syngenta

Propiconazole/Pydiflumetofen

Propiconazole/Pydiflumetofen SE (A21573C) - Acute Eye Irritation Study in Rabbits

Final Report

DATA REQUIREMENT(S): OECD 405 (2012)
EPA 870.2400 (1998)
EU No 2017/735, B.5 (2017)

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COMPLETION DATE: 26 April 2018

PERFORMING LABORATORY: Citoxlab Hungary Ltd.
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LABORATORY PROJECT ID: Report Number: 17/349-005N
Study Number: 17/349-005N
Task Number: TK0186805

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

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS
UNDER SPECIFIED FIFRA PROVISIONS

No claim of confidentiality, on any basis whatsoever, is made for any information contained in this document. I acknowledge that information not designated as within the scope of FIFRA sec. 10(d)(1)(A), (B), or (C) and which pertains to a registered or previously registered pesticide is not entitled to confidential treatment and may be released to the public, subject to the provisions regarding disclosure to multinational entities under FIFRA 10(g).

Company: Syngenta Crop Protection, LLC
410 Swing Road
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Submitter: Adora Clark
Adora Clark, Ph.D.

Date: May 21, 2018

Syngenta is the owner of this information and data. Syngenta has submitted this material to the United States Environmental Protection Agency specifically under the provisions contained in FIFRA as amended and, hereby, consents to use and disclosure of this material by EPA according to FIFRA. In submitting this material to EPA according to method and format requirements contained in PR Notice 2011-3, we do not waive any protection or right involving this material that would have been claimed by the company if this material had not been submitted to the EPA, nor do we waive any protection or right provided under FIFRA Section 3 (concerning data exclusivity and data compensation) or FIFRA Section 10(g) (prohibiting disclosure to foreign and multinational pesticide companies or their agents).

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study has been performed in accordance with the Study Plan, and the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17.).

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

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study.

Signature: Máté Weisz Date: 26 April 2018

Máté Weisz, M.Sc.
Study Director

Performing Laboratory:

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May 23, 2018
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FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

Study Number: 17/349-005N

Study Title: Propiconazole/Pydiflumetofen SE (A21573C) - Acute Eye Irritation Study in Rabbits

Test Item: Propiconazole/Pydiflumetofen SE (A21573C)

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
19 December 2017	Study Plan	19 December 2017	19 December 2017
03 January 2018	Observation	03 January 2018	03 January 2018
23 March 2018	Draft Report	23 March 2018	23 March 2018
25 April 2018	Final Report	25 April 2018	25 April 2018

Signature: Ivett Schleicher, Ph.D.
On Behalf of QA

Date: 26 April 2018

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Syngenta Ltd. (as Sponsor) and Citoxlab Hungary Ltd. (as Test Facility) the study titled "Propiconazole/Pydiflumetofen SE (A21573C) - Acute Eye Irritation Study in Rabbits" was performed, in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 26 Oct 2018

Alyson Leyshon, M.Sc.
Managing Director

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function
Máté Weisz, M.Sc.	Study Director
Erika Rosos-Matting, M.Sc.	Assistant Scientist
Leila Merazga, M.Sc.	Quality Assurance Unit
Ivett Schleicher, Ph.D.	Quality Assurance Unit
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Tamás Mészáros, Ph.D.	Pharmacy
Monique Trevisan Inforzato, B.Sc.	Syngenta Study Manager

Other trained, competent personnel worked on the study as required.

Study dates

Study initiation date:	19 December 2017
Experimental starting date:	03 January 2018
Experimental completion date:	26 January 2018
Receipt of animals:	29 November 2017
Acclimation:	29 November – 02/10/18 January 2018
Treatment:	03 January 2018 (animal no. 2583), 11 January 2018 (animal no. 2380), 19 January 2018 (animal no. 2378)
Observation:	03 – 10 January 2018 (animal no. 2583), 11 – 18 January 2018 (animal no. 2380), 19 – 26 January 2018 (animal no. 2378)

Deviations from the guidelines

Due to technical reasons, relative humidity values (maximum of 76%) outside the expected range of 30-70% were recorded during the study. However, these minor differences of the environmental parameter were considered not to adversely affect the results of or integrity of the study.

