Thiamethoxam

Thiamethoxam FS (A9700J) - Acute Oral Toxicity Study in Rats *(Rattus norvegicus)* Up-and-Down Procedure

Final Report

DATA REQUIREMENT(S): OECD 425, 2008.

AUTHOR (S): Rejane Medeiros da Silva (MSc)

COMPLETION DATE: 26 June 2018

PERFORMING LABORATORY: TECAM Tecnologia Ambiental São Roque Ltda
Estrada do Carmo, 3001
CEP: 18130-970
São Roque/SP - Brazil

LABORATORY PROJECT ID: Report Number: **RL15069/2018TO-B**
Study Number: **15069/2018TO**
Task Number: **TK0308852**

SPONSOR(S): Syngenta Proteção De Cultivos Ltda
Av. Das Nações Unidas, 18.001 - 4º Andar
CEP: 04795-900
São Paulo/SP

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

Study Title: Thiamethoxam FS (A9700J) – Acute Oral Toxicity Study in Rats (*Rattus norvegicus*) Up-and-Down Procedure
Study Number: 15069/2018TO

This study was conducted under my responsibility in accordance to NIT-DICLA-035 (INMETRO, Sep/11, Rev.02) and its complementary documents and the Good Laboratory Practice Principles as published by the OECD (N° 1 [ENV/MC/CHEM (98) 17]) which meet the United States Environmental Protection Agency Good Laboratory Practice Standards [40 CFR Part 160].

This study was conducted in accordance to the written study plan authorized by the Sponsor and TECAM Management and to TECAM standard operating procedures. This report represents a true and accurate record of the obtained results. There were no major known circumstances that may have affected the quality or integrity of the study.

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 substance will be retained in the GLP Archives at TECAM Tecnologia Ambiental.

Rejane Medeiros da Silva — June 26, 2018.

Rejane Medeiros da Silva (MSc)
Study Director

Date

Performing Laboratory: TECAM Tecnologia Ambiental São Roque Ltda
Estrada do Carmo, 3001
CEP: 18130-970
São Roque/SP - Brazil

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

Study Title: Thiamethoxam FS (A9700J)– Acute Oral Toxicity Study in Rats (*Rattus norvegicus*) - Up-and-Down Procedure
Study Number: 15069/2018TO

Based on a quality assurance review, it was concluded that the final report is a true reflection of the raw data.

The final report was examined with respect to the study plan, standard operating procedures and raw data. Proceedings of the study were inspected by process -based inspections.

The inspections were carried out according to the standard operating procedures of the Quality Assurance of TECAM Tecnologia Ambiental.

Dates of inspections and the dates on which the findings were reported to the Study Director and Management are given below. These reports are kept in the GLP Archives at TECAM Tecnologia Ambiental.

Inspection	Date of inspection	Reporting Dates	
		To Study Director	GIT
Study Plan	22 February 2018	22 February 2018	22 February 2018
Experimental Phase	27 February 2018	05 March 2018	05 March 2018
Raw Data	23 May 2018	23 May 2018	23 May 2018
Draft Report	23 May 2018	23 May 2018	23 May 2018
Final Report	26 June 2018	26 June 2018	26 June 2018
English Version	26 June 2018	26 June 2018	26 June 2018

Lilian Mion
Quality Assurance
TECAM Tecnologia Ambiental

26 June 2018
Date

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Rejane Medeiros da Silva (MSc)	Study Director.
Cynthia B. Pestana (PhD)	Test Facility Manager.
Lilian Polakiewicz (MSc)	Deputy Test Facility Manager.
Lilian Mion	Quality Assurance.
Luana dos Santos Bueno	Biologist
Raphael Oliveira de Brito	Technical Support.
Bruna Geovana Figueira Gonçalves	Technical Support.
Karina Namie Fujiya	Technical Support.
Rodrigo Aparecido de Souza	Technical Support.
Daiana Zonta Ramos	Technical Support.
Tiago Zenthofer Salvestro	Technical Support.
Lucimara de Souza Pereira	Technical Support.
Iasmin Ferreira de Araújo	Biologist.
Leticia Martins de Castro	Biologist
Rafael Luiz da Silva	Veterinary.
Eder da Silva Xavier	Biomedic.
Merielen Garcia Nascimento e Pontes	Syngenta Study Manager

