

Profenofos

**Profenofos EC (A8591B) -
Acute Inhalation Toxicity Study (Nose-Only) in Rats**

Final Report

TEST GUIDELINE(S): OECD 403 (2009)
EPA 870.1300 (1998)
EC 440/2008, B.2 (2008)

AUTHOR(S): Imre Biró, M.Sc.

COMPLETION DATE: 29 March 2022

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

LABORATORY PROJECT ID: Report Number: 21/201-004P
Study Number: 21/201-004P
Task Number: TK0612495

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

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410 Swing Road
Post Office Box 18300
Greensboro, NC 27419-8300 USA

Submitter: _____

Date: _____

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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, ENV/MC/CHEM (98) 17.)

This study was conducted in accordance with a written Study Plan and its Amendments, authorized by the Sponsor and Charles River Laboratories Hungary Kft. 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. By virtue of my dated signature I accept the responsibility for the validity of the data.

Signature: _____



Imre Biró, M.Sc.
Study Director

Date: _____

29 March 2022

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
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Post Office Box 18300
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FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

Study Number: 21/201-004P

Study Title: Profenofos EC (A8591B) - Acute Inhalation Toxicity Study (Nose-Only) in Rats

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
20 October 2021	Study Plan	20 October 2021	20 October 2021
03 November 2021	Amendment 1 to the Study Plan	03 November 2021	03 November 2021
23 November 2021	Amendment 2 to the Study Plan	23 November 2021	23 November 2021
24 November 2021	Treatment	24 November 2021	24 November 2021
19 January 2022	Draft Report	19 January 2022	19 January 2022
29 March 2022	Final Report	29 March 2022	29 March 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: *Ivett Schleicher Mott* Date: *29 March 2022*
Ivett Schleicher, Ph.D.
On behalf of QAU

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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 "Profenofos EC (A8591B) - Acute Inhalation Toxicity Study (Nose-Only) in Rats" was performed in compliance with the Principles of Good Laboratory Practice.

Signature: _____

Balász Tóth
Balázs Tóth, Ph.D.
General Manager

Date: _____

29 March 2022

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GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated:

Name	Function
Imre Biró, M.Sc.	Study Director
Nóra Krajcs, Ph.D.	Assistant Scientist
Ivett Schleicher, Ph.D.	Quality Assurance
László Székelyhidi, D.V.M.	Veterinary Control
Tamás Mészáros, Ph.D.	Pharmacy
Ferenc Szűcs	Animal Service Laboratories
András Bálint	Technical Team Leader, Inhalation
Carolina Vaccari, M.Sc.	Syngenta Study Manager

Study dates

Study Initiation Date:	20 October 2021
Experimental Starting Date:	26 October 2021
Experimental Completion Date:	08 December 2021

Sighting Exposure – Group 0.1

Receipt of Animals:	21 October 2021
Inhalation Exposure (Day 0):	05 November 2021
Observation:	05 – 19 November 2021
Necropsy:	19 November 2021

Main Study – Group 1

Receipt of Animals:	11 November 2021
Inhalation Exposure (Day 0):	24 November 2021
Observation:	24 November – 08 December 2021
Necropsy:	08 December 2021

Performing laboratory test substance reference number

210495

Deviations from the guidelines

No deviations from the guidelines occurred during the study.

Deviations from the Study Plan

Due to technical reasons, relative humidity (maximum of 78%) value outside the expected range of 30-70% was recorded once in the animal room during the in-life phase.

This deviation was considered to have no impact on the outcome of the study and interpretation of the results.

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Other

The study documents and samples:

- Study Plan and amendments,
- all raw data,
- sample of the test item,
- 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.

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1.0 EXECUTIVE SUMMARY

1.1 Study Design

This study was performed to assess the acute inhalation toxicity of profenofos EC (A8591B) following a 4-hour exposure to 5 male and 5 female rats at the target concentration of 2 mg/L. The test item was administered as supplied.

The target concentration of 2 mg/L was tested during the animal exposures following the OECD test guideline number 403.

A Sighting Exposure was performed prior to the Main Study with 2 male and 2 female Crl:WI Wistar rats at a target concentration of 2 mg/L.

In the Main Study group, 10 (5 males and 5 females) Crl:WI Wistar rats, were exposed to a target concentration of 2 mg/L profenofos EC (A8591B).

The animals were exposed for 4 hours using a nose-only exposure system, followed by a 14-day observation period. The day of exposure was designated as Day 0. Aerosol concentrations were measured gravimetrically. The particle size distribution of the test aerosol was determined regularly during the exposure period. Clinical observations and bodyweights were recorded throughout the study and at the end of the scheduled period the animals were euthanised and were subjected to a gross examination *post mortem*.

1.2 Results

Atmosphere

Sighting Exposure (Group 0.1):

The mean atmosphere concentration was 1.97 mg/L. The MMAD (Mass Median Aerodynamic Diameter) was 1.83 μm with a GSD (Geometric Standard Deviation) of 1.88.

Main Study (Group 1):

The mean atmosphere concentration was 2.01 mg/L. The MMAD was 1.88 μm with a GSD of 1.86.

Mortality

No mortality occurred during the study.

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Clinical observations

Group 0.1 (Sighting Exposure – 1.97 mg/L)

In the male animals, laboured respiration (slight to moderate), noisy respiration (slight), red-brown staining (on the head, left eye and area around eyes) and wet fur (on the whole body) were observed on Days 0-1. Animals were symptom free from Day 2.

In the female animals, laboured respiration (slight), noisy respiration (slight), lack of grooming, red-brown staining (area around eyes) and wet fur (on the whole body) were observed on Day 0-2. These animals were symptom free from Day 3.

Group 1 (Main Exposure – 2.01 mg/L)

In the male animals, laboured respiration (slight to extreme), noisy respiration (slight to moderate), decreased activity (slight to moderate), sneezing, lack of grooming, head tilt (left), red-brown staining (on the head and/or nose/snout), and wet fur (on the whole body) were noted on Days 0-6. These animals were symptom free from Day 7.

In the female animals, laboured respiration (slight), noisy respiration (slight to moderate), lack of grooming, red-brown staining (on the head or on the nose/snout) and wet fur (on the whole body) were observed on Days 0-1. These animals were symptom free from Day 2.

Red-brown staining and wet fur in all animals of both groups were considered to be related to the restraint and exposure procedures or discomfort of the animals but not to be toxicologically significant.

Bodyweight

Group 0.1 (Sighting Exposure – 1.97 mg/L)

In the male animals, slight body weight loss was noted in both animals on Days 0-1. The body weight gains were normal on Days 1-14.

In the female animals, in case of one out of two animal slight body weight loss was observed on Days 0-1. The body weight gains were normal in both animals on Days 1-14.

Group 1 (Main Exposure – 2.01 mg/L)

In male animals, in four out of five animals slight body weight losses were noted on Days 0-1 and in one male animal slight body weight loss was observed on Days 0-3. The body weight gains were normal on Days 3-14 in all animals.

In four out of five female animals, slight body weight losses were noted on Days 0-1. The body weight gains were normal on Days 1-14 in all female animals.

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Necropsy

Group 0.1 (Sighting Exposure – 1.97 mg/L)

No macroscopic observations were seen on necropsy Day 14 neither in male, nor in female animals.

Group 1 (Main Exposure – 2.01 mg/L)

No macroscopic observations were seen on scheduled necropsy on Day 14 in the animals.

1.3 Conclusion

Under the experimental conditions of this study of 10 rats (5 males and 5 females) when exposed to 2.01 mg/L of profenofos EC (A8591B) for 4 hours, there was no mortality. The acute inhalation median lethal concentration of profenofos EC (A8591B) in CrI:WI Wistar rats is therefore considered to be above 2.01 mg/L (achieved mean concentration).

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2.0 INTRODUCTION

2.1 Purpose

This study was performed to assess the acute inhalation toxicity of profenofos EC (A8591B) following a 4-hour nose-only exposure to male and female Crl:WI rats.

2.2 Regulatory Test Guidelines

The study was designed to meet or exceed the regulatory guidelines shown below:

- OECD Guidelines for the Testing of Chemicals No. 403 "Acute Inhalation Toxicity" (adopted: 2009)
- US Environmental Protection Agency Health Effects Division Test Guideline, OPPTS 870.1300, Acute Inhalation Toxicity (1998)
- Council Regulation (EC) No 440/2008, Annex Part B, B.2: "Acute Toxicity (Inhalation)", Official Journal of the European Union No. L 142, (2008)

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 authorised the conduct of the study.

