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Thiamethoxam

Thiamethoxam SL (A23943A) - Acute Oral Toxicity Study in Rats (Up and Down Procedure)

Final Report

TEST GUIDELINE(S):	OECD 425 (2008) EPA 870.1100 (2002)
AUTHOR(S):	Balázs Mráz, M.Sc.
COMPLETION DATE:	28 April 2022
PERFORMING LABORATORY:	Charles River Laboratories Hungary Kft. H-8200 Veszprém, Szabadságpuszta, hrsz. 028/1., Hungary
LABORATORY PROJECT ID:	Report Number: 21/309-001P Study Number: 21/309-001P Task Number: TK0544297
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, etc.) 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: _____ Date: 28 April 2022

Balázs Mráz, M.Sc.
Study Director

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

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QUALITY ASSURANCE STATEMENT

Study Number: 21/309-001P

Study Title: Thiamethoxam SL (A23943A) - Acute Oral Toxicity Study in Rats (Up and Down Procedure)

This Study has been audited by Quality Assurance in accordance with the applicable Good Laboratory Practice regulations. Audit reports were submitted in accordance with SOPs as follows:

Date of Inspection	Phase(s) Inspected/Audited	Date of report to	
		Management	Study Director
10 January 2022	Study Plan	10 January 2022	10 January 2022
05 January 2022	Treatment	05 January 2022	05 January 2022
13 January 2022	Clinical Observation	13 January 2022	13 January 2022
11 February 2022	Body Weight Measurement	11 February 2022	11 February 2022
17 March 2022	Necropsy	17 March 2022	17 March 2022
23 March 2022	Draft Report	23 March 2022	23 March 2022
26 April 2022	Final Report	26 April 2022	26 April 2022

In addition to the above-mentioned audits, (which may include study specific inspections and/or relevant process based inspections) routine facility inspections were also conducted.

The Final Report reflects the raw data and accurately and completely describes the methods and procedures of the study.

Signature: Veninger-Gartner Edina Date: 28 April 2022

Edina Veninger-Gartner, B.Sc.
On behalf of QA

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 "Thiamethoxam SL (A23943A) - 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: 28 April 2022

Balázs Tóth, Ph.D.
General Manager

GENERAL INFORMATION

Contributors
The following contributed to this report in the capacities indicated:

Name	Function or Department
Balázs Mráz, M.Sc.	Study Director
Ágnes Katona, M.Sc.	Assistant Scientist
Edina Véninger-Gartner, B.Sc.	Quality Assurance
László Székelyhidi, D.V.M.	Veterinary Care
Tamás Mészáros, Ph.D.	Pharmacy
Ferenc Szűcs	Animal Service Laboratories
Carolina Vaccari, Ph.D.	Syngenta Study Manager

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

Study dates

Study Initiation Date	05 January 2022
Experimental Starting Date	13 January 2022
Experimental Completion Date	24 February 2022
Draft Report	25 March 2022
Final Report	28 April 2022
Receipt of Animals	23 December 2021 / 03 February 2022
Acclimatisation	21 / 12 days
Treatment	13 January 2022 (female no. 2707) 18 January 2022 (female no. 2708) 20 January 2022 (female no. 2709) 25 January 2022 (female no. 2710) 27 January 2022 (female no. 2711) 01 February 2022 (female no. 2715) 03 February 2022 (female no. 2716) 08 February 2022 (female no. 2717) 10 February 2022 (female no. 2718) 15 February 2022 (female no. 3326)
Observation	13 – 27 January 2022 (female no. 2707) 18 January - 01 February 2022 (female no. 2708) 20 January 2022 (female no. 2709) 25 January - 08 February 2022 (female no. 2710) 27 January - 10 February 2022 (female no. 2711) 01 February 2022 (female no. 2715) 03 - 17 February 2022 (female no. 2716)

	08 February 2022 (female no. 2717) 10 - 24 February 2022 (female no. 2718) 15 February 2022 (female no. 3326)
Necropsy	27 January 2022 (female no. 2707) 01 February 2022 (female no. 2708) 20 January 2022 (female no. 2709) 08 February 2022 (female no. 2710) 10 February 2022 (female no. 2711) 01 February 2022 (female no. 2715) 17 February 2022 (female no. 2716) 08 February 2022 (female no. 2717) 24 February 2022 (female no. 2718) 15 February 2022 (female no. 3326)

Deviation from the Study Plan
Temperature values (minimum of 17.8°C) outside the expected range of 19-25°C were recorded during the study. Relative humidity values (minimum of 24% and maximum of 79%) outside the expected range of 30-70% were recorded occasionally. These deviations are considered to have no impact on the outcome of the study and interpretation of the results.