Study Dates

Study Initiation Date:	21 March 2018
Acclimatization:	22 to 27 March 2018 (animal 1 - 5000 mg/kg bw); 28 March to 02 April 2018 (animal 2 - 2000 mg/kg bw); 04 to 09 April 2018 (animal 3 - 2000 mg/kg bw); 11 to 16 April 2018 (animal 4 - 2000 mg/kg bw). 18 to 23 April 2018 (animal 5 - 2000 mg/kg bw) 26 April to 01 May 2018 (animal 6 - 2000 mg/kg bw)
Experimental Starting Date:	28 March 2018 (animal 1 - 5000 mg/kg bw); 03 April 2018 (animal 2 - 2000 mg/kg bw); 10 April 2018 (animal 3 - 2000 mg/kg bw); 17 April 2018 (animal 4 – 2000 mg/kg bw); 24 April 2018 (animal 5 - 2000 mg/kg bw). 02 May 2018 (animal 6 - 2000 mg/kg bw).
Experimental Termination Date:	28 March 2018 (animal1 - 5000 mg/kg bw); 17 April 2018 (animal 2 – 2000 mg/kg bw); 24 April 2018 (animal3 – 2000 mg/kg bw); 01 May 2018 (animal 4 – 2000 mg/kg bw). 08 May 2018 (animal 5 – 2000 mg/kg bw). 02 May 2018 (animal 6 – 2000 mg/kg bw).
Study Completion Date:	26 June 2018.
English Version:	26 June 2018.

Performing Laboratory
The present study was conducted at TECAM Tecnologia Ambiental São Roque, located at Estrada do Carmo, 3001, São Roque, SP – Brazil.

The physico-chemical analysis in water was subcontracted and monitored by the Quality Assurance of TECAM.

Study Plan Adherence
Adherence were recorded from the study plan.

Deviation N°01: Due to technical problems, the temperature and humidity were not recorded on 05/04/18. Test period 04/24/18 to 05/8/18, animal 5.

Amendment Nº 01: Item 2.3 of the study plan was changed:
Identification:
From: **Thiamethoxan FS**
For: **Thiamethoxam FS (A9700J)**

Archives
All the original raw data and records of this study are the property of the Sponsor. Data will be properly registered, signed and stored in TECAM´s archives for five years. Test item will be properly stored during the test and after that will be returned to the Sponsor. When possible a sample will be retained for two years or until the expiry date.

TABLE OF CONTENTS

PAGE

1.0 EXECUTIVE SUMMARY

1.1 Study Design

The present study was carried out to provide information about acute toxicity following single oral administration to rats of test substance **Thiamethoxam FS (A9700J)**. The method followed was as per the OECD 425, 2008. Six rats Wistar (*Rattus norvegicus*) females, adults, young and healthy were selected and maintained under controlled environmental conditions. The animals were fasted *overnight* before the administration of test substance. Volumes of administration were calculated as 0.45 mL/100 g bw (body weight) for the dose of 5000 mg/kg bw and 0.19 mL/100 g pc for the dose of 2000mg/kg bw, based on the mass to volume of test substance and on selected dose. One group of one female received the test substance undiluted at dose of 5000 mg/kg bw. Due to the results, obtained five additional groups were treated sequentially at the dose 2000 mg / kg bw of the test substance undiluted. Body weights were measured immediately prior to the administration (day 0), 7 and 14 days after administration. After dosing, animals were observed individually during the first 24 hours, with special attention given during the first 4 hours, and during all the 14 days of test. The animals were euthanized with carbon dioxide and submitted to necropsy after euthanasia or after death.

1.2 Results

Clinical signs of toxicity and death were observed in the animal treated at dose of 5000 mg/kg bw, such as, mild to moderate prostration and mild tremor. The animal died 3 hours after administration of the test substance. In the groups treated at dose of 2000 mg/kg bw, were observed change in stool, mild prostration, moderate ataxia, tremors, seizures and died of animal (animal 6). At the end of the test, the surviving animals presented body weight gain. In relation to necropsy, in the group treated at dose of 5000 mg/kg bw was observed bloody content in the central nervous system. In the group treated 2000 mg/kg bw (animal 6) it was observed lungs with pale multifocal areas.