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3.0 MATERIALS AND METHODS

3.1 Test Item

The following information was provided by the Sponsor.

Name:	Profenofos EC (A8591B)
Batch number:	RAN001-099-019
Design code:	A8591B
Active ingredient content*:	Content of profenofos 73.12% w/w corresponding to 969.03 g/L
Density:	1.3253 g/cm ³
Appearance:	Light yellow liquid
Recertification date:	06 May 2023
Storage conditions:	Room temperature (<30°C)
Safety precautions:	Enhanced safety precautions (nitrile gloves, goggles, face mask (ABEK-P3-filter), lab coat).

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

The copy of the Certificate of Analysis is presented in Appendix 4.

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

Information relating to the identity, active ingredient content and stability of the test item was provided by the Sponsor and identification of the test item on receipt by the Pharmacy Department of Charles River Laboratories Hungary Kft., was made on the basis of these data.

3.1.2 Preparation

An atmosphere was generated from the test item as supplied.

3.1.3 Other materials

Name:	Vaseline
Batch number:	STBJ1482
Expiry date:	31 March 2022
Manufacturer:	Sigma Aldrich
Storage conditions:	Room temperature

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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:	Sighting Study: 2 animals / sex Main Study: 5 animals / sex
Sex:	Males and females (nulliparous and non-pregnant)
Age of animals when treated:	Sighting Study: 9 weeks old Main Study: 8 weeks old
Body weight at exposure:	Sighting Study: males: 344 g; females: 212-216 g Main Study: males: 318-342 g; females: 234-251 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 numbers.
Randomization:	PROVANTIS v.9 software was used in order to verify homogeneity/variation within groups based on actual body weight.
Acclimatization time:	Sighting Study: 15 days; Main Study: 13 days

3.2.2 Husbandry

Animal health:	Only healthy animals were used for the test. The health status was certified by the Veterinarian.
Housing:	Sighting study: Group caging (2 animals, by sex per cage) Main study: Group caging (up to 3 animals, by sex per cage)
Cage type:	Polypropylene solid floor cages (type II or III) with stainless steel mesh lids
Bedding and nesting:	SAFE 3/4-S Hygienic Animal Bedding and nest building material (SAFE Crinklets Natural) produced by J. Rettenmaier & Söhne GmbH+Co. KG, Holzmühle 1, 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:	20.0-24.5°C
Relative humidity:	34-78%
Ventilation:	15-20 air exchanges/hour

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

3.2.3 Food and feeding

The animals were provided with ssniff SM R/M "Autoclavable Complete Feed for Rats and Mice – Breeding and Maintenance" (ssniff Spezialdiäten GmbH, D-59494 Soest, Germany) *ad libitum*. The content of the standard diet and the test report of the diet analysis provided by the manufacturer are retained in the archives of Charles River Laboratories Hungary Kft. The food was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study.

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 considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study.

The quality control analysis is performed once every three months and microbiological assessment is performed monthly, by Veszprém County Institute of State Public Health and Medical Officer Service (H-8200 Veszprém, József Attila utca 36, Hungary). Copies of the relevant Certificates of Analysis are retained in the archive of Charles River Laboratories Hungary Kft.

3.3 Inhalation Exposure

3.3.1 Technical trials

Prior to animal exposures, test item atmospheres were generated within the exposure chamber. During these Technical Trials, test item input rates were varied to achieve the required aerosol concentration of particles with a mass median aerodynamic diameter (MMAD) between 1 to 4 μm and a geometric standard deviation (GSD) in the range of 1.5 to 3.0. Measurements of aerodynamic particle size were performed from the animal's breathing zone using a cascade impactor (Details are presented in Appendix 5.).

3.3.2 Atmosphere generation

The test item was aerosolised using a stainless-steel concentric jet nebuliser (TSE Systems GmbH, Bad Homburg, Germany) located at the top of the exposure chamber. The rate of test item use was controlled by a syringe pump. Compressed air was supplied by means of an oil-free compressor passed through a suitable filter system prior to introduction to the nebuliser.

3.3.3 Animal exposure system

The animals were exposed, nose-only, to an atmosphere of the test item using a TSE Rodent Exposure System (TSE Systems GmbH, Bad Homburg, Germany). This system comprised of

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2 concentric anodised aluminium chambers and a computer control system incorporating pressure detectors and mass flow controllers.

Fresh aerosol from the generation system was constantly supplied to the inner plenum (distribution chamber) of the exposure system from where, under positive pressure, it was distributed to the individual exposure ports. The animals were held in polycarbonate restraint tubes located around the chamber which allowed only the animal's nostrils to enter the exposure port. After passing through the animal's breathing zone, used aerosol entered the outer cylinder from where it was exhausted through a suitable filter system. Atmosphere generation was therefore dynamic. A schematic diagram of the exposure system is presented in Figure 1.

Airflows and relative pressures within the system were constantly monitored and controlled by the computer system thus ensuring a uniform distribution and constant flow of fresh aerosol to each exposure port (breathing zone). The flow of air through each port was at least 0.5 L/min. This flow rate was considered adequate to minimise re-breathing of the test atmosphere as it is about twice the respiratory minute volume of a rat.

Homogeneity of the test atmosphere within the test chamber and amongst the exposure ports was not specifically determined during this study. However, chambers of this design have been fully validated and have shown to produce evenly distributed atmospheres in the animals' breathing zones (Silver, 1946).

3.3.4 Sighting exposure

Sighting Exposure was performed with 2 male and 2 female rats to estimate the test item's inhalation toxicity, identify sex differences in susceptibility and assist in selecting exposure concentration levels for the Main Study.

3.3.5 Main study

Based on the results of the Sighting Exposure a Limit Test was performed with 5 males and 5 females to assess the acute inhalation toxicity of the test item.

3.3.6 Exposure procedure

Each rat was individually held in a tapered, polycarbonate restraining tube fitted onto a single tier of the exposure chamber. Only the nose of each animal was exposed to the test atmosphere.

Following an equilibration period of at least the theoretical chamber equilibration time (T99) (Reference 1.), a sighting group of 4 rats (2 males and 2 females) were exposed to the mean achieved concentration for a period 4 hours. Based on the results of this Sighting Study, a Limit Test was performed, in which a main group of 10 rats (5 males and 5 females) were exposed to the mean achieved concentration for a period 4 hours.

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No control animals were used in the study.

Before the animal exposures, the hairs across the closed eye surface of each animal were wiped with Vaseline, to reduce the test item getting into the eyes while they are in the restraint tube. Details of Vaseline detailed in section 3.1.3.

3.4 Exposure Monitoring

3.4.1 Test atmosphere concentrations

Prior to atmosphere generation, the non-volatile component of the test material was determined by adding a small, known amount of the material to glass fibre filters (Type GF/C, Whatman, GE Healthcare UK Limited UK, Lot No. 17160519). The filters were then dried at atmospheric pressure in a desiccator at room temperature for at least 24 hours and weighed again. The difference in the two weights was taken as the volatile content of the test material and the non-volatile component was calculated as a percentage. The mean non-volatile content of the batch used for the animals' exposure was found to be 97.32% (n = 10) with a standard deviation 0.45%.

The test atmosphere was sampled at regular intervals during the exposure period. Samples were taken from an unoccupied exposure port (representing the animal's breathing zone) by pulling a suitable, known volume of test atmosphere through weighed GF10 glass fibre filters (Type GF10, Whatman, GE Healthcare UK Limited UK, Lot Numbers: A29518736).

After sampling, the filters were dried (under the same conditions as those previously described) and weighed again 24 hours later. The difference in the pre and post sampling weights, corrected by mean of non-volatile content (97.32%) and divided by the volume of atmosphere sampled, was equal to the actual achieved test atmosphere concentration.

Filter samples were collected at the breathing zone (approximately every 10-20 minutes) during each 4-hour exposure period and analysed.

The nominal concentration was calculated by dividing the mass of test material disseminated into the chamber by the total volume of air that went through the chamber during the same period.

3.4.2 Particle size analysis

The particle size of the test atmosphere was determined three times during the exposure period using a 7-stage impactor of Mercer style (TSE Systems GmbH, Bad Homburg, Germany). Such devices employ an inertial separation technique to isolate particles in the discrete aerodynamic size ranges. Samples were taken from an unoccupied exposure port (representing the animal's breathing zone).

The collection substrates and the backup filter were weighed before and after sampling and the weight of test item, collected at each stage, calculated by this difference.

