Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS

FOR AGRICULTURAL PESTICIDES

SILTHIOFAM

N-allyl-4,5-dimethyl-2-(trimethylsilyl)thiophene-3-carbox-amide

TABLE OF CONTENTS

DISCLAIMER[1]

FAO specifications are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements.

Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

Furthermore, pesticides which are manufactured to comply with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable to their manufacture, sale, transportation, storage, handling, preparation and/or use.

FAO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may be arise as a result of, or in connection with, the manufacture, sale, transportation, storage, handling, preparation and/or use of pesticides which are found, or are claimed, to have been manufactured to comply with these specifications.

Additionally, FAO wishes to alert users to the fact that improper storage, handling, preparation and/or use of pesticides can result in either a lowering or complete loss of safety and/or efficacy.

FAO is not responsible, and does not accept any liability, for the testing of pesticides for compliance with the specifications, nor for any methods recommended and/or used for testing compliance. As a result, FAO does not in any way warrant or represent that any pesticide claimed to comply with a FAO specification actually does so.

[1] This disclaimer applies to all specifications published by FAO.

INTRODUCTION

FAO establishes and publishes specifications* for technical material and related formulations of agricultural pesticides, with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 2002, the development of WHO specifications follows the **New Procedure**, described in the 1st edition of "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (2002) - currently available as 3rd revision of the 1st edition (2016) - , which is available only on the internet through the FAO and WHO web sites.

This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPM, rather than the JMPS.]

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently from the year 2000 onwards the publication of FAO specifications under the **New Procedure** has changed. Every specification consists now of two parts namely the specifications and the evaluation report(s):

Part One: **The Specification** of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the "Manual on development and use of FAO and WHO specifications for pesticides".

Part Two: The Evaluation Report(s) of the pesticide, reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the "FAO/WHO Manual on Pesticide Specifications" and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

FAO specifications developed under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. FAO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version.

* NOTE: PUBLICATIONS ARE AVAILABLE ON THE INTERNET AT (http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/ps-new/en/) OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.

PART ONE

SPECIFICATIONS

INFORMATION

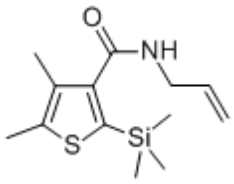
SILTHIOFAM

ISO common nam Silthiofam (ISO 1750, published)
Chemical names

IUPAC *N*-allyl-4,5-dimethyl-2-(trimethylsilyl)thiophene-3-carboxamide
CA 4,5-Dimethyl-*N*-(2-propenyl)-2-(trimethylsilyl)-3 thiophene carboxamide.

Synonym MON65500

Structural formula



Molecular formula $C_{13}H_{21}NOSSi$
Relative molecular mass
267.47

CAS Registry number 175217-20-6
CIPAC number 635
Identity tests HPLC retention time, UV spectrum (for TC) and IR spectrum (for FS).

SILTHIOFAM TECHNICAL MATERIAL

FAO Specification 635 / TC (March 2018*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (635/2016). It should be applicable to TC produced by this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for the products of other manufacturers. The evaluation report (635/2016) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist of silthiofam together with related manufacturing impurities, and shall be beige powder free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (CIPAC 635/TC/M2), (Note 1)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Silthiofam content** (CIPAC 635/TC/M3), (Note 1)

The silthiofam content shall be declared (not less than 980 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

Note 1 The reversed-phase analytical method for the identification and determination of silthiofam in TC and in FS formulations (CIPAC/5004) was adopted as a full CIPAC method at the CIPAC meeting in 2016. Prior to its publication in a Handbook, copies of the method may be obtained through http://cipac.org/index.php/methods-publications/pre-published-methods

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/ps-new/en

SILTHIOFAM SUSPENSION CONCENTRATE FOR SEED TREATMENT

FAO Specification 635 / FS (March 2018*)

This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (635/2016). It should be applicable to FS produced by this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for FS produced by other manufacturers. The evaluation report (635/2016), as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of a suspension of fine particles of technical silthiofam complying with the requirements of FAO specification 635/TC (March 2018), in an aqueous phase together with suitable formulants, including colouring matter (Note 1). After gentle stirring or shaking, the material shall be homogeneous (Note 2), and suitable for further dilution with water if necessary.

