Propiconazole/Isopyrazam

Propiconazole/Isopyrazam WG (A18289B) - Acute Oral Toxicity Study in the Rat (Up and Down Procedure)

Final Report

DATA REQUIREMENT(S): OECD Test Guideline 425 (2008)
EPA OPPTS 870.1100 (2002)

AUTHOR(S): István Buda, M.Sc. (in life and draft report phase)
Istvánné Kiss, M.Sc. (final report phase)

STUDY COMPLETION DATE: 24 November 2011

PERFORMING LABORATORY: CiToxLAB Hungary Ltd.
(formerly known as LAB Research Ltd. before 1st September 2011)
H-8200 Veszprém, Szabadságpuszta,
Hungary

LABORATORY PROJECT ID: Report Number: 11/141-001P
Study Number: 11/141-001P
Task Number: TK0041605

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

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study has been performed in accordance with the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 9/2001. (III. 30.) EüM-FVM joint decree of the Minister of Health and the Minister of Agriculture and Regional Development which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17.).

This study was conducted in accordance with a written Study Plan and its Amendment, authorized by the Sponsor and CiToxLAB Hungary Ltd. management, and followed applicable Standard Operating Procedures.

Signature: Kiss Istvánné Date: 24 November 2011

Istvánné Kiss, M.Sc.
Study Director

Performing Laboratory: CiToxLAB Hungary Ltd.
(formerly known as LAB Research Ltd. before 1st September 2011)
H-8200 Veszprém, Szabadságpuszta, Hungary

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

Study Number: 11/141-001P

Study Title: Propiconazole/Isopyrazam WG (A18289B) – Acute Oral Toxicity Study in the Rat (Up and Down Procedure)

Test Item: Propiconazole/Isopyrazam WG (A18289B)

This study has been inspected, and this report audited by the Quality Assurance Unit in compliance with the Principles of Good Laboratory Practice. As far as it can be reasonably established the methods described and the results incorporated in this report accurately reflect the raw data produced during this study.

All inspections, data reviews and the report audit were reported in written form to the study director and to management. The dates of such inspections and of the report audit are given below:

Date of Inspection	Phase(s) Inspected/Audited	Date of report to	
		Management	Study Director
16 June 2011	Study Plan	16 June 2011	16 June 2011
21 June 2011	Treatment	21 June 2011	21 June 2011
03 August 2011	Draft Report	03 August 2011	03 August 2011
23 November 2011	Final Report	23 November 2011	23 November 2011

Signature: Czuczay Diána Date: 24 November 2011

Diána Czuczay, M.Sc.
QA Inspector

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Syngenta Ltd. (as Sponsor) and CiToxLAB Hungary Ltd. (Test facility), the study titled "Propiconazole/Isopyrazam WG (A18289B) - Acute Oral Toxicity Study in the Rat (Up and Down Procedure)" was performed, in compliance with OECD 425 (October 2008), OPPTS 870.1100 (EPA 712-C-02-190, December 2002) and applicable SOP's of CiToxLAB Hungary Ltd.

Signature: _____ Date: 24 Nov 2011

Christopher Banks, DABT
Managing Director

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function
Istvánné Kiss, M.Sc.	Study Director (final report phase)
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David Cowie PhD.	Syngenta Study Manager

Study dates

Experimental Starting Date	21 June 2011
Experimental Completion Date	15 July 2011
Reception of Animals	17 June 2011
Acclimatization	At least 5 days
Treatment	21 June 2011 (female no. 6936) 22 June 2011 (female no. 6937) 24 June 2011 (female no. 6938) 28 June 2011 (female no. 6939) 30 June 2011 (female no. 6940) 01 July 2011 (female no. 6941)
Observation	21 June 2011 (female no. 6936) 22 June 2011 to 06 July 2011 (female no. 6937) 24 - 27 June 2011 (female no. 6938) 28 June 2011 to 12 July 2011 (female no. 6939) 30 June 2011 (female no. 6940) 01 – 15 July 2011 (female no. 6941)

Deviations from the study plan

Concerning: Study Schedule
According to the Study Plan: Animal receipt: 16 June 2011
Deviation: Animal receipt: 17 June 2011
Reason: Animals arrived later than was planned

This deviation is considered to have no impact on the outcome of the study or the interpretation of the results.