Performing laboratory test substance reference number

170356

Other

The study documents and samples:
- Study Plan,
- all raw data,
- sample of the test item,
- original Study Report and any amendments,
- correspondence

will be archived according to the Hungarian GLP regulations and to applicable SOPs 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

STATEMENT OF DATA CONFIDENTIALITY CLAIMS **2**

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT **3**

FLAGGING STATEMENT **4**

QUALITY ASSURANCE STATEMENT **5**

MANAGEMENT STATEMENT **6**

GENERAL INFORMATION **7**

TABLE OF CONTENTS **9**

1.0 EXECUTIVE SUMMARY **11**

1.1 Study Design....11
1.2 Results....11
1.3 Conclusion....12

2.0 INTRODUCTION **13**

2.1 Purpose....13
2.2 Guidelines....13
2.3 Test Facility....13

3.0 MATERIALS AND METHODS **14**

3.1 Test Substance....14
3.2 Other Materials....14
3.3 Experimental Design....16
3.3.1 Animals....16
3.3.2 Husbandry....16
3.3.3 Food and feeding....16
3.3.4 Water supply and quality control....17
3.4 Pre-Study and Analgesic and Anaesthetic Treatment Procedures....17
3.4.1 *In vitro* study results....17
3.4.2 Identification of pH....17
3.4.3 Pre-study examination....17
3.4.4 Chronology of animal use....18
3.4.5 Analgesic and anaesthetic treatment....18
3.5 Administration of the Test Item....18
3.5.1 Dosage....18
3.5.2 Application of the test item....18

3.5.3 Duration of exposure....19
3.6 Observations and Scoring....19
3.6.1 Clinical observations and evaluation of ocular irritation....19
3.6.2 Scoring and assessment of local reaction....19
3.6.3 Classification of the test item....19
3.6.4 Measurement of body weight....20
3.7 *Post Mortem* Investigations....20
3.7.1 Materials used for euthanasia....20
4.0 RESULTS AND DISCUSSION 21
4.1 Ocular Reactions....21
4.2 Body Weight....21
4.3 Clinical Signs....21
4.4 Mortality....22
5.0 CONCLUSIONS 22
6.0 REFERENCES 22
TABLES SECTION 23
TABLE 1 Individual Draize Scores and Individual Total Scores* for Ocular Irritation....24
TABLE 2 Individual Total Scores and Group Mean Scores for Ocular Irritation Calculated from the Draize Scores....25
TABLE 3 Individual Fluorescein Staining....25
TABLE 4 Individual Body weights and Body Weight Change....26
TABLE 5 Individual Clinical Signs....26
APPENDICES SECTION 27
APPENDIX 1 Certificate of Analysis....28
APPENDIX 2 Pain Reaction....30
APPENDIX 3 Draize Scale for Scoring Ocular Irritation....31
APPENDIX 4 Modified Kay and Calandra Interpretation of Eye Irritation Test....32
APPENDIX 5 GLP Certificate....33

1.0 EXECUTIVE SUMMARY

1.1 Study Design

The primary eye irritation effect of the test item Propiconazole/Pydiflumetofen SE (A21573C) was investigated using three young adult male New Zealand White rabbits. The test item was administered as an installation of a single dose of 0.1 mL into the conjunctival sac of the left eye with the untreated right eyes serving as the control. Scoring of irritation effects was performed approximately 1, 24, 48, 72 hours and 1 week after test material installation. Observations with fluorescein staining were made approximately 24 hours before treatment and then 24, 48, 72 hours and 1 week after treatment. Rabbits were treated with analgesic and anaesthetic as per the regulatory guideline. Results obtained from these three animals were used to classify the test item for irritation potential.

1.2 Results

No Initial Pain Reaction/Pain reaction (IPR/PR) was observed.

One hour after the application, conjunctival redness (score 2), chemosis (score 2) and discharge (score 3) were noted in all three animals. Additionally, corneal opacity (score 1, area 4) were noted in two animals (no. 2380 and 2378).

At 24 hours after the application, conjunctival redness (score 2), chemosis (score 1) and discharge (score 1 or 2) were noted in all three animals. Additionally, corneal opacity (score 1, area 4) were noted in two animals (no. 2380 and 2378). Fluorescein staining was also positive in all three animals.

At 48 hours after application, conjunctival redness (score 2) and chemosis (score 1) were noted in the first animal (no. 2583). Conjunctival redness (score 2), chemosis (score 1) and corneal opacity (score 1, area 4) were noted in the second animal (no. 2380). Conjunctival redness (score 2), discharge (score 1) and corneal opacity (score 1, area 3) were noted in the third animal (no. 2378). Fluorescein staining was also positive in all three animals.

