

**SYN549522**

**SYN549522 SC (A22011B) -  
Acute Oral Toxicity Study in Rats  
(Up and Down Procedure)**

**Final Report**

**DATA REQUIREMENT(S):** OECD 425 (2008)  
EPA 870.1100 (2002)

**AUTHOR(S):** Ádám Appl, M.Sc.

**COMPLETION DATE:** 03 January 2019

**PERFORMING LABORATORY:** Citoxlab Hungary Ltd.  
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Hungary

**LABORATORY PROJECT ID:** Report Number: 18/212-001P  
Study Number: 18/212-001P  
Task Number: TK0317171

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

**VOLUME 1 OF 1 OF STUDY  
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## 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: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENY/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.



Ádám Appl, M.Sc.  
Study Director

03 January 2019  
Date

Performing Laboratory:

Citoxlab Hungary Ltd.  
H-8200 Veszprém, Szabadságpuszta  
Hungary

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## QUALITY ASSURANCE STATEMENT

Study Number: 18/212-001P  
Study Title: SYN549522 SC (A22011B) - Acute Oral Toxicity Study in Rats (Up and Down Procedure)  
Test Item: SYN549522 SC (A22011B)

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
14 August 2018	Study Plan	14 August 2018	14 August 2018
22 August 2018	Treatment	22 August 2018	22 August 2018
19 November 2018	Draft Report	19 November 2018	19 November 2018
02 January 2019	Final Report	02 January 2019	02 January 2019

Signature: Nikollett Németh  
Nikollett Németh, B.Sc.  
QA Inspector

Date: 05 January 2019

## 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 "SYN549522 SC (A22011B) - Acute Oral Toxicity Study in Rats (Up and Down Procedure)" has been performed in compliance with the Principles of Good Laboratory Practice.

Signature: \_\_\_\_\_

Alyson Leyshon, M.Sc.  
Managing Director

Date: 03 Jun 2019

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## GENERAL INFORMATION

### Contributors

The following contributed to this report in the capacities indicated:

Name	Function
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Peter Maslej, D.V.M., Ph.D.	Pathology
Tamás Mészáros, Ph.D.	Pharmacy
Monique Inforzato, B.Sc.	Syngenta Study Manager

Other trained, competent personnel worked on the study.

### Study dates

Study initiation date:	14 August 2018
Experimental starting date:	22 August 2018
Experimental completion date:	11 September 2018
Receipt of animals:	16 August 2018
Acclimatisation period:	At least 6 days
Treatment date:	22 August 2018 (female no. 4575) 24 August 2018 (female no. 4576) 28 August 2018 (female no. 4577)
Observation period:	22 August – 05 September 2018 (female no. 4575) 24 August – 07 September 2018 (female no. 4576) 28 August – 11 September 2018 (female no. 4577)
Necropsy:	05 September 2018 (female no. 4575) 07 September 2018 (female no. 4576) 11 September 2018 (female no. 4577)



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## 1.0 EXECUTIVE SUMMARY

### 1.1 Study Design

An acute oral toxicity study was conducted with 3 female Crl:WI Wistar rats. Animals were treated with a single oral (gavage) dose of SYN549522 SC (A22011B) at a dose level of 5000 mg/kg body weight (bw) followed by a 14-day observation period. The animals were fasted overnight prior to treatment and food was returned 3 hours after dosing.

Individual animals were dosed sequentially at no less than 48 hour intervals. The time intervals between doses were determined by the onset, duration and severity of clinical signs. The first animal was treated at a dose level of 5000 mg/kg bw. As no mortality was observed, 2 additional animals were sequentially dosed at 5000 mg/kg bw such that a total of 3 animals were tested.

Animals were observed individually after dosing at 30 minutes, then 1, 2, 3, 4 and 6 hours post treatment and once each day for 14 days thereafter. Body weight was measured on Day -1, just before dosing (Day 0) and weekly thereafter (Days 7 and 14 (before necropsy)). All animals were euthanised and examined macroscopically at necropsy at the end of the observation period.

### 1.2 Results

There was no mortality during the study.

All animals were symptom-free during the 14-day observation period.

There were no treatment related effects on body weight or body weight gain. Body weights were within the range commonly recorded for this strain and age.

There were no macroscopic observations at necropsy at a dose level of 5000 mg/kg bw.

### 1.3 Conclusion

Under the conditions of this study, the acute oral median lethal dose (LD<sub>50</sub>) of the test item, SYN549522 SC (A22011B) was greater than 5000 mg/kg bw in female Crl:WI Wistar rats.