Deviations from the guideline

Concerning: Acclimatization time
According to the Study Plan: At least 5 days under laboratory conditions
Deviation: The first animal was treated after 4 days acclimatization.
Reason: Later arrival

This deviation is considered to have no impact on the outcome of the study or the interpretation of the results.

These deviations are considered to have no impact on the outcome of the study or the interpretation of the results.

Performing laboratory test substance reference number

110113

Other

The study documents:
- study plan and its amendment,
- all raw data,
- sample of the test item,
- original final study report and any amendments,
- correspondence

will be archived according to the Hungarian GLP and to applicable SOP's in the archives of CiToxLAB Hungary Ltd. 8200 Veszprém, Szabadságpuszta, Hungary.

After the retention time of 15 years has elapsed all the archived materials listed above will be returned to the Sponsor or retained for a further period if agreed by a contract. Otherwise the materials will be discarded.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

1.1 Study Design

An acute oral toxicity (up and down procedure) study was conducted with 6 animals (female RjHan:WI (SPF) rat). As the test item caused mortality in the first treated animal at 2000 mg/kg bodweight (bw), the limit test was terminated and a main test was conducted starting at 550 mg/kg bw. Animals were treated with a single oral (gavage) dose of Propiconazole/Isopyrazam WG (A18289B) at a dose level of 550 or 2000 mg/kg bw followed by a 14 day observation period. The animals were fasted overnight prior to treatment and food was returned approximately 3 hours after dosing.

Surviving animals were observed individually after dosing at 20 and/or 30 minutes, 1, 2, 3, 4 and 6 hours post treatment and once each day for 14 days thereafter. Body weight was measured on Day -1 (prior to removal of food), Day 0 (prior to administration) and weekly thereafter. All surviving animals were examined macroscopically at the end of the study. Moreover, the animals found dead were examined macroscopically and body weight was recorded at necropsy.

1.2 Results

2000 mg/kg body weight (three animals)

Mortality was observed in all animals at 2000 mg/kg bw (3/3).

Clinical signs of toxicity, including decreased activity, prone position,cold body and decreased respiratory rate were observed in all animals (3/3). Additionally, irritability (2/3), incoordination (2/3) and skin pallor (1/3) were seen in rats dosed at 2000 mg/kg bw.

Dark brown discoloration of the stomach mucosa was found in one female at necropsy and was considered to be associated with administration of the test item.

550 mg/kg body weight (three animals)

No mortality was observed following treatment at 550 mg/kg bw (0/3).

Clinical signs of toxicity, including decreased activity and hunched back were observed in all animals (3/3). Additionally, piloerection (1/3) was noted in a single rat dosed at 550 mg/kg bw.

No treatment related macroscopic findings were observed in the 550 mg/kg treatnment group at necropsy

Body weight measurements of the surviving animals during the study showed no indication of a treatment-related effect.

1.3 Conclusion

Under the conditions of this study, the acute oral median lethal dose (LD_{50}) of Propiconazole/Isopyrazam WG (A18289B) was calculated to be 1049 mg/kg bw in female RjHan:WI rats.

2.0 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the acute oral toxicity of the test item Propiconazole/Isopyrazam WG (A18289B) using the Modified Up-and-Down Procedure (ASTM, 1987). The results of the study allowed the test item to be ranked according to most classification systems currently in use.

2.2 Guidelines

The study was performed according to the following guidelines:

- OECD Guideline Reference 425. Acute Oral Toxicity - Up-and-Down Procedure(2008).

- United States Environmental Protection Agency, Health Effects Division Test Guidelines, OPPTS 870.1100 Acute Oral Toxicity EPA 712-C-02-190 (2002).

2.3 Test Facility

This study was performed in an AAALAC-accredited laboratory. The Institutional Animal Care and Use Committee (IACUC) of CiToxLAB Hungary Ltd. reviewed the study plan and authorized the conduct of the study.

3.0 MATERIALS AND METHODS

3.1 Test Substance

Data as supplied by the Sponsor.

Name:	Propiconazole/Isopyrazam WG (A18289B)
Product code:	A18289B
Synonyms:	propiconazole /isopyrazam WG (12.5/12.5)
Batch number:	SMU1AP002
Content of	
propiconazole:	12.1% w/w
isopyrazam:	12.6% w/w
SYN534969:	10.8% w/w
SYN534968	1.75% w/w
Appearance:	dark brown solid
Recertification date:	End of February 2014
Storage conditions:	Room temperature (<30 ^{o}C)
Safety Precautions:	Routine safety precautions (lab coat, safety glasses, gloves, face mask) for unknown materials were applied to assure personnel health and safety.