At 72 hours after application, conjunctival redness (score 1) and chemosis (score 1) were noted in the first animal (no. 2583). Conjunctival redness (score 2), chemosis (score 1) and corneal opacity (score 1, area 4) were noted in the second animal (no. 2380). Conjunctival redness (score 2) and corneal opacity (score 1, area 3) were noted in the third animal (no. 2378). Fluorescein staining was also positive in all three animals.

At 1 week after treatment, no clinical signs and no conjunctival or corneal effects were observed in any animals. Fluorescein staining was negative in all three animals.

The study was terminated 1 week after the treatment of the third rabbit.

The control eye of each animal was symptom-free during the study.

No mortality occurred during the study.

The body weights of all rabbits were considered to be within the normal range of variability.

1.3 Conclusion

The test item Propiconazole/Pydiflumetofen SE (A21573C) was graded as a moderate irritant (Class 5 on a 1 to 8 scale) to the rabbit eye according to the modified Kay and Calandra classification system.

2.0 INTRODUCTION

2.1 Purpose

The purpose of this eye irritation study was to assess the irritancy potential of Propiconazole/Pydiflumetofen SE (A21573C), following a single application to the rabbit eye.

The albino rabbit has been shown to be a suitable model for this type of study and is recommended in regulatory test methods. The results of the study are believed to be of value in predicting the likely eye irritancy potential of the test material to man.

An *in vitro* eye irritation study conducted on isolated chicken eyes with Propiconazole/ Pydiflumetofen SE (A21573C) (Citoxlab code: 17/349-038CS) suggested that the test item is not classified as a severe irritant and not classified as a non-irritant. It was concluded that an *in vivo* study is required for proper classification.

2.2 Guidelines

The study followed the procedures indicated by the following internationally accepted guidelines and recommendations:

- OECD Guidelines for the Testing of Chemicals, Section 4, Number 405 “Acute Eye Irritation/Corrosion”, adopted 02 October 2012.

- United States Environmental Protection Agency, Health Effects Test Guidelines, OPPTS 870.2400, Acute Eye Irritation EPA 712-C-98-195, August 1998.

- Commission Regulation (EU) No 2017/735, B.5 (L 112, 14 February 2017) amending Regulation (EC) No 440/2008.

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 authorised the conduct of the study.

3.0 MATERIALS AND METHODS

3.1 Test Substance

The following information was provided by the Sponsor.

Name:	Propiconazole/Pydiflumetofen SE (A21573C)
Batch number:	1007839
Active ingredient content:	Pydiflumetofen – 13.7% (w/w), corresponding to 151 g/L Propiconazole – 11.6 % (w/w), corresponding to 128 g/L
Appearance:	Beige liquid
Density:	1.100 g/cm^3
Recertification date:	31 October 2020
Storage conditions:	Room temperature (<30 °C)
Safety precautions:	Enhanced safety precautions were applied considering the supplied safety datasheet to assure personnel health and safety.
Hazards:	Causes skin irritation. May cause an allergic skin reaction. Causes eye irritation. May cause cancer. May cause damage to organs through prolonged or repeated exposure.

No adjustment for purity was applied.

A Certificate of Analysis supplied by the Sponsor is given in Appendix 1.

The integrity of supplied data relating to the identity, purity and stability of the test material is the responsibility of the Sponsor.

3.2 Other Materials

For washing and fluorescein control and for treatment:

Name:	Disposable Syringe Luer Solo, 20 mL
Lot No.:	3M09048
Expiry Date:	31 December 2018
Supplier:	B.Braun Melsungen AG

Name:	Saline (0.9% NaCl)
Lot No.:	61461Y05-1
Expiry Date:	31 March 2019
Produced by:	B. Braun Pharmaceuticals SA

Name: Insulin syringe, 1 mL
Lot No.: 2017-04-26
Expiry Date: 26 April 2022
Manufactured by: Jiangxi Hongda Medical Equipment Group Ltd., China

Name: 2% Fluorescein
Dispense codes: S43137 / S43139
Manufacturer: Citoxlab Hungary Ltd.
Expiry Dates: 18 January 2018/ 18 February 2018

The 2% Fluorescein solution was prepared from 10% Fluorescein solution produced by Alcon (Batch numbers: 268003F / 271594F, Expiry dates: 31 August 2018 / 31 October 2018) and Saline solution produced by B. Braun Pharmaceuticals SA (Batch numbers: 72034Y05-1 / 72522Y05-2, Expiry dates: 30 April 2020 / 31 May 2020).

