 and 5 hours post-dose. A hunched posture was recorded during the first 30 minutes to test day 2. The animal was free of clinical signs from test day 6 to 15.

Animal No. 9 (2000 mg/kg) was observed with a slightly ruffled fur and a hunched posture from the first 30 minutes to 3 hours post-dose. A slight sedation was noted at the 2 and 3 hours post-dose. A slightly poor coordination was still recorded at the 3 hours before spontaneous death occurred shortly therafter.

Animal No. 10 (550 mg/kg) showed a slightly ruffled fur from the first 30 minutes to test day 3. No clinical signs were seen from test day 4 to 15.

Animal No. 11 (2000 mg/kg) was observed with a slightly ruffled fur, ventral recumbency, severe convulsions approximately 15 minutes following the treatment. Additionally, vocalization of the animal was noted. It was humanely sacrificed immediately therafter.

Animal No. 14 (550 mg/kg) was observed with a slightly ruffled fur from the first 30 minutes to test day 2. No clinical signs were seen from test day 3 to 15.

Animal No. 15 (2000 mg/kg) showed slightly to moderately ruffled fur and hunched posture from the first 30 minutes to 3 hours post-dose. A slight sedation was noted at the 2 and 3 hours post-dose. The animal was found dead at the 5-hour observation.

9.3 BODY WEIGHTS

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

9.4 MACROSCOPIC FINDINGS

No macroscopic findings were observed at the scheduled and non-scheduled necropsy except in animal Nos. 1 and 11 which were observed with congestion of the lungs and liquid contents in the stomach, respectively.

9.5 MEDIAN LETHAL DOSE

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

Estimated LD_{50} (female rat): is 2000 mg/kg body weight
(Based on an assumed sigma of 0.5)

Approximate 95 % confidence interval is 990.7 to 9320 mg/kg body weight.

10 INDIVIDUAL FINDINGS

10.1 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*														
2000	1	F	Salivation	1																		
			Lateral recumbency	√																		
			No reaction to pinching	√																		
			Rhinorrhea	√+																		
175	2	F	No clinical signs									√	√	√	√	√	√	√	√	√	√	√
			Ruffled fur	1	1	1	1	1	1	1	1											
			Sedation			1	1															
550	3	F	No clinical signs	√										√	√	√	√	√	√	√	√	√
			Ruffled fur		1	1	1	1	1	1	1	1	1									
			Sedation			1	1	1	1													
			Hunched posture				√	√	√													
2000	4	F	No clinical signs														√	√	√	√	√	√
			Ruffled fur		1	1	1	1	1	1	1	1	1	1	1	1						
			Sedation			1	1	1														
			Hunched posture	√	√	√	√	√	√	√												
2000	5	F	No clinical signs												√	√	√	√	√	√	√	√
			Ruffled fur		1	1	1	1	1	1	1	1	1	1								
			Sedation	1	1	2	2	2														
			Hunched posture	√	√	√	√	√	√	√												
			Poor coordination	1	1	1	1	1														
2000	6	F	Lateral recumbency	√																		
			Convulsions	√+																		

Key: 1 slight, 2 moderate, √ noted,+ found dead
* Examinations were performed during the first 30 minutes and approximately 1, 2, 3 and 5 hours after treatment

MORTALITY / CLINICAL SIGNS (CONTINUED)

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*														
550	7	F	No clinical signs	√	√	√			√	√	√	√	√	√	√	√	√	√	√	√	√	√
			Ruffled fur				1	1														
			Sedation				1	1														
			Hunched posture				√	√														
2000	8	F	No clinical signs										√	√	√	√	√	√	√	√	√	√
			Ruffled fur	1	1	1	1	1	1	1	1	1										
			Sedation			1	1	1														
			Hunched posture	√	√	√	√	√	√													
2000	9	F	Ruffled fur	1	1	1	1															
			Sedation			1	1															
			Hunched posture	√	√	√	√															
			Poor coordination				1+															
550	10	F	No clinical signs								√	√	√	√	√	√	√	√	√	√	√	√
			Ruffled fur	1	1	1	1	1	1	1												
2000	11	F	Ruffled fur	1																		
			Ventral recumbency	√																		
			Convulsions	3																		
			Vocalisation	√K																		
550	14	F	No clinical signs							√	√	√	√	√	√	√	√	√	√	√	√	√
			Ruffled fur	1	1	1	1	1	1													
2000	15	F	Ruffled fur	1	1	2	2															
			Sedation			1	1															
			Hunched posture	√	√	√	√	+														