1.3 Conclusion

Under the conditions of this study, the acute oral LD 50 for **Thiamethoxam FS (A9700J)**, was greater than 2000 mg/kg bw in rats.

2.0 INTRODUCTION

2.1 Study Purpose

The present study was carried out to provide information about acute toxicity after single oral dose in rats of test substance **Thiamethoxam FS (A9700J)**, through the determination of the median lethal dose (LD_{50}).

2.2 Study Guidelines

The study was performed according to:
OECD Guideline for testing of chemicals. Acute Oral Toxicity: Up-and-Down Procedure, 425, 27p., 2008.

2.3 Weight of Evidence Analysis

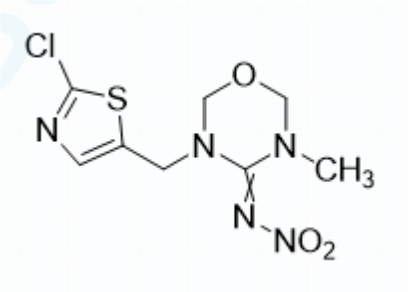
For reasons related to animal welfare, prior to conducting the study a weight of evidence analysis was carried out with the available and relevant data of the test substance. The testing strategy includes data evaluation of toxic effects of the test substance in human and/or animals. Test substances that are known to cause marked pain and distress due to corrosive or severely irritant actions do not need to be tested.

2.4 Animal Welfare

Animals are maintained in the test facility according to local and international requirements described in the current SOPs (Standard Operating Procedures), based on the Guide for the Care and Use of Laboratory Animals (ILAR-NRC, 2011). Animals showing continuing signs of severe distress and/or pain at any stage of the test are humanely killed and the test substance assessed. Procedures for animal care and criteria for making the decision to humanely kill moribund and severely suffering animals are described in detail in the SOPs, based on the *Guidance Document on the Recognition, Assessment and Use of Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evaluation* (OECD 19, 2000).

3.0 MATERIALS AND METHODS

3.1 Test Substance

Identification:	Thiamethoxam FS (A9700J)
Test substance number:	1801806*
Received on:	26 January 2018
Batch Nº:	RPJ001-003- 001
RET number:	1255/2016
Study number:	15069/2018TO
Active ingredient (a.i.):	Thiamethoxam
Declared concentration of a.i.:	350 g/L
Analysed concentration of a.i.:	357.05 g/L* (Appendix 1)
IUPAC name of a.i.:	(EZ)-3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine ***
Number CAS of a.i.:	153719-23-4 ***
Class:	Insecticide ***
Synonymy	A9700J
Structural formula:	
	Thiamethoxam **
Molecular formula:	$C_8H_{10}ClN_5O_3S$ ***
Molecular weight:	291.7 g/mol ***
Manufactured on:	July 2017
Expiry date:	July 2019
Formulation:	Flowable concentrate for seed treatment (FS)
Physical state:	Liquid
Homogeneity:	Homogeneous **
Stability:	Stable under used condition**
Test substance supplied by:	Syngenta Proteção De Cultivos Ltda

* Information provided by TECAM Tecnologia Ambiental
** Sponsor information
*** The Online Pesticide Manual (17th ed., 2015).

3.2 Test System

Species:	*Rattus norvegicus*.
Strain:	Wistar (albino rats).
Source:	TECAM Tecnologia Ambiental.

Justification of species:	The albino rat is the model species recommended by regulatory agencies for evaluation of acute toxicity.
Number and sex:	6 nulliparous and non-pregnant females.
Body weight range and age:	Young adult with 8-11 weeks at start of treatment with body weight between 145.2 g and 221.1 g the weight variation among the animals on day 0 did not exceed 20% of the group mean weight.
Acclimatization:	Animals were acclimatized for 5 days prior to dosing in a climate-controlled room; animals exhibiting abnormal signs were not used for the study.
Housing:	Polysulfone rodent cages with 3 animals per cage.
Identification:	Cage cards displaying animal number, sex, date of birth, sample code, dose and study dates were fixed to each cage; animals were weighed and identified individually with tail marking.

