

SYN550023

**SYN550023 -
Acute Oral Toxicity Study in Rats
(Up and Down Procedure)**

Final Report

TEST GUIDELINE(S): OECD 425 (2008)
EPA 870.1100 (2002)

AUTHOR(S): Csilla Gyömöreiné Nagy, Ph.D.

COMPLETION DATE: 31 May 2021

PERFORMING LABORATORY: Charles River Laboratories Hungary Kft.
H-8200 Veszprém, Szabadságpuszta, hrsz. 028/1.,
Hungary

LABORATORY PROJECT ID: Report Number: 21/062-001P
Study Number: 21/062-001P
Task Number: TK0419883

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

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

The Following Statement Applies To The United States of America:

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
Post Office Box 18300
Greensboro, NC 27419-8300 USA

Submitter: _____ Date: _____

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 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 Charles River Laboratories Hungary Kft. Management, and followed applicable Standard Operating Procedures.

No chemical analysis of the dose formulation was performed as part of this study. Traceability (equipment used, quantities of test item weighed) of dosing form preparations was checked and revealed no abnormalities of consequence. Furthermore, for this study, the formulations were prepared just before the treatment. Consequently, the absence of dose formulation analysis data was considered not to prejudice the overall GLP status of the study and the scientific reliability of the study conclusions.

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. By virtue of my dated signature I accept the responsibility for the validity of the data.

Signature: 
Csilla Gyömöreiné Nagy, Ph.D.
Study Director

Date: 31 MAY 2021

Performing Laboratory: Charles River Laboratories Hungary Kft.
H-8200 Veszprém, Szabadságpuszta, hrsz. 028/1.,
Hungary

To be completed for USA EPA submission only:
Representative of Submitter/Sponsor:

Date

Submitter/Sponsor: Syngenta Crop Protection, LLC
410 Swing Road
Post Office Box 18300
Greensboro, NC 27419-8300 USA

FLAGGING STATEMENT

This page is intentionally left blank. It will be replaced by an appropriate Flagging statement by the sponsor.

QUALITY ASSURANCE STATEMENT

Study Number: 21/062-001P

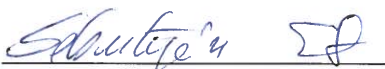
Study Title: SYN550023 - Acute Oral Toxicity Study in Rats (Up and Down Procedure)

Test Item: SYN550023

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
25 March 2021	Study Plan	25 March 2021	25 March 2021
30 March 2021	Treatment	30 March 2021	30 March 2021
21 May 2021	Draft Report	21 May 2021	21 May 2021
31 May 2021	Final Report	31 May 2021	31 May 2021

Signature: 
Eszter Sebestyén, B.Sc.
On behalf of QA

Date: 31 May 2021

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Syngenta Ltd. (as Sponsor) and Charles River Laboratories Hungary Kft. (as Test Facility) the study titled "SYN550023 - Acute Oral Toxicity Study in Rats (Up and Down Procedure)" has been performed in compliance with the Principles of Good Laboratory Practice.

Signature: Balázs Tóth Date: 31 May 2021
Balázs Tóth, Ph.D.
General Manager

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function or Department
Csilla Gyömöreiné Nagy, Ph.D.	Study Director
Erika Rosos-Matting, M.Sc.	Assistant Scientist
Eszter Sebestyén, B.Sc.	Quality Assurance
László Székelyhidi, D.V.M.	Veterinary Care
Tamás Mészáros, Ph.D.	Pharmacy
Ferenc Szűcs	Animal Service Laboratories
Carolina Vaccari, M.Sc.	Syngenta Study Manager

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

Study dates

Study Initiation Date	25 March 2021
Experimental Starting Date	30 March 2021
Experimental Completion Date	27 April 2021
Draft Report	21 May 2021
Final Report	31 May 2021