2 Active ingredient

2.1 **Identity tests** (CIPAC 635/FS/M2), (Note 3)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Silthiofam content** (CIPAC 635/FS/M3, (Note 3)

The silthiofam content shall be declared (g/kg or g/l at 20 ± 2ºC, Note 4) (100 to 250 g/l) and, when determined, the average content measured shall not differ from that declared by more than ± 6%.

3 Physical properties

3.1 **pH range** (MT 75.3, CIPAC Handbook J, p. 131, 2000)

pH range: 6.0 to 9.0

3.2 **Pourability (MT 148.1, CIPAC Handbook F, p.348, 1995)**

Maximum "residue": 4 %

3.3 **Wet sieve test** (MT 185, CIPAC Handbook K, p. 149, 2003) (Note 5)

Maximum: 0.5 % retained on a 75 µm test sieve.

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmps/ps-new/en

3.4 **Persistent foam** (MT 47.3, CIPAC Handbook O, p. 177, 2017) (Note 6)

Maximum: 60 ml after 1 minute.

3.5 **Adhesion to seeds** (MT 194, CIPAC Handbook N, p.145, 2012)

Winter wheat seed: A minimum of 95% of silthiofam shall remain on the seeds after the test.

Barley seed: A minimum of 95% of silthiofam shall remain on the seeds after the test.

4 Storage stability

4.1 Stability at 0°C (MT 39.3, CIPAC Handbook J, p.126, 2000)

After storage at 0 ± 2°C for 7 days, the formulation shall continue to comply with the clause for wet sieve test (3.3).

4.2 Stability at elevated temperature (MT 46.3, CIPAC Handbook J, p.128, 2000)

After storage at 30 ± 2°C for 18 weeks (Note 7), the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 8) and the formulation shall continue to comply with the clauses for:

- pH range (3.1),
- pourability (3.2),
- wet sieve test (3.3),
- adhesion to seeds (3.5).

Note 1 The influence of treatment on germination is of major importance but it is not the subject of a specification clause because no test method is applicable to all types of seeds. To avoid adverse effects, users should apply the formulation strictly according to the recommendations of the manufacturer and should not treat seeds for which effect on germination is not known. Treated seeds should be stored in a suitable container and should be protected from excessive temperature and moisture.

The formulation shall contain a dye or pigment that permanently colours the seed after treatment (red is recommended). In some countries, there may be a legal requirement that a specific colour shall be used. The same colour must not be used for denaturing seeds intended for use as livestock feeding stuffs.

Note 2 Before sampling to verify the formulation quality, inspect the commercial container carefully. On standing, suspension concentrates usually develop a concentration gradient from the top to the bottom of the container. This may even result in the appearance of a clear liquid on the top and/or sediment on the bottom. Therefore, before sampling, homogenize the formulation according to the instructions given by the manufacturer or, in the absence of such instructions, gently shake the commercial container (for example by inverting the closed container several times, large containers must be opened and stirred adequately). After this procedure, the container should not contain a sticky layer of non-dispersed matter at the bottom. A suitable and simple method of checking for a non-dispersed sticky layer ("cake") is by probing with a glass rod or similar device adapted to the size and shape of the container. All the physical and chemical tests must be carried out on a laboratory sample taken after the recommended homogenization procedure.

Note 3 The method for the identification and determination of silthiofam in TC and in FS formulations was adopted at the CIPAC meeting in 2016. Prior to its publication in a Handbook, copies of the method may be obtained through http://cipac.org/index.php/methods-publications/pre-published-methods

Note 4 Unless homogenization is carried out carefully, it is possible for the sample to become aerated. This can lead to errors in the determination of the mass per millilitre, and in calculation of the active ingredient content (in g/l) if methods other than MT 3.3 are used. If the buyer requires both g/kg and g/l at 20°C, then in case of dispute the analytical results shall be calculated as g/kg.

Note 5 This test should detect coarse particles (e.g. caused by crystal growth) or extraneous materials which could cause blockage of spray nozzles or filters of the application equipment.

Note 6 If the product is intended to be used after dilution, persistent foam is to be measured at a concentration of 15% v/v in water. This clause is not applicable where the product is used without dilution.

Note 7 A test at 30°C for 18 weeks is considered appropriate as the formulation may be heat sensitive.

Note 8 Samples of the formulation taken before and after the storage stability test may be analyzed concurrently after the test in order to reduce the analytical error.

PART TWO

EVALUATION REPORTS

SILTHIOFAM

[1] Monsanto sold the intellectual property rights for silthiofam TC and FS to Mitsui & Co., LTD by February 1st 2017. JMPS considers all conclusions in the evaluation report 635/2016 to remain valid unless further notice from Mitsui & Co., LTD.