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## 2.0 INTRODUCTION

### 2.1 Purpose

The purpose of the study was to assess the acute oral toxicity of the test item SYN549522 SC (A22011B) when administered as a single oral gavage dose to female rats at one or more defined dose levels.

This study was performed with vertebrate animals as no *in vitro* alternative is available. The study was designed such that the minimum numbers of animals were used.

### 2.2 Guidelines

The study was performed according to the following guidelines:

- OECD Guideline Reference 425 (2008): Acute Oral Toxicity - Up-and-Down Procedure.
- United States Environmental Protection Agency, Health Effects Test Guidelines, OPPTS 870.1100 Acute Oral Toxicity EPA 712-C-02-190, December 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.

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### 3.0 MATERIALS AND METHODS

#### 3.1 Test Substance

The following information was provided by the Sponsor.

Name:	SYN549522 SC (A22011B)
Batch number:	SMU7JP001
Active ingredient content*:	SYN549522 (a mixture of SYN547386 and SYN548941), 38.1 % w/w corresponding to 448 g/L SYN547386, 34.3 % w/w corresponding to 403 g/L SYN548941, 3.83 % w/w corresponding to 45.0 g/L
Density:	1175 kg/m <sup>3</sup>
Appearance:	Beige liquid
Recertification date:	30 November 2020
Storage conditions:	Room temperature (<30°C)
Safety precautions:	Routine safety precautions (gloves, goggles, face mask, lab coat) for unknown materials were applied to assure personnel health and safety.

\*No correction for active ingredient content was applied.

The Certificate of Analysis is presented in Appendix 2.

##### 3.1.1 Identification and receipt

The test item of a suitable active ingredient content together with all precautions required in the handling and disposal of the test item were supplied by the Sponsor. The identification of the test item was made in the Pharmacy of Citoxlab Hungary Ltd. on the basis of the information provided by Sponsor.

##### 3.1.2 Formulation

The test item was administered undiluted.

## 3.2 Experimental Design

### 3.2.1 Animals

Species and strain:	CrI:WI Wistar rats
Source:	Charles River Laboratories, Research Models and Services, Germany GmbH, Sandhofer Weg 7, D-97633 Sulzfeld, Germany
Hygienic level:	SPF at arrival, standard housing conditions during study.
Justification of strain:	Recognized by international guidelines as a recommended test system.
Number of animals:	3
Sex:	Female rats, nulliparous and non-pregnant.
Age when treated:	Young adult rats, 8-9 weeks old.
Body weight (at dosing):	190-213 g
Identification:	The animals were identified by numbers written on the tail with an indelible marker. The cages were marked with individual identity cards with information about study number, sex, cage number, dose group and individual animal number.
Randomisation:	Selected by hand at time of delivery.
Acclimatisation time:	At least 6 days

### 3.2.2 Husbandry

Animal health:	Only healthy animals were used for the test. The health status was certified by the Veterinarian.
Room number:	522/4 and 522/12
Housing / Enrichment:	Animals were housed individually in Type II. polypropylene/polycarbonate cages. Rodents were housed with deep wood sawdust bedding to allow digging and other normal rodent activities.
Bedding and nesting:	“Lignocel 3/4-S” Hygienic Animal Bedding and “Arbocel crinklets natural” nesting material ( <i>produced by J. Rettenmaier &amp; Söhne GmbH + Co.KG, Germany</i> ) were available to animals during the study.
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature:	20.2 – 24.8 °C
Relative humidity:	36 – 67%
Ventilation:	15-20 air exchanges/hour

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

### 3.2.3 Food and feeding

Animals received ssniff® SM R/M "Autoclavable complete diet for rats and mice – breeding and maintenance" produced by ssniff Spezialdiäten GmbH, D-59494, Soest, Germany (Lot number: 840 33675, Expiry date: 31 January 2019) *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. A detailed description of the contents of the lot used is archived with the raw data at Citoxlab Hungary Ltd.

### 3.2.4 Water supply and quality control

Animals received tap water from the municipal supply from 500 mL bottles *ad libitum*. The water was fit for human consumption and was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study.

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 Attila utca 36., Hungary). The quality control results are retained in the archive at Citoxlab Hungary Ltd.

## 3.3 Administration of the Test Item

### 3.3.1 Dosages

Justification of the dose:

A limit test with a starting dose of 5000 mg/kg bw was selected by the Sponsor as there are specific regulatory requirements to test this dose level. A total of 3 animals were tested. The density of the test item was 1175 kg/m<sup>3</sup> as provided by the Sponsor, therefore the dose volume for the first animal was 4.26 mL/kg bw. The individual dose volumes used are shown below.