3.3 Animal Health and Environmental Monitoring Program

As a program of animal health and environmental monitoring, the following procedures are performed periodically to ensure that contaminant levels are below those that might impact the scientific integrity of the study:

Health status:	Only healthy rats were used for this study. The animals were not vaccinated or treated with anti-infective substances either during the acclimatization and study periods.
Feeding:	Pelleted commercial diet for rodents (Quimtia S.A.) was provided *ad libitum* throughout acclimatization and test periods (except before administration). Food is analyzed by TECAM/SP periodically for microbiological contaminants. The commercial food was considered not to contain any contaminant at levels that affected the purpose or integrity of the study.
Drinking water:	Filtered water was provided *ad libitum* throughout acclimatization and test periods. The drinking water is analyzed periodically for chemical and microbiological contaminants. The drinking water was considered not to contain any contaminant at levels that affected the purpose or integrity of the study.
Bedding:	Aspen wooden chips previously prepared by Biotécnicas and irradiated with gamma radiation were provided for the animals and were changed twice a week.

3.4 Environmental Conditions

The environmental conditions in the room were monitored and recorded daily. The average temperature was 21.6 ºC (animal 1), 21.0 ºC (animal 2), 21.5ºC (animal 3), 21.5ºC (animal 4), 22.8ºC (animal 5) and 23.3ºC (animal 6). The average relative humidity was 69.3 % (animal 1), 65.3 % (animal 2), 62.5 % (animal 3), 61.4 % (animal 4), 58.9 % (animal 5), and 64.5 %

(animal 6). The animals were subjected to photoperiod, automatically controlled 12 hours of light (only artificial light from 7 a.m to 7 p.m.) and 12 hours of dark. The ventilation of the room was approximately 10 to 12 air changes per hour.

3.5 Procedures

A limit test at the dose of 5000 mg/kg bw was selected by the Study Director after justification by the Sponsor that there is specific regulatory requirement to test this dose level. The first treated animal died, then the initial limit test was terminated at 5000 mg/kg bw and a limit test was performed at 2000 mg/kg bw according to Test Guideline OECD 425.

The test substance was administered in sequence to the animals as described in the Table 1. The decision to proceed with the next animal was based in the survival of the previous animal following dosing.

Animals were fasted overnight prior to the test substance administration and returned to ad libitum feeding approximately three hours after treatment. Access to water was not interrupted. On the day of test substance administration, all animals were weighed and identified with colorful pens. The test substance was administered in a single oral dose by gavage using syringe and appropriate cannula. The dose volume was calculated considering the initial body weight, the test substance concentration and the selected dose level. The test substance was administered undiluted.

3.6 Clinical Observation

Body weights were recorded shortly before administration (fasted body weight), weekly thereafter (day 7) and at the end of the study (day 14). Animals were observed individually after dosing during the first 24 hours with special attention given during the first 4 hours. During the 14 days of test, the animals were observed during the 14 days of test, the animals were observed all days for the presence of clinical signs of toxicity. Clinical observations included, but were not limited to, changes in skin and fur, eyes and mucous membranes, respiratory, circulatory, autonomic and central nervous systems, somatomotor activity and behavioural patterns such as salivation tremors and convulsions, changes in the level of motor activity, changes in the behaviour, changes in the level of activity, gait and posture, reactivity to handling or sensory stimuli, altered strength, and stereotypes or bizarre behavior (*e.g.* self mutilation).

3.7 Necropsy

At the end of 14 days, the surviving animals were euthanized with carbon dioxide and submitted to necropsy. Necropsy findings were registered for intestinal tract (duodenum, jejunum, ileum, cecum), central nervous system, liver, kidney, heart, spleen, lymph nodes, respiratory tract (lungs, trachea, bronchi, diaphragm), thyroid, esophagus, stomach, pancreas, muscles, bladder, uterus and ovaries.