SILTHIOFAM

FAO/WHO EVALUATION REPORT 635/2016

Recommendation

The meeting recommended that:

(i) the new FAO specifications for silthiofam TC and FS, proposed by Monsanto and as amended, should be adopted by FAO

Appraisal

The Meeting considered data on silthiofam submitted by Monsanto, in support of new FAO specifications for TC and FS. The data package was broadly in agreement with the requirements of the FAO/WHO Manual on development and use of pesticide specifications (2010 2nd revision of the 1st edition).

Silthiofam is a fungicide with patent protection recently expired (2015) in most countries.

Silthiofam is the ISO common name for *N*-allyl-4,5-dimethyl-2-(trimethylsilyl) thiophene-3-carboxamide (IUPAC) which belongs to the group of amide (or thiophene) fungicides compounds. Silthiofam has not been evaluated by the FAO/WHO JMPR and WHO/IPCS.

Silthiofam was evaluated in the European Union and is included in Regulation (EU) No 540/2011 with a minimum purity of 950 g/kg. The compound is currently registered in Europe, China, Taiwan, United Arab Emirates, South Africa and other countries.

The Meeting considered data and supporting information submitted in 2016 and updated in 2017 by Monsanto, for the development of new FAO specifications for silthiofam TC and FS.

Ireland's regulatory authority as EU Rapporteur Member State confirmed that the confidential data on the manufacturing process and declaration of composition submitted to the FAO were similar to those submitted to the national regulatory authority.

Silthiofam TC is a beige powder. The melting point is 86.1 – 88.3°C (purity 97.7%). Purified silthiofam shows a vapour pressure of 0.08 Pa at 20°C. It has low solubility in water at 40 mg/l at 19.5°C, does not dissociate and has an octanol/water partition coefficient of 3.72 at 19.5°C, indicating a certain lipophilicity. It is readily soluble in organic solvents. Silthiofam is rapidly hydrolysed at pH 4 and 20°C, but is considered to be stable at pH 9 and 20°C. Silthiofam absorbs light at 304 nm. Photolytic DT_{50} was fast (1.8 days in distilled water, solar irradiation month of May) and 15 days (for the River Neckar, month May).

The Meeting was provided with commercially confidential information on the manufacturing process and batch analysis data on all impurities present at or above 1 g/kg and their manufacturing limits in the TC. Mass balances were high (99.91 - 100.41 % in the batch analysis data). The maximum limits for 2 impurities were considered to be rather generous

than statistically justified, however the proposer explained that they has sole supplier for each raw material, but could add additional suppliers in the future, potentially resulting in somewhat higher level of impurities.

The Meeting agreed with the company, that none of the impurities identified met the criteria to consider them as relevant.

The identity of silthiofam can be confirmed by comparison of the retention time of an standard with a sample using HPLC method, and by UV in TC and IR in FS.

The analytical method for the determination of the active ingredient in silthiofam technical and FS is reversed-phase HPLC with UV detection (CIPAC/635). Impurities were determined by GC-FID and HPLC-UV. The analytical methods for the impurities were validated for specificity, linearity, precision and accuracy. However no information on limits of detection and quantification was available. On request by the Meeting, Monsanto submitted data on LOQ, which were determined in the range of 0.07% to 0.09% for 2 significant impurities in the TC. Inorganic impurities like chloride and water were determined using ion chromatography and Karl-Fischer titration, respectively.

The test methods for determination of physico-chemical properties of the TC and FS were OECD, EC and CIPAC, where appropriate.

The draft specificatiosn for TC and FS were essentially in accordance with the requirements of the FAO/WHO Manual (2nd revision of the 1st edition, 2010)

A data package on acute and sub-acute to chronic toxicity, including carcinogenicity and teratogenicity, genotoxicity and ecotoxicology was provided, derived from the technical material manufactured by the proposer. However the purities of the batches used in toxicological and ecotoxicity studies were different from the proposed specification and those used in the 5-batch analysis study. The proposer confirmed that the toxicological and ecotoxicological data were derived from silthiofam having impurity profiles similar to the proposed profile for TC. The toxicological and ecotoxicological studies were performed with silthiofam with slightly higher impurity profiles.

The company provided data to demonstrate that the eye irritation observed did not trigger GHS classification as eye irritant or even mild eye irritant.