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The total amount collected for each stage was used to determine the cumulative amount below each cut-off point size. In this way, the proportion (%) of aerosol less than 0.550, 0.960, 1.550, 2.105, 3.555, 6.655 and 10.550 μm was calculated.

From these data, using software supplied with the impactor (TSE Systems GmbH, Bad Homburg, Germany), the Mass Median Aerodynamic Diameter (MMAD), and Geometric Standard Deviation (GSD) were calculated. These are considered to be valid when particle distribution approximates to a 'normal curve' distribution. In addition, the proportion (%) of aerosol less than 4 μm (considered to be the respirable portion) was determined.

3.4.3 Chamber environmental conditions

The following variables were monitored continuously and recorded during each exposure period by the monitoring system integrated into the exposure system:

- Chamber airflow rates
- Test atmosphere temperature
- Test atmosphere relative humidity

Summaries of the data are presented in Table 3.

3.5 Observations

3.5.1 Clinical observations

All animals were observed for clinical signs at hourly intervals during exposure whilst the animals were still restrained. Following exposure, clinical observations were performed twice on the day of exposure (following removal from the restrainer and approximately one hour after completion of the exposure) and subsequently once daily for 14 days.

Observations included changes in the skin and fur, eyes and mucous membranes and also respiratory, circulatory, autonomic and central nervous system, somatomotor activity and behaviour pattern. Particular attention was directed to observation of tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

3.5.2 Bodyweight

Individual bodyweights were recorded prior to treatment on the day of exposure (Day 0) and on Days 1, 3, 7 and 14.

3.6 *Post Mortem* Investigation

All animals were subjected to macroscopic examination. All animals were exsanguinated under pentobarbital anaesthesia (Euthanimal 40% injection) (details in 3.6.1). After examination of the external appearance, the thoracic and abdominal cavities were opened and the appearance of the tissues and organs were observed. Any gross macroscopic changes

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were recorded. Special attention was given to the respiratory tract for macroscopic signs of irritancy or local toxicity.

3.6.1 Materials used for euthanasia

Name: Euthanimal 40% (400 mg/mL sodium pentobarbital)
Batch No.: 2001004-06
Expiry Date: 31 January 2023
Produced by: Alfasan Nederland BV, The Netherlands

3.7 Evaluation of Data

Data evaluations included the relationship, if any, between the animals' exposure to the test item and the incidence and severity of all abnormalities including mortality, behavioural or clinical changes, bodyweight changes, macroscopic abnormalities or any other toxicological effects.

Data were collected using the software PROVANTIS v.9 or were recorded on data collection sheets taken from the relevant SOPs, then tabulated using PROVANTIS v.9, Microsoft Office Word and/or Excel, as appropriate.

Only Limit Test was performed, the four-hour inhalation LC₅₀ was not calculated.

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4.0 RESULTS AND DISCUSSION

4.1 Test Atmosphere Concentration

The test atmosphere concentration was sampled at approximately equal intervals during the exposure and the actual concentration of the test item calculated. The mean values obtained were:

Group	Mean achieved concentration (mg/L)	Standard Deviation	Nominal Concentration (mg/L)
0.1 (Sighting exposure)	1.97	0.08	6.07
1 (Main Study)	2.01	0.06	10.13

The individual data are presented graphically in Figure 2 and detailed in Table 1.

4.2 Particle Size Analysis

The particle size distribution of the test atmosphere was as follows:

Group	Mean achieved concentration (mg/L)	Mean Mass Median Aerodynamic Diameter (MMAD) (μm)	Geometric Standard Deviation (GSD)	Respirable Fraction (% < 4 μm)
0.1 (Sighting exposure)	1.97	1.83	1.88	89.1
1 (Main Study)	2.01	1.88	1.86	67.5

The particle size analysis showed that the distribution was approximately 'normal', hence the calculations were considered to be valid. The data are presented graphically in Figure 3 and detailed in Table 2.

4.3 Mortality Rates

No mortality occurred during the study.

Mortality data are detailed in Table 4.

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4.4 Clinical Observations

Group 0.1 (Sighting Exposure – 1.97 mg/L)

In the male animals, laboured respiration (slight to moderate), noisy respiration (slight), red-brown staining (on the head, left eye and area around eyes) and wet fur (on the whole body) were observed on Days 0-1. Animals were symptom free from Day 2.

In the female animals, laboured respiration (slight), noisy respiration (slight), lack of grooming, red-brown staining (area around eyes) and wet fur (on the whole body) were observed on Day 0-2. These animals were symptom free from Day 3.

Group 1 (Main Exposure – 2.01 mg/L)

In the male animals, laboured respiration (slight to extreme), noisy respiration (slight to moderate), decreased activity (slight to moderate), sneezing, lack of grooming, head tilt (left), red-brown staining (on the head and/or nose/snout), and wet fur (on the whole body) were noted on Days 0-6. These animals were symptom free from Day 7.

In the female animals, laboured respiration (slight), noisy respiration (slight to moderate), lack of grooming, red-brown staining (on the head or on the nose/snout) and wet fur (on the whole body) were observed on Days 0-1. These animals were symptom free from Day 2.

Red-brown staining and wet fur in all animals of both groups were considered to be related to the restraint and exposure procedures or discomfort of the animals but not to be toxicologically significant.

Individual clinical observations are presented in Appendix 1.

4.5 Bodyweight

Group 0.1 (Sighting Exposure – 1.97 mg/L)

In the male animals, slight body weight loss was noted in both animals on Days 0-1. The body weight gains were normal on Days 1-14.

In the female animals, in case of one out of two animal slight body weight loss was observed on Days 0-1. The body weight gains were normal in both animals on Days 1-14.

Group 1 (Main Exposure – 2.01 mg/L)

In male animals, in four out of five animals slight body weight losses were noted on Days 0-1 and in one male animal slight body weight loss was observed on Days 0-3. The body weight gains were normal on Days 3-14 in all animals.

In four out of five female animals, slight body weight losses were noted on Days 0-1. The body weight gains were normal on Days 1-14 in all female animals.

Individual data, together with bodyweight changes, are presented in Appendix 2.

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4.6 Necropsy

Group 0.1 (Sighting Exposure – 1.97 mg/L)

No macroscopic observations were seen on necropsy Day 14 neither in male, nor in female animals.

Group 1 (Main Exposure – 2.01 mg/L)

No macroscopic observations were seen on scheduled necropsy on Day 14 in the animals.

Individual necropsy data are presented in Appendix 3.

5.0 CONCLUSIONS

Under the experimental conditions of this study of 10 rats (5 males and 5 females) when exposed to 2.01 mg/L of profenofos EC (A8591B) for 4 hours, there was no mortality. The acute inhalation median lethal concentration of profenofos EC (A8591B) in CrI:WI Wistar rats is therefore considered to be above 2.01 mg/L (achieved mean concentration).

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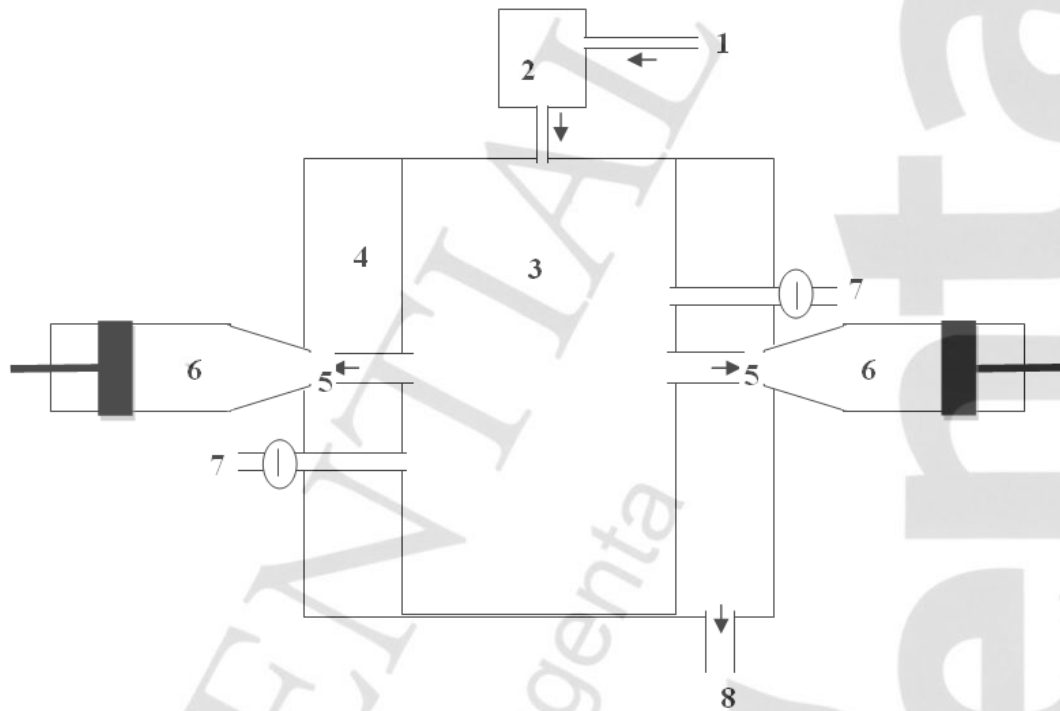
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FIGURE 1