The certificate of analysis is attached in Appendix 2.

Vehicle:	Distilled water
Batch no.:	0110111
Expiry Date:	January 2014
Dose volume:	10 mL/kg bw

3.1.1 Identification, receipt

The test item of a suitable chemical purity together with all precautions required in the handling and disposal of the test item were supplied by the Sponsor. The identification of test item was made in the Central Dispensary Unit of CiToxLAB Hungary Ltd. on the basis of the information provided by Sponsor.

3.1.2 Formulation

Propiconazole/Isopyrazam WG (A18289B) was formulated for treatment doses at 550 and 2000 mg/kg bw (dose volume of 10 mL/kg). The test substance was formulated in distilled water. Homogeneity of the test item in the vehicle was maintained during administration using a magnetic stirrer.

3.2 Experimental Animals

Species and strain:	RjHan:WI rats.
Source:	Janvier.
Hygienic level at arrival:	SPF.
Hygienic level during the study:	Standard housing conditions.
Justification of strain:	Recognized by international guidelines as a recommended test system.
Number of animals:	1 animal/step.
Sex:	Female rats.
Age when treated:	Young adult rats, 9 - 10 weeks old.
Body weight (at dosing):	The weight variation in animals involved in the study was not exceed ± 20 % of the mean weight.
Target Body weight range:	193 – 213 g (at dosing).
Randomization:	Selected by hand at time of delivery.
Acclimatization time:	At least 4 days under laboratory conditions, after health examination. Only animals without any visible signs of illness were used for the study.

3.2.1 Husbandry

Animal health:	Only healthy animals were used for the test. The health status was certified by the veterinarian.
Housing:	Individual caging.
Cage type:	Type II. polypropylene/polycarbonate.
Bedding:	Lignocel Bedding for Laboratory Animals was available to animals during the study.
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature during the study:	22±3 °C.
Relative humidity:	30 – 70 %.
Ventilation:	15-20 air exchanges/hour.
Enrichment:	Rodents were housed with deep wood sawdust bedding to allow digging and other normal rodent activities.

The temperature and relative humidity were recorded twice daily during the study and the acclimation period.

3.2.2 Food and water supply

Animals received ssniff® SM R/M-Z+H "Autoclavable complete feed for rats and mice – breeding and maintenance" produced by ssniff Spezialdiäten GmbH, D-59494 Soest Germany *ad libitum*, and tap water from municipal supply, as for human consumption from 500 mL bottle *ad libitum*. The food was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study. Details of the diet are archived with the raw data.

Water quality control analysis is performed once every three months and microbiological assessment is performed monthly, by Veszprém County Institute of State Public Health and Medical Officer Service (ÁNTSZ, H-8201 Veszprém, József A.u.36., Hungary). The quality control results are retained in the archive at CiToxLAB Hungary Ltd.

3.2.3 Identification

Animals were individually identified by numbers written on the tail with a permanent marker pen. The numbers were given on the basis of the CiToxLAB Hungary Ltd. master file, for each animal allocated to the study.

The boxes were identified by cards holding information on the study code, the sex of animals, the dose group, the cage number and the individual animal number.

3.3 Experimental Design

3.3.1 Doses

Justification of the doses:

Initially, a limit test was performed at a dose level of 2000 mg/kg bw. As the test item caused mortality in the first treated animal, the limit test was terminated and a main test was conducted starting at 550 mg/kg bw. The dose volume used at these concentrations is shown below.

Animal Number	Dosage [mg/kg body weight]	Dose volume (mL/animal)	Viability/Mortality
6936	2000	2.0	Died
6937	550	1.9	Survived
6938	2000	2.0	Died
6939	550	2.1	Survived
6940	2000	2.1	Died
6941	550	2.1	Survived

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

3.3.2 Procedure

The animals received a single oral (gavage) administration of the test item followed by a 14 day observation period. For approximately 16 hours before treatment the animals were fasted, but had free access to water. Animals were weighed before dosing and the food was returned approximately 3 hours after treatment.

Single animals were dosed sequentially following an interval of approximately 48 hours. The time intervals between dosing were determined by the onset, duration and severity of toxic signs. Treatment of an animal at the next dose was performed when no significant clinical signs were noted in the previous animal.