In the course of the evaluation of the dossier, Monsanto contacted FAO and communicated, that the intellectual property rights for silthiofam technical and FS had been sold to Mitsui & Co., LTD, effective February 1st 2017. JMPS considers all conclusions in the evaluation report 635/2016 to remain valid unless further notice from Mitsui & Co., LTD.

<u>Issues identified with the FS formulation specification</u>

The Meeting questioned the applicability of the clause of suspensibility and queried about the dilution range used in the suspensibility test. The proposer explained that the dilution used of 15% and 70% were representative for the range of dilutions used across Europe.

Therefore the Meeting considered this clause was not applicable to the formulation. The proposer agreed to delete this clause.

The Meeting questioned the pH range limits of 6-9. The company explained that silthiofam is being rapidly hydrolysed under acidic conditions, with DT_{50} values of 45 hours at pH 4, 448 days at pH 7 and 314 days at pH 9 and that the bottom limit was selected at pH 6 because no significant loss (due to the hydrolysis of the dissolved fraction of silthiofam) was expected at this pH and that the upper limit was selected at pH 9 because this represented the physical stability limit for some co-formulants. The Meeting agreed that a clause of pH 6-9 should be included in the specification.

The Meeting and Monsanto agreed that it was not necessary to include a clause for particle size distribution.

The Meeting questioned the low temperature of 30 °C chosen for the accelerated storage test instead of 54 °C. Monsanto explained that storage at 54 °C caused a growth of crystals of silthiofam leading to adverse effects on physical-chemical properties of the FS and that this effect was not observed during storage at room temperatures, therefore they considered the formulation to be heat sensitive. The Meeting accepted 30 °C as a sufficiently justified temperature for the accelerated storage test.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 635/2016

USES

Silthiofam is a fungicide classified by FRAC[1] to act on the respiration and ATP production of sensitive pathogens. It is used in agriculture as seed dressing on wheat, barley and triticale against root diseases (Take-all, *Gaeumannomyces graminis* var. Tritici).

IDENTITY OF THE ACTIVE INGREDIENT

ISO common name Silthiofam (ISO 1750, published)

Chemical name(s)

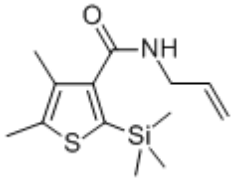
IUPAC *N*-allyl-4,5-dimethyl-2-(trimethylsilyl)thiophene-3-carboxamide

CA 4,5-Dimethyl-*N*-(2-propenyl)-2-(trimethylsilyl)-3-thiophenecarboxamide.

Synonyms

MON65500

Structural formula



Molecular formula

$C_{13}H_{21}NOSSi$

Relative molecular mass

267.47

CAS Registry number

175217-20-6

CIPAC number

635

Identity tests

HPLC retention time, UV spectrum (for TC) and IR spectrum (for FS).

[1] Fungicide Resistance Action Committe: MoA Poster available through http://www.frac.info/docs/default-source/publications/frac-mode-of-action-poster/frac-moa-poster-march-2017f19b282c512362eb9a1eff00004acf5d.pdf?sfvrsn=5fb84a9a_2

Table 1. Physico-chemical properties of pure silthiofam

Parameter	Value(s) and conditions	Purity %	Method reference (and technique if the reference gives more than one)	Study number
Vapour pressure	8.1×10^{-2} Pa at 20 °C	99.67%	EEC A4	291386
Melting point.	88 °C	99.67%	EEC A1	291353
Temperature of decomposition	321.9 – 340°C	98.7%	EEC A2 DSC method	Report 64/93-D2141
Solubility in water	40 mg/l at 19.5 °C at pH 8.7-9.1	99.67%	OECD 105	291432
Octanol/water partition coefficient	log P_{OW} = 3.72 at 19.5 °C	99.67%	OECD 107	291443
Hydrolysis characteristics	Half-life =196 days at 38 °C at pH 9	97.7%*	EEC C7	64/55-1015
Photolysis characteristics	DT_{50} = 1.8 days (for distilled water, month May) and 15 days (for the River Neckar, month May).	97.7%	SETAC section 10 1995	64/71
Dissociation characteristics	No functional groups are ionisable in water within pH range 2.5-12	97.7%*	Glass electrode calibration in methanol/water	64/46-1014
Solubility in organic solvents	n-heptane: 15.5 g/l p-xylene: >250 g/l 1,2-dichloroethane: >250 g/l methanol: >250 g/l acetone: >250 g/l ethyl acetate: >250 g/l at 19.5± 0.5°C	98.7%	OECD 105	291454

*At the time of the testing during the 1995-1999 period, before the industrial production of the product, the 98% purity was considered the highest achievable.