Schematic Diagram of the Exposure System



KEY:	
1:	Metered Air Supply
2:	Aerosol Generation System
3:	Central Plenum
4:	Outer Cylinder
5:	Animal Exposure Port
6:	Animal Restraint Tube
7:	Sample Ports (not used)
8:	Metered Exhaust to Filters

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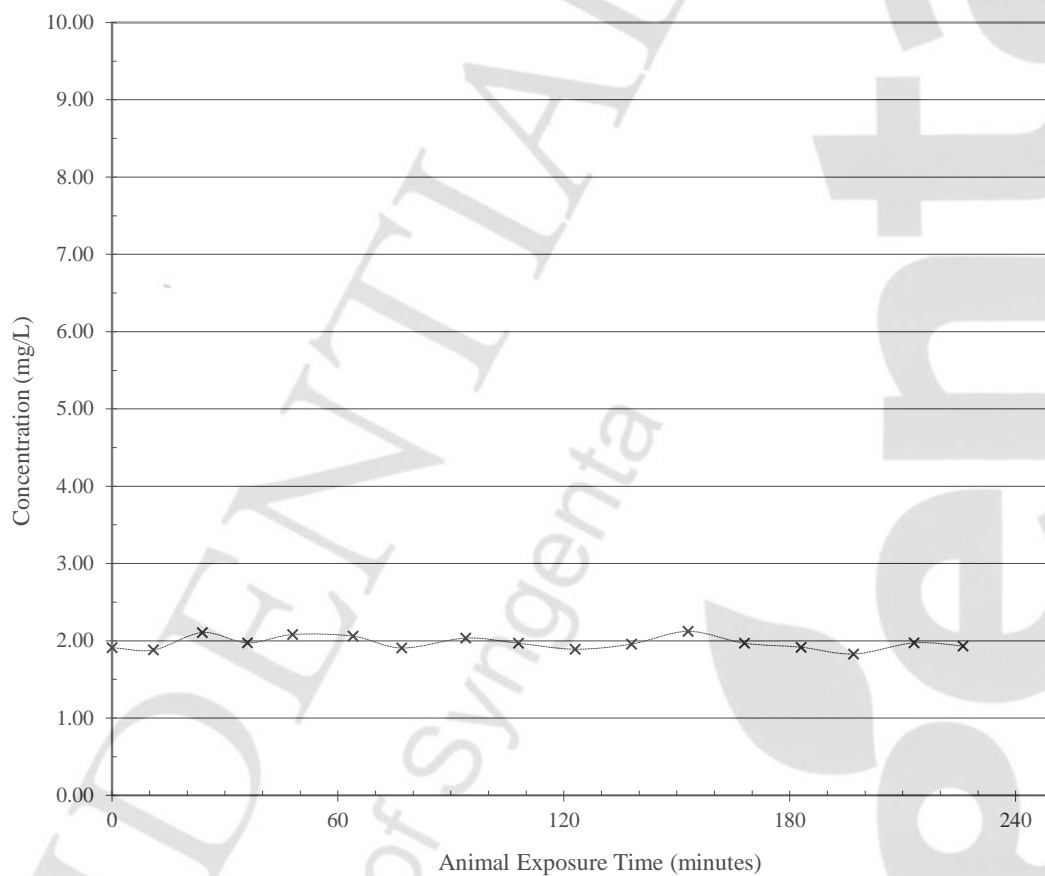
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FIGURE 2 **Achieved Atmosphere Concentrations**

Sighting Exposure – Group 0.1



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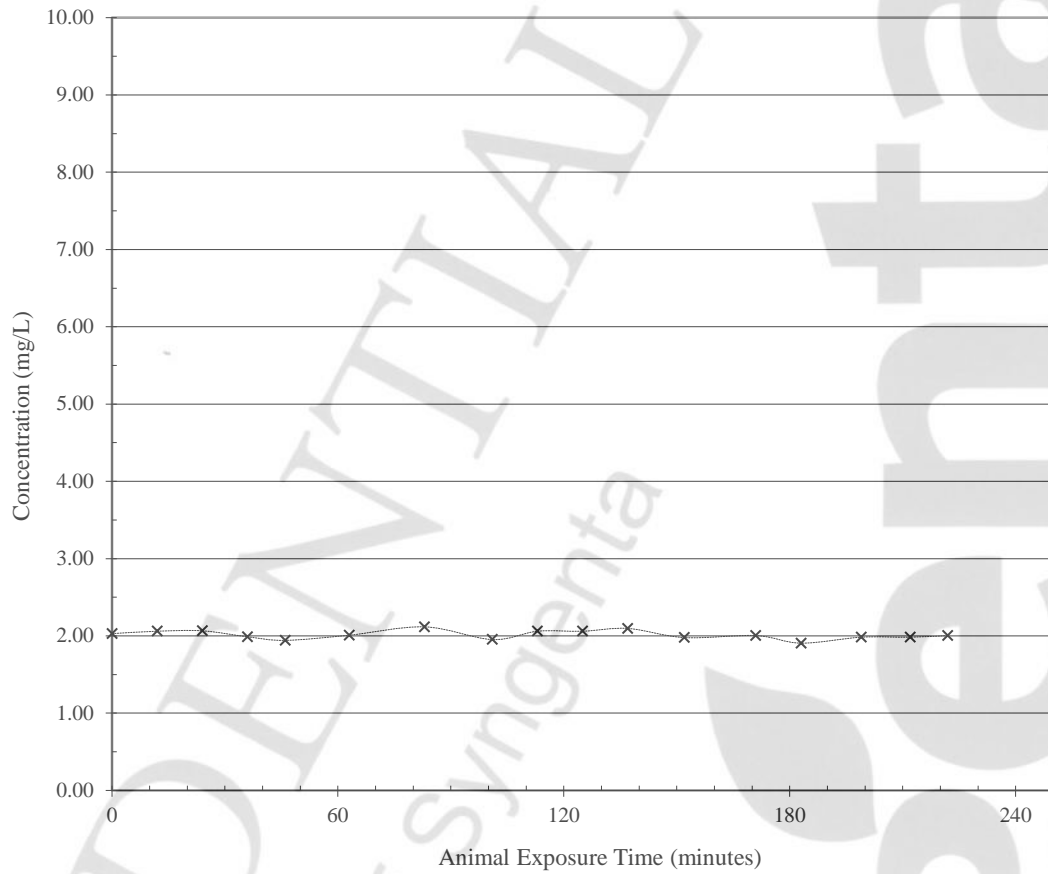
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Main Study – Group 1