Performing laboratory test substance reference number
210612

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, hrsz. 028/1., 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

In this acute oral toxicity (up and down procedure) study, 10 female Crl:WI Wistar rats were given a single oral (gavage) dose of thiamethoxam SL (A23943A) at a dose level of 550 and 2000 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 550 mg/kg bw. The dose selection for the next animal 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 550 mg/kg bw during the study.

At the dose level of 2000 mg/kg bw, four out of six animals were found dead after treatment.

At dose level 550 mg/kg bw decreased activity (4/4), decreased respiratory rate (3/4), laboured breathing (3/4), prostration (4/4), erected fur (2/4), hunched posture (4/4), slight uncoordination (1/4) occurred. All animals were symptom free from Day 2.

At dose level 2000 mg/kg bw decreased activity (6/6), decreased respiratory rate (6/6), laboured breathing (6/6), prostration (6/6), erected fur (3/6), hunched posture (2/6) occurred. Surviving animals were symptom free from Day 3.

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

1.3 Conclusion

Under the conditions of this study, based on the outcome of AOT425StatPgm program, the estimated acute oral median lethal dose (LD50) of the test item thiamethoxam SL (A23943A) was found to be 2000 mg/kg bw in female Crl:WI Wistar rats. The 95% confidence interval is 846.7 to 4430 mg/kg bw.

2.0 INTRODUCTION

2.1 Purpose

The purpose of the study was to assess the acute oral toxicity of the test item thiamethoxam SL (A23943A) 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 for the Testing of Chemicals, Section 4, Test No. 425 Acute Oral Toxicity: Up-and-Down Procedure. OECD Publishing, 2008.

- 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:	Thiamethoxam SL (A23943A)
Batch number:	NSI001-085-017
Design code:	A23943A
Active ingredient content*:	Thiamethoxam content 6.63% w/w
Density:	1.1378 g/cm³
Appearance:	Dark orange homogeneous and translucent liquid
Recertification date:	10 September 2023
Storage conditions:	Room temperature (<30°C)
Safety precautions:	Enhanced safety precautions (nitrile gloves, goggles, face mask (ABEK-P3-filter), lab coat).
Additional information	
Other name:	TMX 75 SL

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

The Certificate of Analysis is presented in Appendix 2.

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

3.1.1 Identification and receipt

The test item was provided by the Sponsor. All precautions required in the handling and disposal of the test item were outlined by the Sponsor and will be archived. The test item was identified on the basis of information provided by the Sponsor in the Pharmacy Department.

3.1.2 Formulation

The test item was administered undiluted and used as supplied by the Sponsor.

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:	10
Sex:	Female rats, nulliparous and non-pregnant
Age when treated:	Young adult rats, 8-12 weeks old
Body weight (at dosing):	204 – 251 g (the weight variation in animals in the study did not exceed ± 20 % of the mean weight slightly)
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:	21 / 12 days

3.2.2 Husbandry

Animal health:	Only healthy animals were used for the test. The health status was certified by the staff Veterinarian.
Room number:	522/8
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 (‘GLP Maxi Fun Tunnels, LBS UK’) was also used.
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:	17.8 – 23.8°C
Relative humidity:	24 - 79%

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 *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. 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 main test was 550 mg/kg bw was selected by the Study Director after a discussion with the Sponsor.

The animals were treated with a single oral (gavage) dose of thiamethoxam SL (A23943A) at a dose level of 550 or 2000 mg/kg bw. Test item was administered undiluted at a constant concentration adjusting for the specific gravity of the test material.

No mortality was observed at the dose level of 550 mg/kg bw during the study. At the dose level of 2000 mg/kg bw, four out of six animals were found dead after treatment.

The density of the test item was 1.1378 g/cm^3 as provided by the Sponsor, therefore the dose volume for the animals was 0.48 mL/kg bw. The individual dose volumes used are shown below.

Animal Number	Dose [mg/kg body weight]	Volume Dosed [mL]	Bodyweight [g]	Mortality
2707	550	0.10	204	Survived
2708	2000	0.38	215	Survived
2709	2000	0.38	214	Found dead
2710	550	0.10	216	Survived
2711	2000	0.38	218	Survived
2715	2000	0.42	238	Found dead
2716	550	0.12	251	Survived
2717	2000	0.44	249	Found dead
2718	550	0.12	245	Survived
3326	2000	0.43	242	Found dead

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 after dosing 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 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 using the software PROVANTIS v.10 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 document. 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.10.