Systemic opiate analgesic:

Name: Bupredine Multidose 0.3 mg/mL (Buprenorphine)
Batch No.: 16D188
Expiry Date: 30 September 2018
Produced by: Le Vet. Beheer B.V.

Topical ocular anaesthetic:

Name: Benoxi 4 mg/mL (Oxybuprocaine chloride)
Batch No.: 050416
Expiry Date: 31 August 2018
Produced by: Unimed Pharma

Non-steroidal anti-inflammatory drug:

Name: Loxicom 5 mg/mL (Meloxicam)
Batch No.: 7041-94C
Expiry Date: 31 July 2018
Produced by: Norbrook Laboratories Ltd.

3.3 Experimental Design

3.3.1 Animals

Species and strain:	New Zealand White rabbit
Source:	S&K-LAP Kft. 2173 Kartal, Császár út 135, Hungary
Justification of strain:	The New Zealand White rabbit is one of the standard strains used for acute irritation toxicity studies.
Number of animals:	3 animals
Sex:	Male
Age of animals at dosing:	~15-17 weeks
Body weight range at dosing:	3990 – 4170 g
Body weight range at termination:	4097 – 4293 g
Identification:	The animals were identified by engraved ear tags. The cages were marked with individual identity cards with information about study number, sex, cage number, dose and individual animal number.
Acclimation time:	35 / 43 / 51 days

3.3.2 Husbandry

Animal health:	Only healthy animals were used for the study, as certified by the staff Veterinarian.
Rooms:	033, 034
Housing/Enrichment:	Rabbits were individually housed in AAALAC approved metal wire rabbit cages. Cages were of an open wire structure and cages were placed together to allow some social interaction with rabbit(s) in adjoining cages.
Light:	12 hours daily from 6.00 a.m. to 6.00 p.m. (and during the analgesic/anaesthetic treatment)
Temperature:	19.6 – 22.5 °C
Relative humidity:	35 – 76 %
Ventilation:	15-20 air exchanges/hour.

The temperature and relative humidity values were measured continuously. The measured range was checked regularly during the acclimation and experimental phases.

3.3.3 Food and feeding

The animals received UNI diet for rabbits produced by Cargill Takarmány Zrt., H-5300 Karcag, Madarasi út, Hungary, *ad libitum*. The batch numbers of the lots used in the study were:

Batch number: 0004489364, expiry date: 11 January 2018,
Batch number: 0004634810, expiry date: 13 March 2018.

The food was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study. A detailed description of the contents of the lots used is archived with the raw data at Citoxlab Hungary Ltd.

3.3.4 Water supply and quality control

The animals received tap water, fit for human consumption, *ad libitum*, from the automatic system supplied by the communal water network. The water was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study.

The quality control analysis is performed once every 3 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.

3.4 Pre-Study and Analgesic and Anaesthetic Treatment Procedures

3.4.1 *In vitro* study results

An *in vitro* eye irritation study was performed prior to treatment on any animal. The results from the *in vitro* eye irritation study (Citoxlab code: 17/349-038CS) in the Isolated Chicken Eye model with Propiconazole/Pydiflumetofen SE (A21573C), in accordance with the guidance from the OECD 438 for this method, suggested that the test item is not classified as a severe irritant and not classified as a non-irritant. It was concluded that an *in vivo* study is required for proper classification.

3.4.2 Identification of pH

The pH of the test item was measured as pH 6.0, permitting the test item to be used in the animal studies.

3.4.3 Pre-study examination

Before the start of the test, both eyes of the provisionally selected test rabbits were examined for evidence of ocular irritation or defect. Additionally, to assess the presence of corneal damage, fluorescein staining was employed at least approximately 24 hours prior to instillation, using a hand-held slit-lamp. Only animals free of ocular damage were used.

3.4.4 Chronology of animal use

The first animal (no. 2583) showed scores of above zero at 1, 24, 48 and 72-hour observation points after treatment and the fluorescein staining was positive at 24, 48 and 72-hour observation points after treatment. This animal became symptom-free after 1 week, thus a second animal (no. 2380) was treated after the 7-day observation of the first animal. The second animal showed scores of above zero at 1, 24, 48 and 72-hour observation points after treatment, the fluorescein staining was positive at 24, 48 and 72-hour observation points after treatment. This animal became symptom-free after 1 week, thus a third animal (no. 2378) was treated after the 7-day observation of the second animal.