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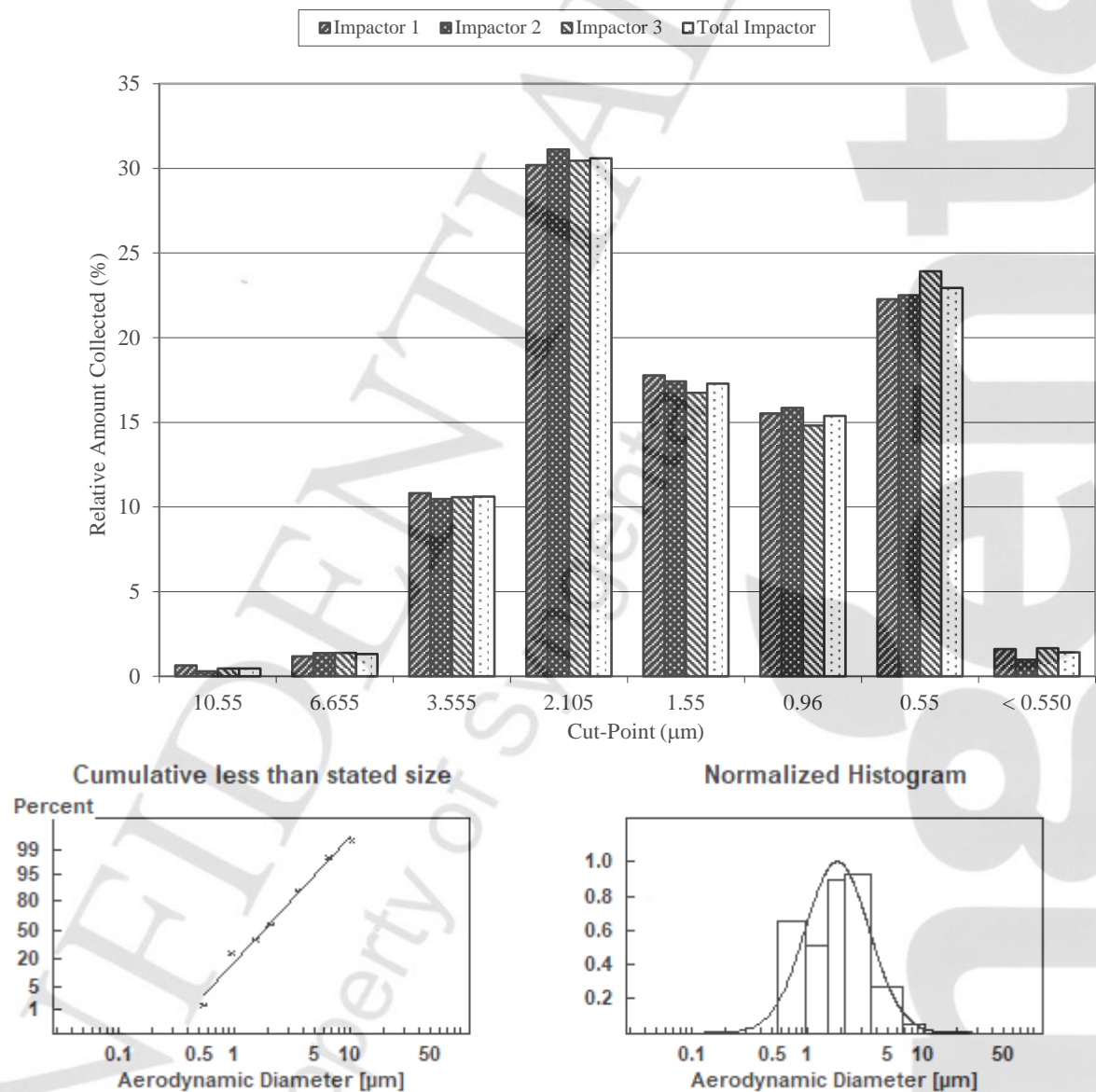
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FIGURE 3 Particle Size Distribution

Sighting Exposure – Group 0.1



The data distribution was considered by the Study Director to be adequately 'normal' for the automated data describing the atmosphere characteristics to be valid.

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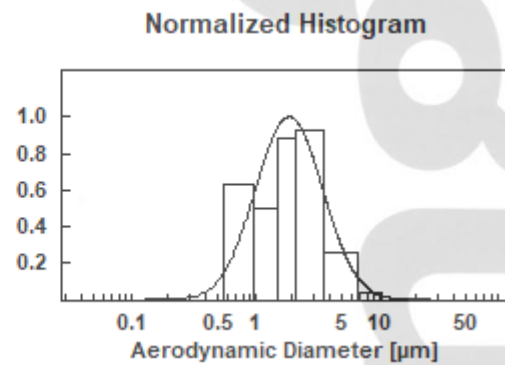
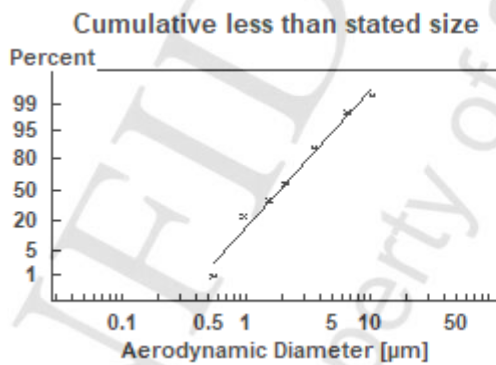
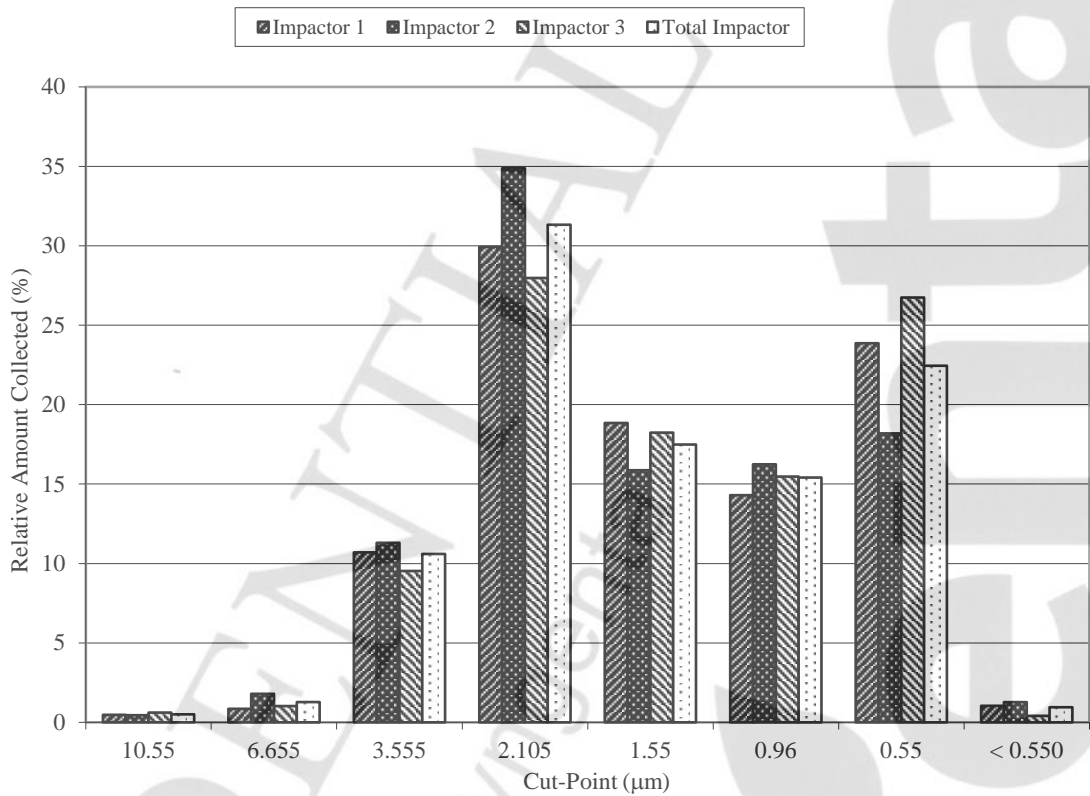
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Main Study – Group 1



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TABLE 1 Test Atmosphere Concentrations**Sighting Exposure – Group 0.1**

Exposure Duration (minutes)	Sample Volume (L)	Amount of Non Volatiles Collected* (mg)	Equivalent Test Item Amount (mg)	Atmospheric Concentration of the Test Item (mg/L)
0	2.0	3.72	3.82	1.91
11	2.0	3.66	3.76	1.88
24	2.0	4.10	4.21	2.11
36	2.0	3.84	3.95	1.97
48	2.0	4.05	4.16	2.08
64	2.0	4.01	4.12	2.06
77	2.0	3.71	3.81	1.91
94	2.0	3.96	4.07	2.03
108	2.0	3.83	3.94	1.97
123	2.0	3.68	3.78	1.89
138	2.0	3.81	3.91	1.96
153	2.0	4.13	4.24	2.12
168	2.0	3.83	3.94	1.97
183	2.0	3.73	3.83	1.92
197	2.0	3.56	3.66	1.83
213	2.0	3.84	3.95	1.97
226	2.0	3.76	3.86	1.93

Mean achieved concentration = 1.97 mg/L

Standard Deviation = 0.08

Amount of Test Item Used (g): 47.74

Total Volume of Air Used (L): 7860

Nominal Concentration (mg/L): 6.07

* = non-volatile content of Profenofos EC (A8591B) was 97.32 %

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Todos os infratores poderão ser processados civil e criminalmente