The LD_{50} 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_{50}.

4.0 RESULTS AND DISCUSSION

4.1 Mortality

No mortality was observed at the dose level of 550 mg/kg bw during the study. At the dose level of 2000 mg/kg bw, four out of six animals were found dead after treatment.

4.2 Clinical Signs

At dose level 550 mg/kg bw decreased activity (4/4), decreased respiratory rate (3/4), laboured breathing (3/4), prostration (4/4), erected fur (2/4), hunched posture (4/4), slight uncoordination (1/4) occurred. All animals were symptom free from Day 2.

At dose level 2000 mg/kg bw decreased activity (6/6), decreased respiratory rate (6/6), laboured breathing (6/6), prostration (6/6), erected fur (3/6), hunched posture (2/6) occurred. Surviving animals were symptom free from Day 3.

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 the surviving animals. 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

A single oral gavage of thiamethoxam SL (A23943A) to Crl:WI Wistar female rats at a dose level of 550 mg/kg bw was not associated with any gross macroscopic observations at necropsy.

In case of one animal found dead 2000 mg/kg bw dose level dark red diffuse discoloration of lungs were observed. In case of the rest of animals of 2000 mg/kg bw dose level no gross macroscopic findings was obsreved at necropsy.

Macroscopic findings are presented in Table 3.

5.0 CONCLUSIONS

Under the conditions of this study, based on the outcome of AOT425StatPgm program, the estimated acute oral median lethal dose (LD_{50}) of the test item thiamethoxam SL (A23943A) was found to be 2000 mg/kg bw in female Crl:WI Wistar rats. The 95% confidence interval is 846.7 to 4430 mg/kg bw.

TABLES SECTION

TABLE 1 Individual Findings – Clinical Signs

DOSE LEVEL: 550 mg/kg bw Treatment on Day 0 **SEX: FEMALE**

Animal Number	Observations	Observation days																				Frequency
		0							1	2	3	4	5	6	7	8	9	10	11	12	13	14	
		0'	30'	1h	2h	3h	4h	6h															
2707	Symptom Free	/	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	13/20
	Respiratory Rate Abnormal, Decreased	/	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/20
	Prostrate	/	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2/20
	Hunched Posture	/	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3/20
	Fur, Erected	/	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2/20
	Uncoordinated	/	-	-	Sl	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/20
	Activity Decreased	/	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	7/20
2710	Symptom Free	/	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14/20
	Respiratory Rate Abnormal, Decreased	/	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3/20
	Breathing, Labored	/	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2/20
	Prostrate	/	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3/20
	Hunched Posture	/	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2/20
	Fur, Erected	/	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2/20
	Activity Decreased	/	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5/20
2716	Symptom Free	/	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14/20
	Respiratory Rate Abnormal, Decreased	/	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2/20
	Breathing, Labored	/	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/20
	Prostrate	/	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3/20
	Hunched Posture	/	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3/20
	Activity Decreased	/	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6/20
2718	Symptom Free	/	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14/20
	Breathing, Labored	/	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3/20
	Prostrate	/	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3/20
	Hunched Posture	/	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3/20
	Activity Decreased	/	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5/20

Standard Footnotes:
+ = present
- = absent
h = hour (s)
' = minute
D = Found dead
M = Moribund
Frequency of observation = number of occurrence of observation / total number of observations
/ = No clinical observation (was) done at 0'

Severities:
Sl = Slight/Small/Few/Small amount
Mo = Moderate/Several/Moderate amount
Ex = Severe/Large/Many/Large/Extreme amount

DOSE LEVEL: 2000 mg/kg bw Treatment on Day 0 **SEX: FEMALE**

Animal Number	Observations	Observation days																				Frequency
		0							1	2	3	4	5	6	7	8	9	10	11	12	13	14	
		0'	30'	1h	2h	3h	4h	6h															
2708	Symptom Free	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	13/21
	Respiratory Rate Abnormal, Decreased	-	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6/21
	Breathing, Labored	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6/21
	Prostrate	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7/21
	Hunched Posture	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	1/21
	Fur, Erected	-	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3/21
	Activity decreased	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7/21
2709D	Respiratory Rate Abnormal, Decreased	-	+	+	+	+																	4/5
	Breathing, Labored	+	+	+	+	+																	5/5
	Prostrate	+	+	+	+	+																	5/5
	Activity decreased	+	+	+	+	+																	5/5
	Found Dead	-	-	-	-	-	D																-
2711	Symptom Free	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	12/21
	Respiratory Rate Abnormal, Decreased	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7/21
	Breathing, Labored	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6/21
	Prostrate	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7/21
	Hunched Posture	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	2/21
	Fur, Erected	-	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3/21
	Activity decreased	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7/21