3.8 Statistical analysis

The *Acute Oral Toxicity (Guideline 425) Statistical Program* AOT425StatPgm (Version: 1.0, 2006) was used for all data analyses including: dose progression selections, stopping criteria determinations and LD_{50}.

4.0 RESULTS AND DISCUSSION

4.1 Mortality and Clinical Signs

Clinical signs of toxicity and death were observed in the animal treated at dose of 5000 mg/kg bw, such as, mild to moderate prostration, mild tremor, the animal died 3 hours after administration of the test substance (Table 2). Treatment with **Thiamenthoxam FS (A9700J)** at dose of 2000 mg/kg bw caused change in stool, mild prostration, moderate ataxia, tremors, and seizures and death of one animal (animal 6). Individual clinical observations during the experimental period are presented in Tables 5 to 8.

4.2 Body Weight

Individual and group mean body weights of treated animals on days 0, 7 and 14, as well as body weight changes after 14 days of test and volume of administration are presented in Tables 3 and 4. At the end of the test, all surviving animals presented body weight gain.

4.3 Necropsy

The group treated with the dose of 5000 mg / kg bw presented bloody content in the central nervous system. In the group treated 2000 mg/kg bw (animal 6) it was observed lungs with pale multifocal areas. Individual findings for all animals are shown in Tables 9 and 10.

5.0 CONCLUSIONS

Under the test conditions of this study, the acute oral LD 50 for **Thiamethoxam FS (A9700J)**, was greater than 2000 mg/kg bw in rats.

6.0 REFERENCES

Acute Oral Toxicity (OECD Test Guideline 425) Statistical Programme (AOT 425 StatPgm).

Version: 1.0, 2006.

ILAR. Institute for Laboratory Animal Resources - National Research Council. Guide for care and use of laboratory animals. Washington: National Academy Press, 2011. 220p.

INMETRO. NIT-DICLA-035 – "Principles of Good Laboratory Practice – GLP", Rev. 02, September/2011 and its complementary documents.

OECD Guideline for testing of chemicals. Acute Oral Toxicity – Acute Toxic Class Method 425, 14p., 2008.

OECD Environmental Health and Safety Publications, Series on Testing and Assessment. Guidance Document on the Recognition, Assessment, and Use of Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evaluation. No. 19. Paris, 2000.

Turner, J.A. The Online Pesticide Manual. 17.ed. United Kingdom: BCPC, 2015. Available at: http://www.bcpc.org/.

TABLES SECTION

TABLE 1 Doses, Intervals and Volume of Administration

Animal Number	Dose Level (mg/kg bw)	Dose Volume (mL/100 g bw)	Intervals between Dose Levels (Days)	Mortality
1	5000	0.45	0	Yes
2	2000	0.19	6	No
3	2000	0.19	7	No
4	2000	0.19	7	No
5	2000	0.19	7	No
6	2000	0.19	8	Yes

TABLE 2 Mortality between Treated Animals

Dose (mg/kg bw)	Number of Animals	Number of Deaths	Mortality (%)
5000	1	1	100
2000	5	1	20

TABLE 3 Individual (bw) and Mean Body Weight and Volume of Administration of Females Treated With 5000 mg/kg bw of Thiamethoxam FS (A9700J)

Female number	Volume of administration (mL)	Administration time	Body weight (g)			
			Day 0*	Day 7	Day 14	Day 14 - Day 0*
1	0.86	9h12	190.0	---	---	---
Body weight mean			**-**			

* Day 0: fasted body weight; ---: animals dead in day 0.

TABLE 4 Individual (bw) and Mean Body Weight and Volume of Administration of Females Treated With 2000 mg/kg bw of Thiamethoxam FS (A9700J)

Female number	Volume of administration (mL)	Administration time	Body weight (g)			
			Day 0*	Day 7	Day 14	Day 14 - Day 0*
2	0.36	8h55	191.6	194.5	193.4	+ 1.8
3	0.28	9h13	145.2	162.9	174.1	+28.9
4	0.42	9h30	221.1	237.2	249.6	+28.5
5	0.36	8h35	190.3	205.2	207.3	+17.0
6	0.39	8h15	206.6	---	---	---
Body weight mean			**191.0**	**199.9**	**206.1**	**19.05**

*Day 0: fasted body weight; ---: animals dead in day 0.