Animal Number	Dose [mg/kg body weight]	Volume Dosed [mL]	Bodyweight [g]	Mortality
4575	5000	0.91	213	Survived
4576	5000	0.86	202	Survived
4577	5000	0.81	190	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

A single oral (gavage) dose was followed by a 14-day observation period. The animals were fasted overnight prior to treatment. Water was still available, *ad libitum* overnight. Animals were weighed before dosing and the food was returned 3 hours after the treatment.

Individual animals were dosed sequentially following an interval of at least 48 hours. The time intervals between doses were determined by the onset, duration and severity of clinical signs.

### 3.4 Observations

#### 3.4.1 Clinical observations

Animals were observed individually after dosing at 30 minutes, then at 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 were assessed.

Particular attention was directed to observation of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

#### 3.4.2 Body weight measurement

The body weights were recorded on Days -1 (prior to removal of food), 0 (before treatment), 7 and 14 (before necropsy).

### 3.5 Post Mortem Investigations

All animals were subjected to gross macroscopic evaluation. All animals were euthanised under pentobarbital anaesthesia (Euthanival 40%, 400 mg/ml, details in 3.5.1) at the end of the observation period. 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 and the animals were discarded.

#### 3.5.1 Material used for euthanasia

Name:	Euthanival 40% (Pentobarbital sodium, 400 mg/mL)
Lot No.:	1609291-03
Expiry Date:	31 October 2019
Produced by:	Alfasan Nederland BV

### 3.6 Data Evaluation

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

The LD<sub>50</sub> was calculated using the AOT425StatPgm program. This program was prepared for the US Environmental Protection Agency by Westat, May 2001 and updated by the US EPA June 2003. This program was constructed using the most appropriate method to estimate the LD<sub>50</sub>.

## 4.0 RESULTS AND DISCUSSION

### 4.1 Mortality

No mortality occurred during the study.

### 4.2 Clinical Signs

All animals were symptom-free during the 14-day observation period.

Individual clinical observations and mortality results are presented in Table 1.

### 4.3 Body Weights

There were no treatment related effects on body weight or body weight gain. Body weights were within the range commonly recorded for this strain and age.

Individual body weights are presented in Table 2.

### 4.4 Necropsy Findings

There were no macroscopic observations at necropsy at a dose level of 5000 mg/kg bw.

Macroscopic findings are presented in Table 3. The Pathology Report is presented in Appendix 1.

## 5.0 CONCLUSIONS

Under the conditions of this study, the acute oral median lethal dose (LD<sub>50</sub>) of the test item, SYN549522 SC (A22011B) was greater than 5000 mg/kg bw in female Crl:WI Wistar rats.

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**TABLE 1 Individual Findings – Clinical Signs**

**DOSE LEVEL: 5000 mg/kg bw, Treatment on Day 0**

**SEX: FEMALE**

Cage No.	Animal Number	Observations	Observation days													Frequency		
			0						1	2	3	4	5	6	7		8-14	
			30'	1h	2h	3h	4h	6h										
1	4575	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
2	4576	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
3	4577	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20

**Remarks:**

+ = present

h = hour (s)

' = minute

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

**TABLE 2 Body Weight and Body Weight Gain****DOSE LEVEL: 5000 mg/kg bw, Treatment on Day 0****SEX: FEMALE**

Cage No.	Animal Number	Body weight (g)				Body Weight Gain (g)			
		-1	0	7	14	-1-0	0-7	7- 14	-1 - 14
1	4575	229	213	251	282	-16	38	31	53
2	4576	217	202	238	251	-15	36	13	34
3	4577	206	190	222	232	-16	32	10	26
<b>Mean:</b>		217.3	201.7	237.0	255.0	-15.7	35.3	18.0	37.7
<b>Standard deviation:</b>		11.5	11.5	14.5	25.2	0.6	3.1	11.4	13.9

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**TABLE 3 Macroscopic Findings****DOSE LEVEL: 5000 mg/kg bw, Treatment on Day 0****SEX: FEMALE**

<b>Cage No.</b>	<b>Animal Number</b>	<b>Necropsy Date/ Necropsy Day</b>	<b>External Observations</b>	<b>Internal Observations</b>	<b>Organ/Tissue</b>
1	4575	05 Sept 2018 Day 14	No external observations recorded	No internal observations recorded	Not applicable
2	4576	07 Sept 2018 Day 14	No external observations recorded	No internal observations recorded	Not applicable
3	4577	11 Sept 2018 Day 14	No external observations recorded	No internal observations recorded	Not applicable

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## APPENDIX 1 Pathology Report

Study code. 18/212-001P

### PATHOLOGY REPORT

#### INTRODUCTION

The objective of the study was to assess the acute oral toxicity of SYN549522 SC (A22011B) when administered in a single dose to rats at a dose level of 5000 mg/kg bw.