Receipt of Animals 25 March 2021

Treatment 30 March 2021 (female no. 9432)
01 April 2021 (female no. 9433)
07 April 2021 (female no. 9434)
09 April 2021 (female no. 9435)
13 April 2021 (female no. 9436)

Observation 30 March – 13 April 2021 (female no. 9432)
01 April – 15 April 2021 (female no. 9433)
07 April – 21 April 2021 (female no. 9434)
09 April – 23 April 2021 (female no. 9435)
13 April – 27 April 2021 (female no. 9436)

Necropsy 13 April 2021 (female no. 9432)
15 April 2021 (female no. 9433)
21 April 2021 (female no. 9434)
23 April 2021 (female no. 9435)
27 April 2021 (female no. 9436)

Deviation from the guideline and Study Plan

No deviation occurred during the study.

Performing laboratory test substance reference number

210064

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 Charles River Laboratories Hungary Kft. H-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.

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1.0 EXECUTIVE SUMMARY

1.1 Study Design

In this acute oral toxicity (up and down procedure) study, 5 female Crl:WI rats were given a single oral (gavage) dose of SYN550023 at dose level of 2000 mg/kg body weight (bw).

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 2000 mg/kg bw. The dose selection for the next animals followed the recommendation of AOT425StatPgm software, based on available results.

Animals were observed individually at 30 minutes, and 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), before dosing (on Day 0), on Day 7 and on Day 14. All animals were euthanized and examined macroscopically at the end of the observation period.

1.2 Results

No mortality was observed at the dose level of 2000 mg/kg bw during the study.

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

There was no test item related effect on body weight or body weight gain in any animals. Body weights were within the range commonly recorded for this strain and age.

A single oral gavage of SYN550023 to Crl:WI female rats at dose level of 2000 mg/kg bw was not associated with any gross observations at necropsy.

1.3 Conclusion

Under the conditions of this study, the acute oral median lethal dose (LD₅₀) of the test item SYN550023 was found to be greater than 2000 mg/kg bw in female Crl:WI Wistar rats.

2.0 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the acute oral toxicity of the test item SYN550023 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 Guidelines 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 Charles River Laboratories Hungary Kft. reviewed the Study Plan and authorized the conduct of the study.

3.0 MATERIALS AND METHODS

3.1 Test Substance

The following information was provided by the Sponsor:

Name:	SYN550023
Batch/Lot number:	SMU0IP0001
Chemical name:	[3-(2-methoxy-4-prop-1-ynyl-phenyl)-4-oxo-2-bicyclo[3.2.1]oct-2-enyl] methyl carbonate
Other name:	SYN550023 tech., SYN550023C
Active ingredient content*:	Content of SYN550023 96.6 % w/w
Appearance:	Yellowish solid
Purity:	Considered as 100%
Recertification date:	30 September 2022
Storage conditions:	Room temperature (< 30°C)
Safety precautions:	Routine safety precautions (nitrile gloves, goggles, face mask, lab coat) were applied considering the supplied safety datasheet to assure personnel health and safety.

**Note: No adjustment for active ingredient content was applied.*

The Certificate of Analysis is presented in Appendix 3.

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 Charles River Laboratories Hungary Kft. on the basis of the information provided by the Sponsor.

3.1.2 Formulation

The test item was freshly formulated at concentration of 200 mg/mL in the vehicle in the Pharmacy of Charles River Laboratories Hungary Kft. on the day of administration. The formulation was stirred with a magnetic stirrer until completion of treatment. The vehicle was prepared at the test facility and used for maximum of one month.

Vehicle:

Name: 0.5% Carboxymethylcellulose (CMC)

Dose volume: 10 mL/kg bw

Dispense codes: S23095 / S23096

Expiry Date: 09 April 2021 / 08 May 2021

Storage condition: Refrigerated

Vehicle components:

Name: Carboxymethylcellulose powder

Batch number: BCBN1690V

Manufacturer: Sigma-Aldrich

Expiry Date: 31 Jan 2026

Storage condition: Room temperature, protected from humidity

Name: Distilled water

Batch number: 202011110

Manufacturer: Magilab Kft.