TABLE 5 Clinical Observation of Females Treated With 5000 kg/kg bw of Thiamethoxam FS (A9700J) in the First 4 Hours After Administration of Test Substance

Female Number	Clinical Observation (Hours)				
	0.5	1	2	3	4
1	4L	4L	6L,4M	1	-

Code	Signs	Code	Signs
NA	No alterations	9	Diarrhea
1	Death	10	Salivation
2	Coma	11	Dyspnea
3	Convulsions	12	Absence of grooming
4	Prostration	13	Stool changes
5	Ataxia	L	Mild
6	Tremors	M	Moderate
7	Alteration of skin and fur (piloerection)	S	Severe
8	Alteration of mucosa		

TABLE 6 Clinical Observation of Females Treated With 2000 kg/kg bw of Thiamethoxam FS (A9700J) in the First 4 Hours After Administration of Test Substance

Female Number	Clinical Observation (Hours)				
	0.5	1	2	3	4
2	NA	NA	NA	NA	NA
3	NA	NA	NA	NA	NA
4	NA	NA	4L	4L	4L
5	NA	NA	NA	NA	NA
6	NA	4L	4L,5M,6,3	1	-

Code	Signs	Code	Signs
NA	No alterations	9	Diarrhea
1	Death	10	Salivation
2	Coma	11	Dyspnea
3	Convulsions	12	Absence of grooming
4	Prostration	13	Stool changes
5	Ataxia	L	Mild
6	Tremors	M	Moderate
7	Alteration of skin and fur (piloerection)	S	Severe
8	Alteration of mucosa		

TABLE 7 Clinical Observation of Females Treated with 5000 mg/kg bw of Thiamethoxam FS (A9700J) on the Days 1-14

Female Number	Clinical Observation (Days)													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
6	---	---	---	---	---	---	---	---	---	---	---	---	---	---

---: animals dead in day 0.

TABLE 8 Clinical Observation of Females Treated with 2000 mg/kg bw of Thiamethoxam FS (A9700J) on the Days 1-14

Female	Clinical Observation (Days)													
Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2	13	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
3	13	13	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
4	13	13	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
5	13	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
6	---	---	---	---	---	---	---	---	---	---	---	---	---	---

---: animals dead in day 0.

Code	Signs	Code	Signs
NA	No alterations	9	Diarrhea
1	Death	10	Salivation
2	Coma	11	Dyspnea
3	Convulsions	12	Absence of grooming
4	Prostration	13	Stool changes
5	Ataxia	L	Mild
6	Tremors	M	Moderate
7	Alteration of skin and fur (piloerection)	S	Severe
8	Alteration of mucosa		

TABLE 9 Individual Necropsies of Females Treated with 5000 mg/kg bw of Thiamethoxam FS (A9700J)

Macroscopic Observations	Animal Number
	1
CNS	5
Lungs	NA
Trachea	NA
Thyroid	NA
Esophagus	NA
Bronchi	NA
Heart	NA
Diaphragm	NA
Stomach	NA
Intestine	NA
Spleen	NA
Pancreas	NA
Liver	NA
Lymph nodes	NA
Muscles	NA
Kidneys	NA
Bladder	NA
Ovaries	NA

CNS: Central Nervous System.

Code	Macroscopic findings	Code	Macroscopic findings
NA	No alteration	5	Bloody content
1	Congestion	6	Gas content
2	Multifocal pale areas	D	Discrete
3	Hemorrhagic focus	M	Moderate
4	Hemorrhagic spots	S	Severe

TABLE 10 Individual Necropsies of Females Treated with 2000 mg/kg bw of Thiamethoxam FS (A9700J)