3.4.5 Analgesic and anaesthetic treatment

Sixty minutes (60 ±10 min) prior to test substance application, a systemic opiate analgesic was administered by subcutaneous injection under direct Veterinary supervision. Repeat injections were given on the first day as appropriate to maintain an adequate level of analgesia.

Five minutes (5 ±1.5 min) prior to test substance application, a topical ocular anaesthetic was applied to each eye (including the control eye) to ensure direct comparison of any ocular observations.

Eight hours (8 to 9 hr) after test substance application, a systemic opiate analgesic and a non-steroidal anti-inflammatory drug (NSAID) were administered by subcutaneous injection under direct Veterinary supervision. The systemic opiate analgesic was injected again ~12 hours after the post-treatment analgesic and then every 12 hours, and NSAID injected every ~24 hours, until eye scores were zero.

Systemic opiate analgesic: Bupredine Multidose (0.3 mg/mL buprenorphine) 0.01 mg/kg.
Topical ocular anaesthetic: Benoxi (4 mg/mL oxybuprocaine chloride) one-two drops/eye.
Nonsteroidal anti-inflammatory drug: Loxicom (5 mg/mL meloxicam) 0.5 mg/kg.

3.5 Administration of the Test Item

3.5.1 Dosage

A single amount of 0.1 mL of Propiconazole/Pydiflumetofen SE (A21573C) was administered to the left eye of each animal.

3.5.2 Application of the test item

The test substance was placed in the conjunctival sac of the left eye of the animal after gently pulling the lower lid away from the eyeball. The lids were then gently held together for at least one second in order to prevent loss of the material.

The untreated contralateral eye served as the control.

3.5.3 Duration of exposure

Both eyes of the test animals were rinsed with physiological saline solution following fluorescein control: 24, 48, 72 hours and 1 week after test item application as part of the fluorescein observation process.

3.6 Observations and Scoring

3.6.1 Clinical observations and evaluation of ocular irritation

Scoring of irritation effects was performed approximately 1, 24, 48, 72 hours and 1 week after test material installation. Observations with fluorescein staining were made approximately 24 hours before treatment and then 24, 48, 72 hours and 1 week after treatment.

The duration of the observation period was sufficient to identify reversibility or irreversibility of changes. Any clinical signs of toxicity or signs of ill-health during the study were recorded. All rabbits were examined for distress at least twice daily, with observations at least 6 hours apart. Clinical observations or signs of ill-health were recorded.

3.6.2 Scoring and assessment of local reaction

The eye irritation scores were evaluated according to the scoring system by Draize (1977) and OECD 405 (02 October 2012) shown in Appendix 3.

3.6.3 Classification of the test item

The numerical values corresponding to each animal, tissue and observation time were recorded. The data relating to the conjunctivae were designated by the letters A (redness), B (chemosis) and C (discharge), those relating to the iris designated by the letter D and those relating to the cornea by the letters E (degree of opacity) and F (area of cornea involved). For each tissue the score was calculated as follows:

Score for conjunctivae	=	(A + B + C) x 2
Score for iris	=	D x 5
Score for cornea	=	(E x F) x 5

Using the numerical data obtained a modified version of the system described by Kay J H and Calandra J C (1962), J. Soc. Cosmet. Chem. 13, 281 289 (see Appendix 4) was used to classify the ocular irritancy potential of the test material. This was achieved by adding together the scores for the cornea, iris and conjunctivae for each time point for each rabbit. The group means of the total scores for each observation were calculated. The highest of these group means (the maximum group mean score) together with the persistence of the reactions enabled classification of the eye irritancy potential of the test material.

3.6.4 Measurement of body weight

Individual body weight was recorded on the day of treatment and before euthanasia (Table 4).

3.7 *Post Mortem* Investigations

At the end of the observation period, animals were euthanised by intramuscular injections of ketamine 10% (Ketanest) and xylazine 2% (Nerfasin) followed by intravenous pentobarbital sodium (Euthanimal 40%) anaesthesia. Following confirmation of death, the carcasses were discarded without further examination. Details of materials employed for euthanasia are retained in the raw data and detailed in Section 3.7.1.