Main Study – Group 1

Exposure Duration (minutes)	Sample Volume (L)	Amount of Non Volatiles Collected* (mg)	Equivalent Test Item Amount (mg)	Atmospheric Concentration of the Test Item (mg/L)
0	2.0	3.95	4.06	2.03
12	2.0	4.01	4.12	2.06
24	2.0	4.02	4.13	2.07
36	2.0	3.87	3.98	1.99
46	2.0	3.78	3.88	1.94
63	2.0	3.91	4.02	2.01
83	2.0	4.12	4.23	2.12
101	2.0	3.80	3.90	1.95
113	2.0	4.01	4.12	2.06
125	2.0	4.01	4.12	2.06
137	2.0	4.08	4.19	2.10
152	2.0	3.85	3.96	1.98
171	2.0	3.90	4.01	2.00
183	2.0	3.71	3.81	1.91
199	2.0	3.86	3.97	1.98
212	2.0	3.86	3.97	1.98
222	2.0	3.90	4.01	2.00

Mean achieved concentration = 2.01 mg/L

Standard Deviation = 0.06

Amount of Test Item Used (g): 79.95[†]

Total Volume of Air Used (L): 7890

Nominal Concentration (mg/L): 10.13

* = non-volatile content of Profenofos EC (A8591B) was 97.32 %

[†] Container loaded with test item was knocked over and some test item was spilled out before weighting of it at the end of exposure, that is why the nominal concentration is false higher.

SEGREDOS INDUSTRIAIS

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Todos os infratores poderão ser processados civil e criminalmente

TABLE 2 Test Atmosphere Particle Size Distribution Data

Sighting Exposure – Group 0.1

Stage Number	Cut Point (µm)	Amount Collected (mg)			Total Collected per Stage (mg)
		Sample 1	Sample 2	Sample 3	
1	10.550	0.06	0.03	0.05	0.14
2	6.655	0.11	0.14	0.15	0.40
3	3.555	1.01	1.07	1.15	3.23
4	2.105	2.82	3.18	3.31	9.31
5	1.550	1.66	1.78	1.82	5.26
6	0.960	1.45	1.62	1.61	4.68
7	0.550	2.08	2.30	2.60	6.98
Filter	< 0.550	0.15	0.10	0.18	0.43
Total Amount Collected (mg)					30.43
Size Range (µm)		Total Mass/stage (mg)		Cumulative Mass (%)	
< 0.550		0.43		1.41	
0.550 - 0.960		6.98		24.35	
0.960 - 1.550		4.68		39.73	
1.550 - 2.105		5.26		57.02	
2.105 – 3.555		9.31		87.61	
3.555 - 6.655		3.23		98.23	
6.655 – 10.550		0.40		99.54	
> 10.550		0.14		100.00	

Mean achieved concentration = 1.97 mg/L

Mean Mass Median Aerodynamic Diameter (MMAD) = 1.83 µm

Geometric Standard Deviation (GSD) = 1.88

Respirable Fraction (% < 4µm) = 89.1 %

SEGREDOS INDUSTRIAIS

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Main Study – Group 1

Stage Number	Cut Point (µm)	Amount Collected (mg)			Total Collected per Stage (mg)
		Sample 1	Sample 2	Sample 3	
1	10.550	0.05	0.06	0.06	0.17
2	6.655	0.09	0.24	0.10	0.43
3	3.555	1.13	1.51	0.93	3.57
4	2.105	3.16	4.66	2.73	10.55
5	1.550	1.99	2.12	1.78	5.89
6	0.960	1.51	2.17	1.51	5.19
7	0.550	2.52	2.43	2.61	7.56
Filter	< 0.550	0.11	0.17	0.04	0.32
Total Amount Collected (mg)					33.68
Size Range (µm)		Total Mass/stage (mg)		Cumulative Mass (%)	
< 0.550		0.32		0.95	
0.550 - 0.960		7.56		23.40	
0.960 - 1.550		5.19		38.81	
1.550 - 2.105		5.89		56.29	
2.105 – 3.555		10.55		87.62	
3.555 - 6.655		3.57		98.22	
6.655 – 10.550		0.43		99.50	
> 10.550		0.17		100.00	

Mean achieved concentration = 2.01 mg/L

Mean Mass Median Aerodynamic Diameter (MMAD) = 1.88 µm

Geometric Standard Deviation (GSD) = 1.86

Respirable Fraction (% < 4µm) = 88.7%

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Todos os infratores poderão ser processados civil e criminalmente

TABLE 3 Test Chamber Environmental and Equilibration Data**Sighting Exposure – Group 0.1**

Measurement	Mean Value	Minimum	Maximum
Air Flow In (Inner Plenum) (L/min)	29.9	27.4	31.0
Air Flow Out (Outer Cylinder) (L/min)	31.0	30.7	31.2
Temperature* (°C)	22.7	22.0	23.5
Relative Humidity† (%)	52.0	49.2	55.1

Theoretical Chamber Equilibration Time (T₉₉):

$$T_{99} = (4.605 \times (\text{Chamber Volume} / \text{Chamber Flow rate})) \text{ (Silver, 1946)}$$

Chamber volume (inner plenum) = 3.85 L (Pauluhn, 1994)

T₉₉ (Minimum Acceptable Equilibration Time) = 1 minute

Actual equilibration time allowed = 23 minutes

* Temperature was measured by handheld thermometer.

† The chamber humidity was measured by handheld hygrometer.

SEGREDOS INDUSTRIAIS

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Main Study – Group 1

Measurement	Mean Value	Minimum	Maximum
Air Flow In (Inner Plenum) (L/min)	29.9	25.5	31.0
Air Flow Out (Outer Cylinder) (L/min)	31.0	30.8	31.1
Temperature* (°C)	23.7	23.1	24.2
Relative Humidity† (%)	34.5	33.0	36.0

Theoretical Chamber Equilibration Time (T_{99}):

$$T_{99} = (4.605 \times (\text{Chamber Volume} / \text{Chamber Flow rate})) \text{ (Silver, 1946)}$$

Chamber volume (inner plenum) = 3.85 L (Pauluhn, 1994)

T_{99} (Minimum Acceptable Equilibration Time) = 1 minute

Actual equilibration time allowed = 24 minutes

* Temperature was measured by handheld thermometer.

† The chamber humidity was measured by handheld hygrometer.

SEGREDOS INDUSTRIAIS

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TABLE 4 Mortality Data

Day Number	Number of Deaths			
	Group 0.1		Group 1	
	Male	Female	Male	Female
0 (During Exposure)	0	0	0	0
0 (After Exposure)	0	0	0	0
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0
8 – 14	0	0	0	0
Total Deaths	0/2	0/2	0/5	0/5
Grand Total Deaths	0/4		0/10	

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Todos os infratores poderão ser processados civil e criminalmente

APPENDICES SECTION

CONFIDENTIAL
Property of Syngenta



SEGREDOS INDUSTRIAIS

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APPENDIX 1 Individual Clinical Observations

SIGHTING EXPOSURE
DOSE GROUP:
CONCENTRATION:

0.1
1.97 mg/L

SEX: MALE

Animal number	Observations	Days of study														Frequency					
		0 (exposure)					1	2	3	4	5	6	7	8	9		10	11	12	13	14
		1h	2h	3h	4h	5h															
1466♂	Normal	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	13 /19
	Laboured respiration	Sl	Sl	Sl	Mo	Mo	Sl	-	-	-	-	-	-	-	-	-	-	-	-	-	6 /19
	Noisy respiration	-	-	-	Sl	Sl	Sl	-	-	-	-	-	-	-	-	-	-	-	-	-	3 /19
	Red-brown staining - Head	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2 /19
	Wet fur- Whole body	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2 /19
1467♂	Normal	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	13 /19	
	Laboured respiration	Sl	Sl	Sl	Mo	Mo	Sl	-	-	-	-	-	-	-	-	-	-	-	-	6 /19	
	Noisy respiration	-	-	-	Sl	Sl	Sl	-	-	-	-	-	-	-	-	-	-	-	-	3 /19	
	Red-brown staining - Left eye	-	-	-	+		-	-	-	-	-	-	-	-	-	-	-	-	-	1 /19	
	Red-brown staining - Area around eyes	-	-	-		+	-	-	-	-	-	-	-	-	-	-	-	-	-	1 /19	
	Wet fur- Whole body	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	2 /19	

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

SEGREDOS INDUSTRIAIS

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SIGHTING EXPOSURE

DOSE GROUP:

0.1

CONCENTRATION:

1.97 mg/L

SEX: FEMALE

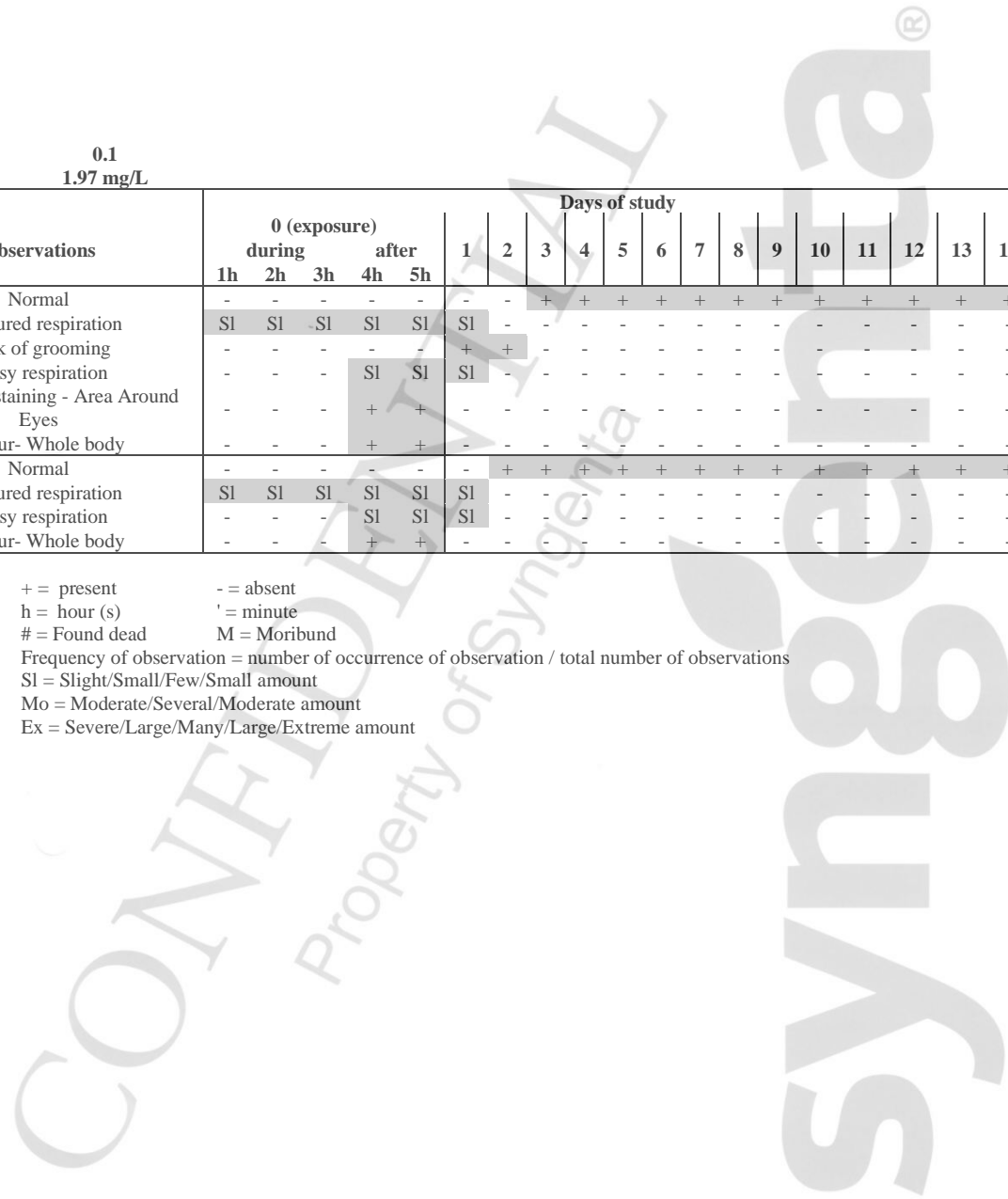
Animal number	Observations	Days of study														Frequency					
		0 (exposure)					1	2	3	4	5	6	7	8	9		10	11	12	13	14
		during 1h	2h	3h	after 4h	5h															
1482 ♀	Normal	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	12 /19
	Laboured respiration	Sl	Sl	Sl	Sl	Sl	Sl	-	-	-	-	-	-	-	-	-	-	-	-	-	6 /19
	Lack of grooming	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	2 /19
	Noisy respiration	-	-	-	Sl	Sl	Sl	-	-	-	-	-	-	-	-	-	-	-	-	-	3 /19
	Red-brown staining - Area Around Eyes	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2 /19
	Wet fur- Whole body	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2 /19
	Normal	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	13 /19
1491 ♀	Laboured respiration	Sl	Sl	Sl	Sl	Sl	Sl	-	-	-	-	-	-	-	-	-	-	-	-	6 /19	
	Noisy respiration	-	-	-	Sl	Sl	Sl	-	-	-	-	-	-	-	-	-	-	-	-	3 /19	
	Wet fur- Whole body	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	2 /19	
	Normal	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	13 /19	

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



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MAIN STUDY
DOSE GROUP: 1
CONCENTRATION: 2.01 mg/L

SEX: MALE

Animal number	Observations	Days of study																	Frequency			
		0 (exposure)					1	2	3	4	5	6	7	8	9	10	11	12		13	14	
		during	after																			
1h	2h	3h	4h	5h																		
2023♂	Normal	+	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	10	/19
	Activity decreased	-	-	-	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	3	/19
	Laboured respiration	-	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19
	Lack of grooming	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19
	Noisy respiration	-	-	-	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19
	Red-brown staining - Head	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19
	Red-brown staining - Nose/Snout	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19
	Sneezing	-	-	-	-	-	-	+	+	+	+	-	-	-	-	-	-	-	-	-	4	/19
	Wet fur - Whole body	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19
2009♂	Normal	+	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	10	/19
	Activity decreased	-	-	-	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	3	/19
	Laboured respiration	-	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19
	Lack of grooming	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19
	Noisy respiration	-	-	-	Mo	Mo	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	3	/19
	Red-brown staining - Head	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	3	/19
	Sneezing	-	-	-	-	-	-	+	+	+	+	-	-	-	-	-	-	-	-	-	4	/19
Wet fur - Whole body	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19	
2006♂	Normal	+	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	9	/19
	Activity decreased	-	-	-	Mo	Mo	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	5	/19
	Head tilt left	-	-	-	-	-	-	+	+	+	+	+	-	-	-	-	-	-	-	-	5	/19
	Laboured respiration	-	SI	SI	Ex	Mo	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	5	/19
	Lack of grooming	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19
	Noisy respiration	-	-	-	-	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19
	Red-brown staining - Head	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19
	Wet fur - Whole body	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19

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:

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

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Todos os infratores poderão ser processados civil e criminalmente

MAIN STUDY
DOSE GROUP: 1
CONCENTRATION: 2.01 mg/L

SEX: MALE

Animal number	Observations	Days of study														Frequency						
		0 (exposure)					1	2	3	4	5	6	7	8	9		10	11	12	13	14	
		during	1h	2h	3h	4h																5h
2017♂	Normal	+	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	11	/19
	Activity decreased	-	-	-	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	3	/19
	Laboured respiration	-	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19
	Lack of grooming	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19
	Noisy respiration	-	-	-	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	3	/19
	Red-brown staining - Nose/Snout	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19
	Sneezing	-	-	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	3	/19
	Wet fur - Whole body	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19
2013♂	Normal	+	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	11	/19
	Activity decreased	-	-	-	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	3	/19
	Laboured respiration	-	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19
	Lack of grooming	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19
	Noisy respiration	-	-	-	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	3	/19
	Red-brown staining - Head	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19
	Sneezing	-	-	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	3	/19
	Wet fur - Whole body	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19

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:

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

SEGREDOS INDUSTRIAIS

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Todos os infratores poderão ser processados civil e criminalmente

MAIN STUDY
DOSE GROUP: 1
CONCENTRATION: 2.01 mg/L

SEX: FEMALE

Animal number	Observations	Days of study														Frequency							
		0 (exposure)					1	2	3	4	5	6	7	8	9		10	11	12	13	14		
		during	1h	2h	3h	4h																5h	
2031♀	Normal	+	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14	/19
	Laboured respiration	-	SI	SI	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	/19
	Lack of grooming	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19
	Noisy respiration	-	-	-	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	/19
	Red-brown staining - Nose/Snout	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19
	Wet fur - Whole body	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19
2035♀	Normal	+	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	14	/19	
	Laboured respiration	-	SI	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	/19	
	Lack of grooming	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19	
	Noisy respiration	-	-	-	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	3	/19	
	Red-brown staining - Nose/Snout	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19	
	Wet fur - Whole body	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19	
2039♀	Normal	+	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	14	/19	
	Laboured respiration	-	SI	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	/19	
	Lack of grooming	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19	
	Noisy respiration	-	-	-	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	3	/19	
	Red-brown staining - Head	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	/19	
	Wet fur - Whole body	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	/19	