Expiry Date: 19 May 2021

Storage condition: Room temperature

There was no chemical analysis of the dose formulation.

3.2 Experimental Design

3.2.1 Animals

Species and strain:	Crl: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:	5 (1 animal/step)
Sex:	Female rats, nulliparous and non-pregnant
Age when treated:	Young adult rats, 9-11 weeks old
Body weight (at dosing):	230 – 242 g (the weight variation in animals in the study did not exceed ± 20 % of the mean weight)
Identification:	The animals were identified by numbers written on the tail with an indelible pen. The cages were marked with individual identity cards with information about study number, sex, cage number, dose group and individual animal number.
Randomization:	Selected by hand at time of delivery
Acclimatisation time:	At least 5 days

3.2.2 Husbandry

Animal health:	Only healthy animals were used for the test. The health status was certified by the Veterinarian.
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. Additional enrichment (hiding tunnels) were also used during the study.
Bedding / Nesting:	SAFE 3/4 S certified wooden chips and SAFE crinklets natural nest building material produced by J. Rettenmaier & Söhne GmbH + CO.KG (D-73494 Rosenberg, Germany) were available to animals during the study. Copies of the Certificate of Analysis are retained in the Archive at Charles River Laboratories Hungary Kft.
Light:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature:	19.1-24.6°C
Relative humidity:	30-60%
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" (Batch no.: 713 70882, Expiry date: 30 April 2021) produced by ssniff Spezialdiäten GmbH, D-59494 Soest, Germany *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 diets are archived with the raw data at Charles River Laboratories Hungary Kft.

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-8200 Veszprém, József Attila utca 36, Hungary). The quality control results are retained in the archive at Charles River Laboratories Hungary Kft.

3.3 Administration of the Test Item

3.3.1 Dosages

Justification of the doses:

The starting dose of the limit test was 2000 mg/kg bw after discussion with the Sponsor.

The animals were treated with a single oral (gavage) dose of SYN550023 at the dose level of 2000 mg/kg bw. The dose volume was 10 mL/kg bw of the formulated test item in the appropriate vehicle. The individual dose volumes used are shown below.

Animal Number	Dose [mg/kg body weight]	Volume Dosed [mL]	Bodyweight [g]	Mortality
9432	2000	2.3	234	Survived
9433	2000	2.3	230	Survived
9434	2000	2.4	239	Survived
9435	2000	2.4	240	Survived
9436	2000	2.4	242	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 toxic signs.

3.4 Observations

3.4.1 Clinical observations

Animals were observed individually at 30 minutes, 1, 2, 3, 4 and 6 hours after dosing, then once each day for 14 days. Individual observations were performed on the skin, fur, eyes, mucous membranes, somatomotor activity and behaviour pattern as well as respiratory, circulatory, autonomic and central nervous systems.

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 Day -1 (prior to removal of food), on Day 0 (before dosing), on Day 7 and on Day 14 (before necropsy) in all animals until termination.

3.5 Post Mortem Investigations

All animals were subjected to gross macroscopic evaluation. All surviving animals were euthanised under pentobarbital anaesthesia (Euthanimal 40%, details in section 3.5.1) at the end of the observation period. After examination of the external appearance, the cranial, thoracic and abdominal cavities were opened then 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:	Euthanimal 40% (sodium pentobarbital)
Lot No.:	2001004-06
Expiry Date:	31 January 2023
Produced by:	Alfasan Nederland BV, Kuipersweg 9, Woerden, The Netherlands

3.6 Data Evaluation

Type, severity and duration of clinical observations are described in the tables and results of this report. Body weight and body weight changes are summarised in tabular form. Necropsy findings are described and summarised in tabular form.

Data were recorded on the appropriate forms from the relevant SOPs of Charles River Laboratories Hungary Kft., and then tabulated using the Microsoft Office Word and/or Excel or collected using the software PROVANTIS v.9.