3.7.1 Materials used for euthanasia

Name:	Ketanest 100 mg/ml (ketamine)
Batch No.:	H1023-10
Expiry Date:	31 March 2019
Produced by:	Bela-pharm GmbH & Co. KG, Germany
Name:	Nerfasin 20 mg/ml (xylazine)
Batch No.:	16A134
Expiry Date:	31 December 2018
Produced by:	Le Vet B.V., The Netherlands
Name:	Euthanimal 40% (pentobarbital sodium)
Lot No.:	1609291-03
Expiry Date:	31 October 2019
Produced by:	Alfasan Nederland BV, The Netherlands

4.0 RESULTS AND DISCUSSION

4.1 Ocular Reactions

Individual ocular reactions and individual total scores results are presented in Table 1 and 2.

No Initial Pain Reaction/Pain reaction (IPR/PR) was observed.

One hour after the application, conjunctival redness (score 2), chemosis (score 2) and discharge (score 3) were noted in all three animals. Additionally, corneal opacity (score 1, area 4) were noted in two animals (no. 2380 and 2378).

At 24 hours after the application, conjunctival redness (score 2), chemosis (score 1) and discharge (score 1 or 2) were noted in all three animals. Additionally, corneal opacity (score 1, area 4) were noted in two animals (no. 2380 and 2378). Fluorescein staining was also positive in all three animals.

At 48 hours after application, conjunctival redness (score 2) and chemosis (score 1) were noted in the first animal (no. 2583). Conjunctival redness (score 2), chemosis (score 1) and corneal opacity (score 1, area 4) were noted in the second animal (no. 2380). Conjunctival redness (score 2), discharge (score 1) and corneal opacity (score 1, area 3) were noted in the third animal (no. 2378). Fluorescein staining was also positive in all three animals.

At 72 hours after application, conjunctival redness (score 1) and chemosis (score 1) were noted in the first animal (no. 2583). Conjunctival redness (score 2), chemosis (score 1) and corneal opacity (score 1, area 4) were noted in the second animal (no. 2380). Conjunctival redness (score 2) and corneal opacity (score 1, area 3) were noted in the third animal (no. 2378). Fluorescein staining was also positive in all three animals.

At 1 week after treatment, no clinical signs and no conjunctival or corneal effects were observed in any animals. Fluorescein staining was negative in all three animals.

The study was terminated 1 week after the treatment of the third rabbit.

The control eye of each animal was symptom-free during the study.

4.2 Body Weight

The body weights of all rabbits were considered to be within the normal range of variability.

Individual body weights and body weight changes are given in Table 4.

4.3 Clinical Signs

No clinical signs of systemic toxicity were observed in any animal in this study (Table 5).

4.4 Mortality

No mortality occurred during the study.

5.0 CONCLUSIONS

The test item Propiconazole/Pydiflumetofen SE (A21573C) was graded as a moderate irritant (Class 5 on a 1 to 8 scale) to the rabbit eye according to the modified Kay and Calandra classification system.

6.0 REFERENCES

Kay JH. Calandra JC. (1962): Interpretation of eye irritation tests. J Soc Cosmet Chem 13:281–289.

Varga-Kanizsai B. (2018). Propiconazole/Pydiflumetofen SE (A21573C) – *In Vitro* Eye Irritation Test in Isolated Chicken Eyes. Citoxlab Hungary study code: 17/349-038CS.

TABLES SECTION

TABLE 1 Individual Draize Scores and Individual Total Scores* for Ocular Irritation

Based on Kay J H and Calandra J C (1962)

Rabbit number and sex	**2583, male**					**2380, male**					**2378, male**				
IPR	0					0					0				
PR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Time after treatment	1 Hr	24 Hr	48 Hr	72 Hr	1 W	1 Hr	24 Hr	48 Hr	72 Hr	1 W	1 Hr	24 Hr	48 Hr	72 Hr	1 W
CORNEA															
E = Degree of Opacity	0	0	0	0	0	1	1	1	1	0	1	1	1	1	0
F = Area of Cornea involved	0	0	0	0	0	4	4	4	4	0	4	4	3	3	0
* Score (E x F) x 5	0	0	0	0	0	20	20	20	20	0	20	20	15	15	0
IRIS															
D	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
* Score (D x 5)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CONJUNCTIVAE															
A = Redness	2	2	2	1	0	2	2	2	2	0	2	2	2	2	0
B = Chemosis	2	1	1	1	0	2	1	1	1	0	2	1	0	0	0
C = Discharge	3	2	0	0	0	3	1	0	0	0	3	2	1	0	0
* Score (A+B+C) x 2	14	10	6	4	0	14	8	6	6	0	14	10	6	4	0
* Total Score	14	10	6	4	0	34	28	26	26	0	34	30	21	19	0