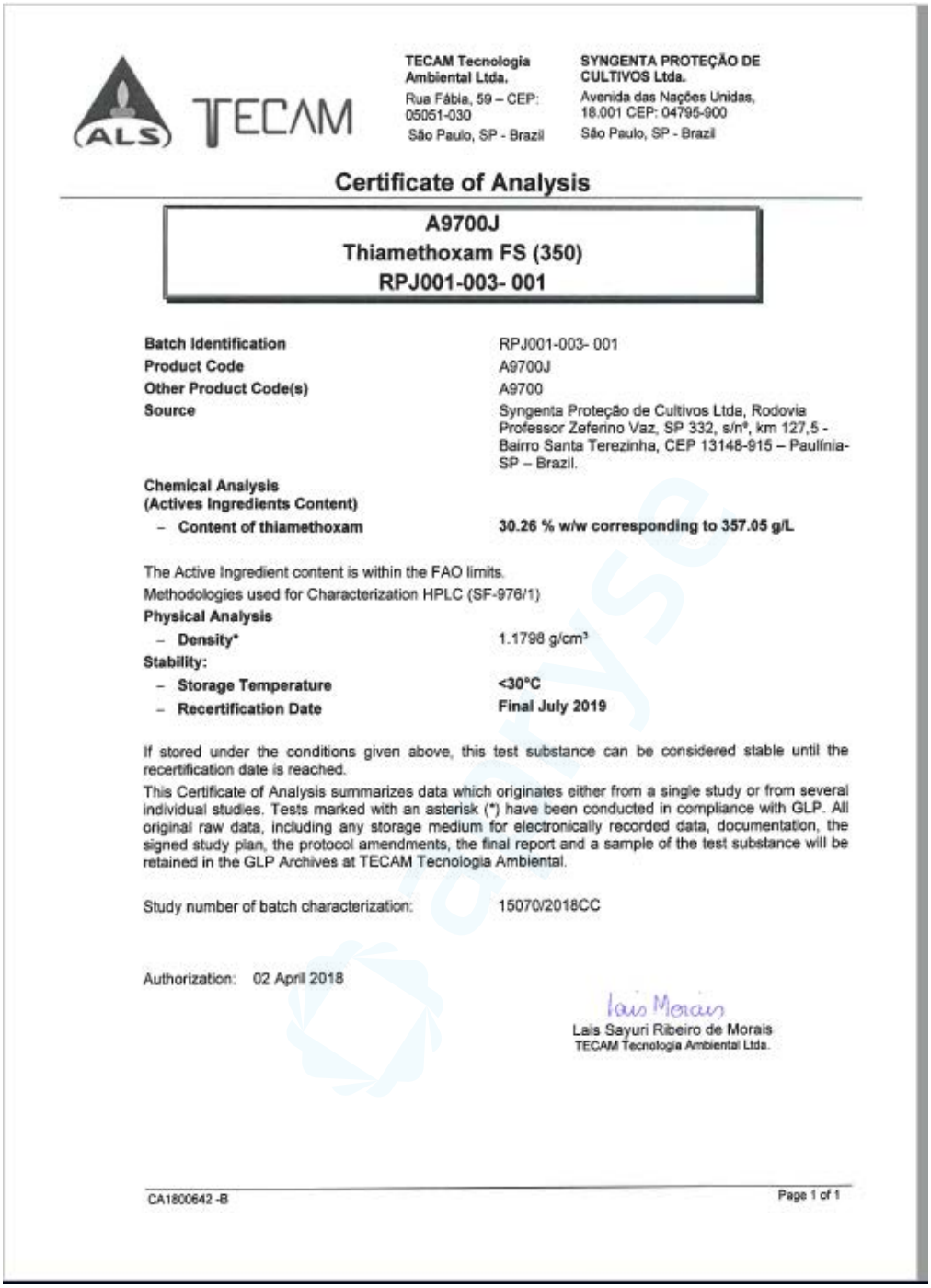
Macroscopic Observations	Female Number				
	2	3	4	5	6
CNS	NA	NA	NA	NA	NA
Lungs	NA	NA	NA	NA	2
Heart	NA	NA	NA	NA	NA
Thyroid	NA	NA	NA	NA	NA
Trachea	NA	NA	NA	NA	NA
Esophagus	NA	NA	NA	NA	NA
Diaphragm	NA	NA	NA	NA	NA
Liver	NA	NA	NA	NA	NA
Spleen	NA	NA	NA	NA	NA
Kidneys	NA	NA	NA	NA	NA
Stomach	NA	NA	NA	NA	NA
Pancreas	NA	NA	NA	NA	NA
Intestines	NA	NA	NA	NA	NA
Bladder	NA	NA	NA	NA	NA
Muscles	NA	NA	NA	NA	NA
Linph nodes	NA	NA	NA	NA	NA
Uterus	NA	NA	NA	NA	NA
Ovarium	NA	NA	NA	NA	NA

CNS: Central Nervous System.