Key: 1 slight, 2 moderate, 3 marked, √ noted, K killed in extremis, + found dead

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

10.2 BODY WEIGHTS

Dose mg/kg bw	Animal No.	Sex	Day -1 (prior to removal of food)	Day 1 (prior to treatment)	Day 8	Day 15
2000	1	F	188.4	184.0	-	-
175	2	F	191.7	184.7	202.9	205.5
550	3	F	196.0	187.5	213.0	218.5
2000	4	F	197.2	192.1	202.6	215.7
2000	5	F	175.8	173.4	183.4	189.4
2000	6	F	203.2	198.0	-	-
550	7	F	196.9	186.3	202.6	212.4
2000	8	F	196.1	194.5	197.6	202.9
2000	9	F	186.3	171.3	-	-
550	10	F	197.2	190.7	208.3	221.9
2000	11	F	184.9	173.9	-	-
550	14	F	195.7	194.7	197.3	214.9
2000	15	F	200.7	190.1	-	-

Body weights are presented in grams.

10.3 MACROSCOPIC FINDINGS

Dose mg/kg body weight	Animal No.	Sex	Mode of death	Findings
2000	1	F	D	Congestion of the lungs
175	2	F	S	No macroscopic findings
550	3	F	S	No macroscopic findings
2000	4	F	S	No macroscopic findings
2000	5	F	S	No macroscopic findings
2000	6	F	D	No macroscopic findings
550	7	F	S	No macroscopic findings
2000	8	F	S	No macroscopic findings
2000	9	F	D	No macroscopic findings
550	10	F	S	No macroscopic findings
2000	11	F	K	Stomach: Contents liquid
550	14	F	S	No macroscopic findings
2000	15	F	D	No macroscopic findings

S: scheduled necropsy, K: killed in extremis, D found dead

11 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

A13775A

CGA64250/SAN619/azoxystrobin
EC (125/030/100)

J4907/92

Batch Identification	**J4907/92**
Product Code	**A13775A**
Other Product Code(s)	CGA64250/SAN619/azoxystrobin EC (125/030/100)

Chemical Analysis
(Active Ingredient Content)

– **Identity of the Active Ingredients ***	**confirmed**
– **Content of CGA64250 ***	**123 g/l, corresponds to 12.0 % w/w**
– **Content of SAN619 ***	**29.4 g/l, corresponds to 2.87 % w/w**
– **Content of azoxystrobin ***	**100 g/l, corresponds to 9.78 % w/w**

Methodology used for Characterization cap. GC

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

Physical Analysis

– **Appearance**	**brownish liquid**
– **Density ***	**1025 kg/m^3**

Stability:

– **Storage Temperature**	**< 30°C**
– **Reanalysis Date**	**February 2010**

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.

Characterization: 117283

Authorization:

12-Feb-2007

Dr. R. Kettner
Analytical Development & Product Chemistry

12 GLP – CERTIFICATION

The Swiss GLP Monitoring Authorities

Swiss Federal Office of Public Health

Swiss Agency for the Environment, Forests and Landscape

Swissmedic Swiss Agency for Therapeutic Products

Statement of GLP Compliance

It is hereby confirmed that

during the period of — April 22, 25 – 29, 2005
May 09 – 13, 2005

the following Facilities of — **RCC Ltd**
4452 Itingen
Switzerland

were inspected by the Federal Office of Public Health, the Swiss Agency for Therapeutic Products and the Swiss Agency for the Environment, Forests and Landscape with respect to the compliance with the Swiss legislation on Good Laboratory Practice.

Facilities	**Areas of expertise ***
- Test Facility: Toxicology	**TOX, ACC, OTH (Safety Pharmacology, Alternative Test Systems)**
- Test Facility: Environmental Chemistry & Pharmanalytics	**ACC, ECT, ENF, EMN, PCT, RES, OTH (Animal Metabolism)**
- Archive Facilities	

The inspections were performed in agreement with the OECD Guidelines for National GLP Inspections and Audits. It was found that the aforementioned test facilities were operating in compliance with the Swiss Ordinance relating to Good Laboratory Practice [RS 813.016.5] at the time they were inspected.

Federal Office of Public Health
The Director

Bern, November 2005

Prof. Th. Zeltner

* TOX = Toxicology ; ACC = Analytical and Clinical Chemistry ; ECT = Environmental toxicity on aquatic and terrestrial organisms ; ENF = Behaviour in water, soil and air. Bioaccumulation ; EMN = Studies on effects on mesocosms and natural ecosystems; PCT = Physical-chemical testing ; RES = Residue studies ; OTH = Other, to be specified.