IPR: Initial pain reaction
PR: Pain reaction
Hr: Hour(s)
W: Week(s)

TABLE 2 Individual Total Scores and Group Mean Scores for Ocular Irritation Calculated from the Draize Scores

Rabbit Number and Sex	* Individual Total Scores At:				
	1 Hour	24 Hours	48 Hours	72 Hours	1 Week
2583, male	14	10	6	4	0
2380, male	34	28	26	26	0
2378, male	34	30	21	19	0
* Group Total	82	68	53	49	0
* Group Mean Score	27.33	22.67	17.67	16.33	0

*: Kay J H and Calandra J C (1962)

TABLE 3 Individual Fluorescein Staining

Rabbit Number and sex	Fluorescein Staining (treated eye)				
	24 Hours Prior to Instillation	24 Hours After Instillation	48 Hours After Instillation	72 Hours After Instillation	1 Week After Instillation
2583, male	-	+	+	+	-
2380, male	-	+	+	+	-
2378, male	-	+	+	+	-

- : Absence of Fluorescein Stain
+ : Presence of Fluorescein Stain

TABLE 4 Individual Body weights and Body Weight Change

Rabbit Number and Sex	Individual Body Weight (g)		Body Weight Change (g)
	Before treatment	At termination	
2583, male	4060	4169	109
2380, male	4170	4293	123
2378, male	3990	4097	107

TABLE 5 Individual Clinical Signs

Rabbit Number and Sex	Day 0	Day 1	Day 2	Day 3	Week 1
2583, male	N	N	N	N	N
2380, male	N	N	N	N	N
2378, male	N	N	N	N	N

N: Symptom-free

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis

syngenta

Syngenta Crop Protection, LLC
Analytical and Product Chemistry
Greensboro, NC 27409

Certificate of Analysis

A21573C

Batch ID 1007839 (GP170913)

Test Substance Name:	CGA64250/SYN545974 SE (125/150)
Common Name:	Propiconazole/Pydiflumetofen SE (125/150)
Design Code:	A21573C
Batch ID:	1007839
Other ID:	GP170913
Source:	Syngenta Crop Protection LLC.,US ,410 Swing Road,Greensboro, NC 27409,

Chemical Analysis

AI	% w/w	g/L
Pydiflumetofen	13.7	151
Propiconazole	11.6	128

Identity of the Active Ingredients: Confirmed

Methodology Used for Characterization: LC , mass spectrometry, oscillating density meter

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

Isomer Assay

Analyte	Isomer	% w/w	g/L
CGA93590	1H-1,2,4-triazole, 1-{[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl}-, cis-	6.73	74
CGA93591	1H-1,2,4-triazole, 1-{[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl}-, trans-	4.84	53.2

COA Number: USGR170462

Page 1 of 2

APPENDIX 1 Certificate of Analysis (Continued)

Physical Analysis

Property	Value	Units
Density	1.100	g/cm3

Appearance: Beige liquid

Storage Temperature: <30°C

Re-certification Date:End of Oct/2020

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

The stability of this test substance will be determined concurrently through reanalysis of material held in inventory under GLP conditions at Syngenta Crop Protection, LLC, Greensboro, NC.

This Certificate of Analysis is summarizing data from a study that has been performed in compliance with Good Laboratory Practices per 40 CFR Part 160. Raw data, documentation, protocols, any amendments to study protocols and reports pertaining to this study are maintained in the Syngenta Crop Protection Archives in Greensboro, NC.

Study Number: USGR170462

Authorization: Kirt Durand

Kirt Durand — Date: Oct. 13, 2017

Analytical and Product Chemistry Department

COA Number: USGR170462 Page 2 of 2

APPENDIX 2 Pain Reaction

When the test material is instilled in the eye there may be an initial local pain reaction (IPR) and local pain reaction (PR). The reaction was graded as follows:

IPR/PR Score	Reaction by Animal	Descriptive Rating
0	No response	No pain
1	A few blinks only, normal within one or two minutes	Practically no pain
2	Rabbit blinks and tries to open eye, but reflex closes it	Slight pain
3	Rabbit holds eye shut and puts pressure on lids, may rub eye with paw	Moderate pain
4	Rabbit holds eye shut vigorously, may squeal	Severe pain
5	Rabbit holds eye shut vigorously, may squeal, claw at eye, jump and try to escape	Very severe pain

NOTE: If an IPR/PR score of 4 or 5 is observed, or if more than transient score 3 is observed, then the rabbit is treated with "rescue analgesia".