Code	Macroscopic findings	Code	Macroscopic findings
NA	No alteration	5	Bloody content
1	Congestion	6	Gas content
2	Multifocal pale areas	D	Discrete
3	Hemorrhagic focus	M	Moderate
4	Hemorrhagic spots	S	Severe

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis for Thiamethoxam FS (A9700J)



TECAM Tecnologia Ambiental Ltda.
Rua Fábia, 59 – CEP: 05051-030
São Paulo, SP - Brazil

SYNGENTA PROTEÇÃO DE CULTIVOS Ltda.
Avenida das Nações Unidas, 18.001 CEP: 04795-900
São Paulo, SP - Brazil

Certificate of Analysis

A9700J
Thiamethoxam FS (350)
RPJ001-003- 001

Batch Identification	RPJ001-003- 001
Product Code	A9700J
Other Product Code(s)	A9700
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 – Brazil.
Chemical Analysis (Actives Ingredients Content)	
– **Content of thiamethoxam**	**30.26 % w/w corresponding to 357.05 g/L**

The Active Ingredient content is within the FAO limits.
Methodologies used for Characterization HPLC (SF-976/1)

Physical Analysis	
– **Density***	1.1798 g/cm³
Stability:	
– **Storage Temperature**	**<30°C**
– **Recertification Date**	**Final July 2019**

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. 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 substance will be retained in the GLP Archives at TECAM Tecnologia Ambiental.

Study number of batch characterization: 15070/2018CC

Authorization: 02 April 2018

Lais Morais
Lais Sayuri Ribeiro de Morais
TECAM Tecnologia Ambiental Ltda.

CA1800642 -B

Page 1 of 1

APPENDIX 2 Recognition of Compliance with the Principles on Good Laboratory Practice

Federal Republic of Brazil
Ministry of Industry, Foreign Trade and Services
National Institute of Metrology, Quality and Technology - INMETRO

General Coordination for Accreditation

Brazilian Compliance Monitoring Authority for the Principles of Good Laboratory Practice – GLP

Statement of GLP Compliance

GLP Recognition No. GLP 0012 — Inicial Recognition: 06-09-2002

Tecam Tecnologia Ambiental São Roque Ltda.
Estrada do Carmo, 3.001 – Sorocamirim – São Roque - São Paulo - SP – Brasil

The General Coordination for Accreditation of Inmetro grants to the above mentioned test facility the recognition of compliance with the OECD Principles of Good Laboratory Practice as part of the Brazilian GLP Monitoring Program to carry out non-clinical health and environmental safety studies, as describe in the scope below:

Areas of expertise	Categories of Test Items
Toxicity studies; Mutagenicity studies; Environmental toxicity studies on aquatic and terrestrial organisms.	Pesticides, Their Components and Suchlike; Pharmaceutical Products; Cosmetics; Wood Preservative; Food Additives; Feed Additives; Veterinary Products; Sanitizers; Industrial Chemical Products; Genetically Modified Organisms; Remedial for treatments of effluents and natural ecosystems.

Note: Categories of test items "pesticides", "pharmaceutical products", "cosmetics", "wood preservative", "feed additives", "veterinary products", "sanitizers", "remedial for treatments of effluents and natural ecosystems" and "industrial chemical" are covered by Brazil´s full adherence to the OECD Council Acts related to the Mutual Acceptance of Data (MAD) on Good Laboratory Practice.

Assinado de forma digital
por ALDONEY FREIRE COSTA
Dados: 2016.09.05 08:31:37
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Aldoney Freire Costa
General Coordinator for Accreditation

The recognition status shall be checked at the address http://www.inmetro.gov.br/monitoramento_BPL/certificados

MOD-CGCRE-027 – Rev. 05 – Apr. JUN/16 – Pg. 01/01