Standard Footnotes:

+ = present - = absent
h = hour (s) ' = minute
D = Found dead M = Moribund
Frequency of observation = number of occurrence of observation / total number of observations
/ = No clinical observation (was) done at 0'

Severities:

Sl = Slight/Small/Few/Small amount
Mo = Moderate/Several/Moderate amount
Ex = Severe/Large/Many/Large/Extreme amount

DOSE LEVEL: 2000 mg/kg bw Treatment on Day 0 **SEX: FEMALE**

Animal Number	Observations	Observation days																				Frequency
		0							1	2	3	4	5	6	7	8	9	10	11	12	13	14	
		0'	30'	1h	2h	3h	4h	6h															
2715D	Respiratory Rate Abnormal, Decreased	-	+	+	+																		3/4
	Breathing, Labored	+	+	+	+																		4/4
	Prostrate	+	+	+	+																		4/4
	Fur, Erected	-	+	+	+																		3/4
	Activity decreased	+	+	+	+																		4/4
	Found Dead	-	-	-	-	D																	-
2717D	Respiratory Rate Abnormal, Decreased	-	-	+	+	+																	3/5
	Breathing, Labored	+	+	+	+	+																	5/5
	Prostrate	+	+	+	+	+																	5/5
	Activity decreased	+	+	+	+	+																	5/5
	Found Dead	-	-	-	-	-	D																-
3326D	Respiratory Rate Abnormal, Decreased	-	+	+	+	+																	4/5
	Breathing, Labored	+	+	+	+	+																	5/5
	Prostrate	+	+	+	+	+																	5/5
	Activity decreased	+	+	+	+	+																	5/5
	Found Dead	-	-	-	-	-	D																-

Standard Footnotes:
+ = present
- = absent
h = hour (s)
' = minute
D = Found dead
M = Moribund
Frequency of observation = number of occurrence of observation / total number of observations
/ = No clinical observation (was) done at 0'

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: 550 mg/kg bw Treatment on Day 0 **SEX: FEMALE**

Animal Number	Body weight (g) Days				Day/B.W. (g) Death	Body weight gain (g) between days		
	-1	0	7	14		0-7	7-14	0-14
2707	219	204	244	255	-	40	11	51
2710	235	216	250	255	-	34	5	39
2716	263	251	267	282	-	16	15	31
2718	259	245	259	260	-	14	1	15
Mean:	244.0	229.0	255.0	263.0	-	26.0	8.0	34.0
Standard deviation:	20.8	22.6	10.1	12.9	-	13.0	6.2	15.1

DOSE LEVEL: 2000 mg/kg bw Treatment on Day 0 **SEX: FEMALE**

Animal Number	Body weight (g) Days				Day/B.W. (g) Death	Body weight gain (g) between days		
	-1	0	7	14		0-7	7-14	0-14
2708	227	215	240	260	-	25	20	45
2709D	233	214	-	-	0/214	-	-	-
2711	237	218	254	254	-	36	0	36
2715D	253	238	-	-	0/238	-	-	-
2717D	270	249	-	-	0/249	-	-	-
3326D	256	242	-	-	0/242	-	-	-
Mean:	246.0	229.3	247.0	257.0	-	30.5	10.0	40.5
Standard deviation:	16.3	15.4	9.9	4.2	-	7.8	14.1	6.4

Standard Footnotes: **D = Found dead** **M = Moribund**

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

TABLE 3 Macroscopic Findings

DOSE LEVEL: 550 mg/kg bw Treatment on Day 0 **SEX: FEMALE**

Animal Number	Necropsy Day	External Observations	Internal Observations	Organ/Tissue
2707	Day 14	No external observations recorded	No internal observations recorded	Not applicable
2710	Day 14	No external observations recorded	No internal observations recorded	Not applicable
2716	Day 14	No external observations recorded	No internal observations recorded	Not applicable
2718	Day 14	No external observations recorded	No internal observations recorded	Not applicable