The main test was completed having met one of the stopping criteria (5 reversals occured in 6 consecutive animals tested). Once the stopping criteria was attained, the estimated LD_{50} was calculated from the animal outcomes at test termination.

3.4 Observations

3.4.1 Clinical observations

Surviving animals were observed individually after dosing at 20 and/or 30 minutes, 1, 2, 3, 4, and 6 hours after dosing and once each day for 14 days thereafter. Individual observations were performed on the skin and fur, eyes and mucous membranes and also respiratory, circulatory, autonomic and central nervous system, somatomotor activity and behaviour pattern. Particular attention was directed to observation of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

3.4.2 Body weight measurement

The body weights of the surviving animals were recorded on Day -1 and Days 0 (beginning of the experiment) 7 and 14 (surviving animals). The body weight of animals found dead were recorded at necropsy.

3.5 Necropsy

All animals were subjected to a macroscopic examination. Surviving animals were exsanguinated under pentobarbital anaesthesia. After examination of the external appearance, the cranial, thoracic and abdominal cavities were opened and the appearance of the tissues and organs were observed. All gross pathological changes were recorded for each animal on the post mortem record sheets.

3.6 Data Evaluation

The type, severity and duration of clinical observations were recorded. Body weight and body weight changes were summarized in tabular form. Necropsy findings were described and summarized in tabular form.

Data was 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

Mortality was observed in all animals receiving a single dose of Propiconazole/Isopyrazam WG (A18289B) at 2000 mg/kg bw (3/3). No mortality was observed following treatment at 550 mg/kg bw (0/3).

4.2 Body Weights

Body weight and body weight changes of the surviving animals during the study showed no indication of a treatment-related effect.

4.3 Clinical Signs

In rats dosed at 2000 mg/kg bw, clinical signs of toxicity, including decreased activity, prone position, cold body and decreased respiratory rate were observed in all animals (3/3). Additionally, irritability (2/3), incoordination (2/3) and skin pallor (1/3) were seen.

At a dose level of 550 mg/kg bw, clinical signs of toxicity, including decreased activity and hunched back were observed in all animals (3/3). Additionally, piloerection (1/3) was noted.

4.4 Macroscopic Findings

A single 2000 mg/kg bw oral gavage dose of Propiconazole/Isopyrazam WG (A18289B) to the RjHan: WI female rat led to the death of 2 animals on day 0 (2h & 4h post administration respectively) and 1 animal on day 3. Test item-related brown discolored stomach mucosa was seen in 1 female rat at necropsy and was considered to be treatment related.

In animals receiving 550 mg/kg bw of Propiconazole/Isopyrazam WG (A18289B) and terminated to the necropsy on Day 14, no gross observations were noted.

5.0 CONCLUSIONS

Under the conditions of this study, the acute oral median lethal dose (LD_{50}) of Propiconazole/Isopyrazam WG (A18289B) was calculated to be 1049 mg/kg bw in female RjHan:WI rats.

TABLES SECTION

TABLE 1 Individual Findings – Clinical Signs

DOSE LEVEL: 2000 mg/kg bw **SEX: FEMALE**

Cage No.	Animal Number	Observations	Observation days										Frequency
			0							1	2	3	4-14	
			20'	30'	1h	2h	3h	4h	6h					
1	6936#	Activity decreased	2	3	3	Found Dead								3/3
		Irrability	1	-	-									1/3
		Prone position	-	+	+									2/3
		Incoordination	+	-	-									1/3
		Cold to touch	-	-	+									1/3
		Respiratory rate decreased	-	-	1									1/3
		Found Dead	-	-	-	+								-
3	6938#	Activity decreased	2	3	3	3	3	3	3	3	3	Found Dead		9/9
		Irrability	2	-	-	-	-	-	-	-	-			1/9
		Prone position	-	+	+	+	+	+	+	+	+			8/9
		Incoordination	+	-	-	-	-	-	-	-	-			1/9
		Cold to touch	-	-	-	-	+	+	+	+	+			5/9
		Respiratory rate decreased	-	-	-	-	1	1	1	1	1			5/9
		Palaness	-	-	-	-	-	-	-	+	+			2/9
		Found Dead	-	-	-	-	-	-	-	-	-	+		-
5	6940#	Activity decreased	/	2	3	3	3	Found Dead						4/4
		Prone position		+	+	+	+							4/4
		Cold to touch		-	+	+	+							3/4
		Respiratory rate decreased		-	1	1	1							3/4
		Found Dead		-	-	-	-	+						-