APPENDIX 3 Draize Scale for Scoring Ocular Irritation

1. CONJUNCTIVAE

(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal	0
Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2
Diffuse beefy red	3

(B) Chemosis

No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids half closed to completely closed	4

(C) Discharge

No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs a considerable area around the eye	3

*** THE TOTAL SCORE = (A + B + C) x 2 MAXIMUM TOTAL = 20**

2. IRIS

(D) Values

Normal	0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive)	1
No reaction to light, haemorrhage, gross destruction (any or all of these)	2

*** THE TOTAL SCORE = D x 5 MAXIMUM TOTAL = 10**

3. CORNEA

(E) Degree of Opacity (most dense area used)

No opacity	0
Scattered or diffuse areas, details of iris clearly visible	1
Easily discernible translucent areas, details of iris slightly obscured	2
Opalescent areas, no details of iris visible, size of pupil barely discernible	3
Opaque, iris not discernible through the opacity	4

(F) Area of Cornea Involved

One quarter (or less) but not zero	1
Greater than one quarter but less than half	2
Greater than half but less than three quarters	3
Greater than three quarters, up to whole area	4

*** THE TOTAL SCORE = (E x F) x 5 MAXIMUM TOTAL = 80**

*** MAXIMUM TOTAL SCORE POSSIBLE = 110**

*: Total scores according to Kay and Calandra system (1962)

APPENDIX 4 Modified Kay and Calandra Interpretation of Eye Irritation Test

MAXIMUM MEAN SCORE		PERSISTENCE OF SCORE	DESCRIPTION RATING (AND CLASS)	
0.0 to 0.5	Group mean total score at 24 hours = 0 Group mean total score at 24 hours > 0		Non-irritant Practically non-irritant	(1) (2)
0.5 to 2.5	Group mean total score at 24 hours = 0 Group mean total score at 24 hours > 0		Practically non-irritant Minimal irritant	(2) (3)
2.5 to 15	Group mean total score at 48 hours = 0 Group mean total score at 48 hours > 0		Minimal irritant Mild irritant	(3) (4)
15 to 25	Group mean total score at 72 hours = 0 Group mean total score at 72 hours > 0		Mild irritant Moderate irritant	(4) (5)
25 to 50	Group mean total score at 7 days 20 or less	More than half of the individual total scores at 7 days 10 or less	Moderate irritant	(5)
		More than half of the individual total scores at 7 days > 10 but no individual total score at 7 days > 30	Moderate irritant	(5)
		More than half of the individual total scores at 7 days > 10 and any individual score at 7 days > 30	Severe irritant	(6)
	Group mean total score at 7 days > 20		Severe irritant	(6)
50 to 80	Group mean total score at 7 days 40 or less	More than half of the individual total scores at 7 days 30 or less	Severe irritant	(6)
		More than half of the individual total scores at 7 days > 30 but no individual total scores at 7 days > 60	Severe irritant	(6)
		More than half of the individual total scores at 7 days > 30 and individual total score at 7 days > 60	Very severe irritant	(7)
	Group mean total score at 7 days > 40		Very severe irritant	(7)
80 to 100	Group mean total score at 7 days 80 or less	More than half of the individual total scores at 7 days 60 or less	Very severe irritant	(7)
		More than half of the individual total scores at 7 days > 60 but no individual total score at 7 days > 100	Very severe irritant	(7)
		More than half of the individual total scores at 7 days > 60 and individual total score at 7 days > 100	Extremely severe irritant	(8)
	Group mean total score at 7 days > 80		Extremely severe irritant	(8)
100 to 110	Group mean total score at 7 days 80 or less		Very severe irritant	(7)
	Group mean total score at 7 days > 80		Extremely severe irritant	(8)

APPENDIX 5 GLP Certificate

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Ref. no: OGYI/19440-7/2015
Admin.: Szatmári Andrea
Date: 22 September, 2015

GOOD LABORATORY PRACTICE (GLP)
CERTIFICATE

It is hereby certified that the test facility

CiToxLAB Hungary Ltd.

H-8200 Veszprém, Szabadságpuszta

is able to carry out

physico-chemical testing, toxicity studies, in vitro studies and mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, 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: **02-04. June 2015.**

Dr. József Reiter
Deputy Director-General

Note: Translation of the Stamp on the official document ("Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet"): ("National Institute of Pharmacy and Nutrition"