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:

SI = Slight/Small/Few/Small amount
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Todos os infratores poderão ser processados civil e criminalmente

MAIN STUDY
DOSE GROUP: 1
CONCENTRATION: 2.01 mg/L

SEX: FEMALE

Animal number	Observations	Days of study																	Frequency		
		0 (exposure)					1	2	3	4	5	6	7	8	9	10	11	12		13	14
		during	after																		
1h	2h	3h	4h	5h																	
2042♀	Normal	+	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	14 /19
	Laboured respiration	-	SI	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4 /19
	Lack of grooming	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	1 /19
	Noisy respiration	-	-	-	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2 /19
	Red-brown staining - Head	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2 /19
	Wet fur - Whole body	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2 /19
2038♀	Normal	+	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	14 /19
	Laboured respiration	-	SI	SI	SI	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4 /19
	Lack of grooming	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	1 /19
	Noisy respiration	-	-	-	Mo	Mo	SI	-	-	-	-	-	-	-	-	-	-	-	-	-	3 /19
	Red-brown staining - Head	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2 /19
	Wet fur - Whole body	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2 /19

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:

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APPENDIX 2 Individual Bodyweight Data

SIGHTING EXPOSURE

DOSE GROUP:

0.1

CONCENTRATION:

1.97 mg/L

SEX: MALE

Animal Number	Body weight (g) on days					Body weight gain (g) between days				
	0	1	3	7	14	0-1	1-3	3-7	7-14	0-14
1466♂	344	318	333	363	386	-26	15	30	23	42
1467♂	344	312	320	351	384	-32	8	31	33	40
Mean:	344.0	315.0	326.5	357.0	385.0	-29.0	11.5	30.5	28.0	41.0
Standard deviation:	0	4.2	9.2	8.5	1.4	4.2	5.0	0.7	7.1	1.4

DOSE GROUP:

0.1

CONCENTRATION:

1.97 mg/L

SEX: FEMALE

Animal Number	Body weight (g) on days					Body weight gain (g) between days				
	0	1	3	7	14	0-1	1-3	3-7	7-14	0-14
1482♀	216	201	214	228	241	-15	13	14	13	25
1491♀	212	213	218	231	239	1	5	13	8	27
Mean:	214.0	207.0	216.0	229.5	240.0	-7.0	9.0	13.5	10.5	26.0
Standard deviation:	2.8	8.5	2.8	2.1	1.4	11.3	5.7	0.7	3.5	1.4

MAIN STUDY

DOSE GROUP:

1

CONCENTRATION:

2.01 mg/L

SEX: MALE

Animal Number	Body weight (g) on days					Body weight gain (g) between days				
	0	1	3	7	14	0-1	1-3	3-7	7-14	0-14
2023♂	324	300	310	333	372	-24	10	23	39	48
2009♂	318	290	301	336	376	-28	11	35	40	58
2006♂	326	299	311	340	386	-27	12	29	46	60
2017♂	342	314	321	348	394	-28	7	27	46	52
2013♂	322	306	305	337	370	-16	-1	32	33	48
Mean:	326.4	301.8	309.6	338.8	379.6	-24.6	7.8	29.2	40.8	53.2
Standard deviation:	9.2	8.9	7.5	5.7	10.1	5.1	5.3	4.6	5.4	5.6

DOSE GROUP:

1

CONCENTRATION:

2.01 mg/L

SEX: FEMALE

Animal Number	Body weight (g) on days					Body weight gain (g) between days				
	0	1	3	7	14	0-1	1-3	3-7	7-14	0-14
2031♀	241	226	235	243	255	-15	9	8	12	14
2035♀	234	239	249	253	265	5	10	4	12	31
2039♀	241	238	242	259	275	-3	4	17	16	34
2042♀	234	221	231	242	250	-13	10	11	8	16
2038♀	251	246	249	260	269	-5	3	11	9	18
Mean:	240.2	234.0	241.2	251.4	262.8	-6.2	7.2	10.2	11.4	22.6
Standard deviation:	7.0	10.2	8.1	8.6	10.2	8.1	3.4	4.8	3.1	9.2

Standard footnotes:

= Found dead

M = Moribund

- = No data

SEGREDOS INDUSTRIAIS

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APPENDIX 3 Individual Necropsy Findings

SIGHTING EXPOSURE
CONCENTRATION: 1.97 mg/L

SEX: MALE

Dose group	Animal Number	Necropsy Day	External Observations	Internal Observations	Organ/Tissue
0.1	1466♂	Day 14	No external observations recorded	No internal observations recorded	Not applicable
	1467♂	Day 14	No external observations recorded	No internal observations recorded	Not applicable

CONCENTRATION: 1.97 mg/L

SEX: FEMALE

Dose group	Animal Number	Necropsy Day	External Observations	Internal Observations	Organ/Tissue
0.1	1482♀	Day 14	No external observations recorded	No internal observations recorded	Not applicable
	1491♀	Day 14	No external observations recorded	No internal observations recorded	Not applicable

MAIN STUDY

CONCENTRATION: 2.01 mg/L

SEX: MALE

Dose group	Animal Number	Necropsy Day	External Observations	Internal Observations	Organ/Tissue
1	2023♂	Day 14	No external observations recorded	No internal observations recorded	Not applicable
	2009♂	Day 14	No external observations recorded	No internal observations recorded	Not applicable
	2006♂	Day 14	No external observations recorded	No internal observations recorded	Not applicable
	2017♂	Day 14	No external observations recorded	No internal observations recorded	Not applicable
	2013♂	Day 14	No external observations recorded	No internal observations recorded	Not applicable

CONCENTRATION: 2.01 mg/L

SEX: FEMALE

Dose group	Animal Number	Necropsy Day	External Observations	Internal Observations	Organ/Tissue
1	2031♀	Day 14	No external observations recorded	No internal observations recorded	Not applicable
	2035♀	Day 14	No external observations recorded	No internal observations recorded	Not applicable
	2039♀	Day 14	No external observations recorded	No internal observations recorded	Not applicable
	2042♀	Day 14	No external observations recorded	No internal observations recorded	Not applicable
	2038♀	Day 14	No external observations recorded	No internal observations recorded	Not applicable

Standard footnotes:

= Found dead

M = Moribund

- = No data

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ALS Laboratórios LS Ltda.
Rua Fábila, 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

A8591B
Profenofos EC (960)
RAN001-099-019

Batch Identification	RAN001-099-019
Product Code	A8591B
Other Product Code(s)	A8591; CGA15324 EC (960); EXF23490E
EUP number	514/2020 Expiry date: 26/02/2023
Received on	12 May 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 Profenofos *** **73.12 % w/w corresponding to 969.03 g/L**

The Active Ingredient content is within the FAO limits.
Methodology used for Characterization: CG-FID (SF-1135/1)

Physical Analysis

– **Density *** **1.3253 g/cm³**

Stability:

– **Storage Temperature** **<30°C**
– **Recertification Date** **06 May 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: 25926/2021CC

Authorization: 26 May 2021

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

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APPENDIX 5 Attempts to Achieve the target concentration of 2 mg/L

Technical Trial	Test Item Concentration (% w/w)	Test Item Flow (mL/hr)	Air Flow In (set) (L/min)	Achieved Test Atmosphere Concentration (mg/L)	MMAD (µm)	GSD
1	100	30-50	30	4.99-6.85	2.20	1.89
1	100	7-15	30	1.78-3.26	1.90	1.82
2*	100	8.0-8.40	30	1.57-2.03	1.88;1.88	1.84;1.85

*Note: This setting was used for animal exposures.

SEGREDOS INDUSTRIAIS

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APPENDIX 6 Good Laboratory Practice (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

Digitalisan 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 Élelmezés-egészségügyi Intézet") - ("National Institute of Pharmacy and Nutrition"); ("Hatósági Ellenőrzési Főosztály") - (Inspectorate Division); and at the signature: ("Digitálisan aláírta") - (Digitally signed); ("Dátum") - ("Date").

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Report Number: 21/201-004P

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