DOSE LEVEL: 550 mg/kg bw **SEX: FEMALE**

Cage No.	Animal Number	Observations		Observation days										Frequency
				0						1	2	3	4-14	
			20'	30'	1h	2h	3h	4h	6h					
2	6937	Symptom Free	/	+	-	-	-	-	-	+	+	+	+	15/20
		Activity decreased		-	1	1	1	1	1	-	-	-	-	5/20
		Hunched back		-	-	-	+	+	+	-	-	-	-	3/20
		Piloerection		-	-	-	+	-	-	-	-	-	-	1/20
4	6939	Symptom Free	/	+	+	-	-	-	-	+	+	+	+	16/20
		Activity decreased		-	-	1	1	1	1	-	-	-	-	4/20
		Hunched back		-	-	-	+	+	-	-	-	-	-	2/20
6	6941	Symptom Free	/	+	+	-	-	-	-	-	-	+	+	14/20
		Activity decreased		-	-	1	1	1	1	1	1	-	-	6/20
		Hunched back		-	-	-	+	+	+	+	+	-	-	5/20

Remarks: +: present -: absent

h=hour (s) ': minutes

= found dead / : Not examined at that timepoint

Treatment day= Day 0

Frequency of observation = number of occurence of observation / total number of observations

Severities: 1=Slight/Small/Few; 2=Moderate/Medium; 3=Marked/Large/Many

TABLE 2 Body Weight and Body Weight Gain

DOSE LEVEL: 2000 mg/kg bw									SEX: FEMALE
Cage No.	Animal No.	Body weight (g) Days				Body Weight Gain (g)			
		-1	0	7	14	-1-0	0-7	7- 14	-1 - 14
1	6936#	205	198	-	-	-7	-	-	-
3	6938#	217	203	-	-	-14	-	-	-
5	6940#	229	213	-		-16	-	-	-
Mean:		217.0	204.7	-	-	-12.3	-	-	-
Standard deviation:		12.0	7.6	-	-	4.7	-	-	-

DOSE LEVEL: 550 mg/kg bw									SEX: FEMALE
Cage No.	Animal No.	Body weight (g) Days				Body Weight Gain (g)			
		-1	0	7	14	-1-0	0-7	7- 14	-1 - 14
2	6937	207	193	214	248	-14	21	34	41
4	6939	227	212	235	245	-15	23	10	18
6	6941	219	211	230	239	-8	19	9	20
Mean:		217.7	205.3	226.3	244.0	-12.3	21.0	17.7	26.3
Standard deviation:		10.1	10.7	11.0	4.6	3.8	2.0	14.2	12.7

Remarks: Treatment day= Day 0

#= Found dead

= No data

TABLE 3 Macroscopic Findings

DOSE LEVEL: 2000 mg/kg bw					SEX: FEMALE
Cage No.	**Animal ID**	**Necropsy Date**	**External Observations**	**Internal Observations**	**Organ/Tissue**
1	6936#	21 June 2011	No external observations recorded	Non collapesd	Lungs
				Dark discoloration, brown, diffuse, mucosa	Stomach
3	6938#	27 June 2011	No external observations recorded	Non collapesd	Lungs
				Dark discoloration, red, diffuse all lobes	
5	6940#	30 June 2011	No external observations recorded	Non collapesd	Lungs
				Dark discoloration, red, diffuse all lobes	

DOSE LEVEL: 550 mg/kg bw					SEX: FEMALE
Cage No.	**Animal ID**	**Necropsy Date**	**External Observations**	**Internal Observations**	**Organ/Tissue**
2	6937	06 July 2011	No external observations recorded	No internal observations recorded	Not applicable
4	6939	12 July 2011	No external observations recorded	No internal observations recorded	Not applicable
6	6941	15 July 2011	No external observations recorded	No internal observations recorded	Not applicable

Remark: # = Found Dead

APPENDICES SECTION

APPENDIX 1 Pathology Report

PATHOLOGY REPORT

INTRODUCTION

The objective of the study was to assess the acute oral toxicity of Propiconazole/Isopyrazam WG (A18289B) when administered in a single dose to rats at one or more defined dose levels. The results of the study allows the calculation of the estimated oral LD_{50} of the test item and permits the test item to be ranked according to most classification systems currently in use.