#### METHODS

All animals were euthanized upon completion of the observation period on Day 14. Rats were anaesthetized 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.

#### TERMINAL (DAY 14)

##### Macroscopic Findings

There was no evidence of the macroscopic observations at a dose level of 5000 mg/kg bw.

#### CONCLUSION

A single oral gavage of SYN549522 SC (A22011B) to Crl:WI female rats dosed at 5000 mg/kg bw with a 14 day of observation period was not associated with any macroscopic changes.

  
Peter Maslej, D.V.M., Ph.D.  
Director of Pathology

06 Dec 2018  
Date

RESULTADOS DE TESTES E OUTROS DADOS NÃO DIVULGADOS

Report Number: 18/212-001P

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Estes resultados de testes e outros dados não divulgados são confidenciais e de propriedade da SYNGENTA PROTEÇÃO DE CULTIVOS LTDA., protegidos na forma da Lei 10.603/02 e do artigo 195, XIV da Lei 9.279/96

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Todos os infratores poderão ser processados civil e criminalmente

APPENDIX 2 Certificate of Analysis



Syngenta Crop Protection AG  
 GLP Testing Facility WMU  
 Analytical Development & Product Chemistry  
 Breitenloh 5  
 4333 Munchwilten, Switzerland

Certificate of Analysis

**A22011B**  
**SYN549522 SC (450)**  
**SMU7JP001**

**Batch Identification** SMU7JP001  
 Other Batch ID 1013163  
**Product Code** A22011B  
 Other Product Code(s) SYN549522 SC (450)

**Chemical Analysis (Active Ingredient content)**

- Identity of the Active Ingredient(s)\* confirmed
- Content of SYN549522\* 38.1 % w/w corresponding to 448 g/l
- Content of SYN547386\* 34.3 % w/w corresponding to 403 g/l
- Content of SYN548941\* 3.83 % w/w corresponding to 45.0 g/l

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

Methodology used for Characterization / Recertification HPLC, chiral HPLC, oscillating density meter

**Physical Analysis**

- Appearance beige liquid
- Density\* 1175 kg/m<sup>3</sup>

**Stability:**

- Storage Temperature < 30 °C
- Recertification Date End of November 2020

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 AG, Switzerland.

Study number of batch characterization: CHMU170748  
 Study number(s) of batch recertification: --

Authorization: 30-November-2017

Dr. Christian Mink  
 Analytical Development & Product Chemistry

**RESULTADOS DE TESTES E OUTROS DADOS NÃO DIVULGADOS**

Report Number: 18/212-001P

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## APPENDIX 3 Structured Study Summary

### Structured Study Summary Table

Test substance design code	A22011B
Test substance batch code	SMU7JP001
Test substance purity (% w/w)	SYN549522 (a mixture of SYN547386 and SYN548941): 38.1 % w/w corresponding to 448 g/L SYN547386: 34.3 % w/w corresponding to 403 g/L SYN548941: 3.83 % w/w corresponding to 45.0 g/L
Study number	18/212-001P
Study type	MAMMALIAN ACUTE ORAL
Lab Reference	Citoxlab Hungary Ltd.
Study guidelines	OECD 425 (2008), OPPTS 870.1100
Nonstandard elements	
Species	Rat
Strain	CrI:WI Wistar
TK data collected?	No
Dose units	mg/kg bw
Substance vehicle	none
Dosing approach	Constant Volume
LD50 - Male	
LD50 - Female	Greater than 5000

### Structured Study Results Table

Gender	Dose (mg/kg bw)	Number of animals dosed	Number of animals survived	Adverse Clinical Observations
Female	5000	3	3	-

#### RESULTADOS DE TESTES E OUTROS DADOS NÃO DIVULGADOS

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APPENDIX 4 GLP Certificate



H-1051 Budapest, Zrínyi u. 3.  
1372 P.O. Box:450.  
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460  
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Ref. no: OGYÉI/22762-5/2018

Admin.: Dr. Juhász Uzonka

Date: 03 August 2018

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, mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, analytical and clinical chemistry, pathology studies, preparation of microscopic tissue sections, reproduction toxicology, in vitro studies, inhalation toxicology, 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: 07-11 May 2018.

Tarjáni Ibolda  
Head of Inspectorate

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

RESULTADOS DE TESTES E OUTROS DADOS NÃO DIVULGADOS

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