The LD₅₀ 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 LD₅₀.

4.0 RESULTS AND DISCUSSION

4.1 Mortality

No mortality was observed at the dose level of 2000 mg/kg bw 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 was no test item related effect on body weight or body weight gain in any animals. Body weights were within the range commonly recorded for this strain and age.

Individual body weights are presented in Table 2.

4.4 Macroscopic Findings

A single oral gavage of SYN550023 to Crl:WI female rats at dose level of 2000 mg/kg bw was not associated with any gross observations at necropsy.

Macroscopic findings are presented in Table 3.

5.0 CONCLUSIONS

Under the conditions of this study, the acute oral median lethal dose (LD₅₀) of the test item SYN550023 was found to be greater than 2000 mg/kg bw in female Crl:WI Wistar rats.

TABLES SECTION

TABLE 1 Individual Findings – Clinical Signs

DOSE LEVEL: 2000 mg/kg bw, Treatment on Day 0															SEX: FEMALE	
Cage No.	Animal Number	Observations	Observation days													
			0						1	2	3	4	5	6	7-14	Frequency
			30'	1h	2h	3h	4h	6h								
1	9432	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
2	9433	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
3	9434	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
4	9435	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
5	9436	Symptom Free	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20

Standard**footnotes:**

+ = present

- = absent

h = hour (s)

' = minute

= Found dead

M = Moribund

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

Severities:

Sl = Slight/Small/Few/Small amount

Mo = Moderate/Several/Moderate amount

Ex = Severe/Large/Many/Large/Extreme amount

TABLE 2 Body Weight and Body Weight Gain

DOSE LEVEL: 2000 mg/kg bw, Treatment on Day 0						SEX: FEMALE		
Cage No.	Animal Number	Body weight (g)				Body Weight Gain (g)		
		Days						
		-1	0	7	14	0-7	7- 14	0 - 14
1	9432	255	234	271	290	37	19	56
2	9433	251	230	248	258	18	10	28
3	9434	256	239	261	273	22	12	34
4	9435	262	240	268	274	28	6	34
5	9436	259	242	282	291	40	9	49
Mean:		256.6	237.0	266.0	277.2	29.0	11.2	40.2
Standard deviation:		4.2	4.9	12.6	13.7	9.4	4.9	11.8

Standard footnotes: # = Found dead M = Moribund

Note: Day -1 prior to fasting, Day 0 prior to administration

TABLE 3 Macroscopic Findings**DOSE LEVEL: 2000 mg/kg bw, Treatment on Day 0****SEX: FEMALE**

Cage No.	Animal Number	Necropsy Day	External Observations	Internal Observations	Organ/Tissue
1	9432	Day 14	No external observations recorded	No internal observations recorded	Not applicable
2	9433	Day 14	No external observations recorded	No internal observations recorded	Not applicable
3	9434	Day 14	No external observations recorded	No internal observations recorded	Not applicable
4	9435	Day 14	No external observations recorded	No internal observations recorded	Not applicable
5	9436	Day 14	No external observations recorded	No internal observations recorded	Not applicable

Standard footnotes: **# = Found dead** **M = Moribund** **- = No data**

APPENDICES SECTION

APPENDIX 1 AOT 425 Report (Limit Test)

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Date/Time: 2021. április 28., szerda, 14:45:01
Data file name: 21-062-001P.dat
Last modified: 2021. 04. 28. 14:45:01

Test/Substance: SYN550023
Test type: Limit Test
Limit dose (mg/kg): 2000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	9432	2000	O	O
2	9433	2000	O	O
3	9434	2000	O	O
4	9435	2000	O	O
5	9436	2000	O	O

(X = Died, O = Survived)

Dose Recommendation: The limit test is complete.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
2000	5	0	5
All Doses	5	0	5

Statistical Estimates:

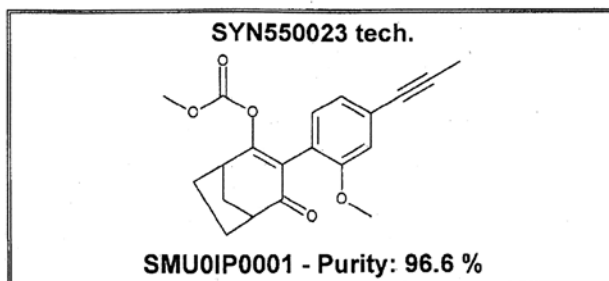
The LD50 is greater than 2000 mg/kg.

APPENDIX 2 Certificate of Analysis



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

Certificate of Analysis



Batch Identification	SMU0IP0001
Other Batch ID	1155250
Product Code	SYN550023 tech.
Other Product Code(s)	SYN550023C
ISO Common Name	---
CA Reg. No.	---
CA Index Name	---
IUPAC Name	[3-(2-methoxy-4-prop-1-ynyl-phenyl)-4-oxo-2-bicyclo[3.2.1]oct-2-enyl] methyl carbonate
Molecular formula	C ₂₆ H ₂₀ O ₅
Molecular mass	340.375
Chemical Analysis	
- Identity of SYN550023*	confirmed
- Content of SYN550023*	96.6 % w/w
	The detailed results of the characterization are listed in the final report
Methodology used for Characterization	LC, GC, IC, Karl Fischer Titration, Fraunhofer diffraction method
Physical Analysis	
- Appearance*	yellowish solid
- Particle size *	47.3 µm (Median of size distribution)
Stability:	
- Storage Temperature	< 30 °C
- Recertification Date	End of September 2022

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: CHMU200860

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

Authorization: 24-SEP-2020

Stefan Ehmele
 Analytical Development & Product Chemistry

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APPENDIX 3 Structured Study Summary

Structured Study Summary Table

Test substance design codes	SYN550023
Test substance batch code	SMU0IP0001
Active ingredient content*	Content of SYN550023 96.6 % w/w
Study number	21/062-001P
Study type	MAMMALIAN ACUTE ORAL
Lab Reference	Charles River Laboratories Hungary Kft.
Study guidelines	OECD 425 (2008), OPPTS 870.1100 (2002)
Nonstandard elements	
Species	Rat
Strain	Crl:WI Wistar
TK data collected?	No
Dose units	mg/kg bw
Substance vehicle	0.5% Carboxymethylcellulose
Dosing approach	diluted
LD ₅₀ - Male	-
LD ₅₀ - Female	>2000 mg/kg bw

**Note: No adjustment for active ingredient content was applied.*

Structured Study Results Table

Gender	Dose (mg/kg bw)	Number of animals dosed	Number of animals survived	Clinical Observations
Female	2000	5	5	NA

APPENDIX 4 GLP Certificate



Hatósági Ellenőrzési Főosztály

1051 Budapest, Zrínyi utca 3.
Levélcíme: 1372 Postafiók 450
Tel.: +36 1 886 9300, Fax: +36 1 886 9460
E-mail: ogyei@ogyei.gov.hu
Web: www.ogyei.gov.hu

Ref. no: OGYÉI/29520-2/2021

Admin.: Dr. Szaller Zoltán

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

It is hereby certified that the test facility

Charles River Laboratories Hungary Kft.

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.

This certificate is valid up to 11th of May, 2022.

Dr. Lukács
Ferenc
József
Dr. Ferenc Lukács
Head of Inspectorate

Digitalisan aláírta:
Dr. Lukács Ferenc
József
Dátum: 2021.05.06
13:04:14 +02'00'

Note: Translation of the text of the certificate in the header: ("Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet") - ("National Institute of Pharmacy and Nutrition"); ("Hatósági Ellenőrzési Főosztály") - (Inspectorate Division) and at the signature: ("Digitálisan aláírta") - (Digitally signed); ("Dátum") - ("Date").