RESULTS AND DISCUSSION

Surviving animals were euthanized upon completion of the treatment period on Day 14. Rats were anesthetized with pentobarbital, followed by exsanguination. Gross pathology consisted of an external examination, including identification of all clinically-recorded lesions, as well as a detailed internal examination. Histopathological examination was not performed.

MORTALITY

Three females were found dead on Day 0 or 3. Necropsy was performed on 3/3 females dosed at 2000 mg/kg bw.

FOUND DEAD

Dark brown discoloration of the stomach mucosa found in 1/3 female at necropsy was considered to be associated with administration of the test item.

Dark/red discoloration and/or non-collapsed lungs were considered to be commonly observed changes in found dead animals.

TERMINAL (DAY 14)

Macroscopic Findings

There was no evidence of the observations at a dose level of 550 mg/kg bw at necropsy.

CONCLUSION

A single oral gavage of Propiconazole/Isopyrazam WG (A18289B) to the RjHan: WI female led to the death of 3 animals at a dose level of 2000 mg/kg bw on Day 0 or 3. Test item-related brown discolored stomach mucosa was seen in 1/3 female rat at necropsy.

APPENDIX 1 Pathology Report (Continued)

In animals receiving 550 mg/kg bw of Propiconazole/Isopyrazam WG (A18289B)) and terminated to the necropsy on Day 14, no gross observations were noted.

23 NOV 2011

Peter Maslej, D.V.M., Ph.D. Date
Head, Pathology Department

APPENDIX 2 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

A18289B
propiconazole/isopyrazam WG (12.5/12.5)
SMU1AP002

Batch Identification	**SMU1AP002**
Product Code	**A18289B**
Other Product Code(s)	propiconazole/isopyrazam WG (12.5/12.5)
Chemical Analysis (Active Ingredient Content)	
– **Identity of propiconazole ***	**confirmed**
– **Identity of isopyrazam ***	**confirmed**
– **Content of propiconazole ***	**12.1 % w/w**
– **Content of isopyrazam (sum of epimer)***	**12.6 % w/w**
– **Content of SYN534969 (syn-epimer of isopyrazam)***	**10.8 % w/w**
– **Content of SYN534968 (anti-epimer of isopyrazam)***	**1.75 % w/w**
Methodology used for Characterization	Cap.-GC

The Active Ingredient content is within the FAO limits.

Physical Analysis	
– **Appearance**	**dark brown solid**

Stability:	
– **Storage Temperature**	**< 30°C**
– **Recertification Date**	**End of February 2014**
–	

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: 122357

Authorization:

09 March 2011

E. Ebi
Analytical Development & Product Chemistry

APPENDIX 3 GLP Certificate

ORSZÁGOS GYÓGYSZERÉSZETI INTÉZET
National Institute of Pharmacy

FŐIGAZGATÓ
1051 Budapest, Zrínyi u. 3.
tel: (1) 8869-320
fax: (1) 8869-480
e-mail: szepezdi.zsuzsanna@ogyi.hu

Ref. no: OGYI/8242-11/2010
Admin.: Urbin Magdolna Zita
Date: 16 December, 2010

GOOD LABORATORY PRACTICE (GLP)
CERTIFICATE

It is hereby certified that the test facility

LAB Research Kft.

(Base facility: H-8201 Veszprém, Szabadságpuszta, Hungary)

is able to carry out

physico-chemical testing, toxicity studies, mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air;bio-accumulation , safety pharmacology testing, reproduction toxicology, inhalation toxicology, analytical chemistry and contract archiving

in compliance with the Principles of GLP (Good Laboratory Practice) and also complies with the corresponding OECD/European Community requirements.

Date of the inspection: **4-8 October, 2010.**

Zsuzsanna Szepezdi, Ph. D.
Director-General

The facility name until 1st September 2011 was LAB Research Ltd. From that date, the registered name has been CiToxLAB Hungary Ltd., this information has been transmitted to the GLP competent authority. The above GLP certificate is valid for this facility (now known as CiToxLAB) until the certificate expires (16 December 2012).

Translation (from Hungarian to English):
Stamp Translation = Országos Gyógyszerészeti Intézet (OGYI) = National Institute of Pharmacy
Főigazgató = Director-General