DOSE LEVEL: 2000 mg/kg bw Treatment on Day 0 **SEX: FEMALE**

Animal Number	Necropsy Day	External Observations	Internal Observations	Organ/Tissue
2708	Day 14	No external observations recorded	No internal observations recorded	Not applicable
2709D	Day 0	No external observations recorded	Discoloration, dark; red, diffuse Failure to collapse	Lungs
2711	Day 14	No external observations recorded	No internal observations recorded	Not applicable
2715D	Day 0	No external observations recorded	No internal observations recorded	Not applicable
2717D	Day 0	No external observations recorded	No internal observations recorded	Not applicable
3326D	Day 0	No external observations recorded	No internal observations recorded	Not applicable

Standard Footnotes: **D = Found dead** **M = Moribund** **- = No data**

APPENDICES SECTION

APPENDIX 1 AOT 425 REPORT (Main Test)

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

Date/Time: 2022. március 29., kedd, 8:11:08
Data file name: 21_309_001P.dat
Last modified: 2022. 03. 29. 8:10:04

Test/Substance: 21/309-001P
Test type: Main Test
Limit dose (mg/kg): 2000
Assumed LD50 (mg/kg): Default
Assumed sigma (mg/kg): 0.5

Recommended dose progression: 2000, 550, 175, 55, 17.5, 5.5, 1.75

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	2707	550	O	O
2	2708	2000	O	O
3	2709	2000	X	X
4	2710	550	O	O
5	2711	2000	O	O
6	2715	2000	X	X
7	2716	550	O	O
8	2717	2000	X	X
9	2718	550	O	O
10	3326	2000	X	X

(X = Died, O = Survived)

Dose Recommendation: The main test is complete.

Stopping criteria met: 5 reversals in 6 tests.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
550	4	0	4
2000	2	4	6
All Doses	6	4	10

Statistical Estimate based on long term outcomes:

Estimated LD50 = 2000 (The one dose with partial response).
95% PL Confidence interval is 846.7 to 4430.

APPENDIX 2 Certificate of Analysis

ALS Laboratórios LS Ltda.
Rua Fábia, 59 – CEP: 05051-030
São Paulo, SP - Brazil

SYNGENTA PROTEÇÃO DE CULTIVOS Ltda.
Rua Doutor Rubens Gomes Bueno nº 691,
11º andar, Torre Sigma
CEP 04730-000 – Bairro Várzea de Baixo
São Paulo-SP – Brazil

Certificate of Analysis

A23943A
Thiamethoxam SL (075)
NSI001-085-017

Batch Identification	NSI001-085-017
Product Code	A23943A
Other Product Code(s)	A23943A; EXF23867A; CGA293343 SL (075); Thiamethoxam SL (075)
EUP number:	739/2021 Expiry date: 26/04/2024
Received on:	28 September 2021
Source	Syngenta Proteção de Cultivos Ltda. Rodovia Professor Zeferino Vaz, SP 332, s/nº, km 127,5 – Bairro Santa Terezinha, CEP 13148-915 – Paulínia-SP – Brasil
Chemical Analysis (Active Ingredients Content)	
– **Content of Thiamethoxam ***	**6.63 % w/w corresponding to 75.42 g/L**

The Active Ingredient content is within the FAO limits.
Methodology used for Characterization: HPLC (SF-1151/1)

Physical Analysis	
– **Appearance**	Homogeneous and translucent
– **Color**	6/12 – 5YR (Dark Orange)
– **Physical state**	Liquid
– **Density ***	1.1378 g/cm³
Stability:	
– **Storage Temperature**	**<30°C**
– **Recertification Date**	**10 September 2023**

If stored under the conditions given above, this test item 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. All original raw data, including any storage medium for electronically recorded data, documentation, the signed study plan, the protocol amendments, the final report and a sample of the test item will be retained in the GLP Archives at ALS Laboratórios LS Ltda.

Study number of batch characterization: 26785/2021CF and 26787/2021CC

Authorization: 10 November 2021

Victor F. G. da Silva
Victor Ferreira Gomes da Silva
ALS Laboratórios LS Ltda.

CA2144073 -B

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APPENDIX 3 GLP Certificate

OGYÉI Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet

Hatósági Ellenőrzési Főosztály

1051 Budapest, Zrínyi utca 3.
Levélcím: 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
Digitálisan aláírta: Dr. Lukács Ferenc József
Dátum: 2021.05.06 13:04:14 +02'00'

Dr. Ferenc Lukács
Head of Inspectorate

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