Table 2. Chemical composition and properties of silthiofam technical materials (TC)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 99.9 – 100.4 % and percentages of unknowns were 0.06-0.09 %.
Declared minimum [a.i.] content	980 g/kg
Relevant impurities ≥ 1 g/kg and maximum limits for them	None
Relevant impurities **<** 1 g/kg and maximum limits for them:	None
Stabilisers or other additives and maximum limits for them:	None

Parameter	Value and conditions	Purity %	Method reference	Study number
Melting temperature range of the TC	86.1 – 88.3°C there is indication of decomposition (discolored samples after cooling)	97.7%	EEC A1	NPD-94126324-T Report 64/64-104
Solubility in organic solvents	>10 g/l n-heptane at 20°C >250 g/l xylene at 20°C >200 g/l 1,2-dichloroethane at 20°C >250 g/l acetone at 20°C >250 g/l ethyl acetate at 20°C	98.8%	CIPAC MT 157	NPD-94126324-T Report 64/64-104

FORMULATIONS AND CO-FORMULATED ACTIVE INGREDIENTS

The main formulation type available is a suspension concentrate for seed treatment, a 635 g/l FS. Silthiofam is not co-formulated with other pesticides. This formulation is registered and sold in most EU countries and China.

METHODS OF ANALYSIS AND TESTING

The analytical method for the active ingredient (including identity tests) is a full CIPAC method. The results of the collaborative trial were were presented at the CIPAC Meeting in Athens and provisionally adopted. In the meantime, the method has become a full method.

Briefly, silthiofam is determined by reversed phase LC using UV detection at 260 nm and internal standardisation.

The methods for determination of impurities are based on gas chromatography with flame ionisation detector (GC-FID) for the determination of volatile impurities. Chloride is determined by anion chromatography. Residual water is determined by Karl Fischer titration.

Test methods for determination of physico-chemical properties of the technical active ingredient were OECD or EEC, while those for the formulations were CIPAC, as indicated in the specifications.

PHYSICAL-CHEMICAL PROPERTIES

The physical-chemical properties of the formulated product, the methods for testing them and the limits proposed for the 635/FS formulation, comply with the requirements of the FAO/WHO Manual (2010, 2nd revision of the 1st edition).

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

The active ingredient silthiofam is expressed as silthiofam (g/L at 20 ± 2°C for liquid formulations).

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Notes.

(i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from silthiofam having impurity profiles similar to those referred to in the table 2 above.

(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table 3. Toxicology profile of silthiofam technical material, based on acute toxicity, irritation and sensitization.

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number
Rat males & females	Acute oral toxicity	91.8 %	Guideline OECD 401. Silthiofam in corn oil was administered by gavage to 5/sex fasted Sprague-Dawley CD® rats. The dose was 5000 mg a.s./kg bw, application volume : 10 ml/kg bw. Observations were made for 14 days post-dose.	LD_{50} = > 5000 mg/kg bw	95-1335 PL-95-241
Rat males & females	Acute dermal toxicity	91.8 %	Guideline OECD 402. Silthiofam was applied under occlusive dressing to the clipped skin of 5/sex fasted Sprague-Dawley CD® rats. The exposure was for 24 hours to a dose of 5000 mg a.s./kg bw. The test substance was ground and moistened with 0.9% saline before application. Observations were made for 14 days post-dose.	LD_{50} = > 5000 mg/kg bw	95-1336 PL-95-242
Rat males & females	Acute inhalation toxicity	97.4 %	Guideline OECD 403. 5/sex Sprague-Dawley CD® rats were exposed to 4 hour inhalation exposure of silthiofam at a level of 2.8 mg a.s./L air. Chamber air flow rate was 68 L/min.	LC_{50} = > 2.8 mg/lit air (max attainable concentration)..	MSL 14866 ML-96-158
Rabbit males & females	skin irritation	91.8 %	Guideline OECD 404. Silthiofam was applied under semi-occlusive dressing to the clipped skin of 4 male and 2 female NZW rabbits. The exposure was for 4 hours to a dose of 5000 mg a.s./kg bw. The test substance was ground and moistened with 0.9% saline before application. Observations were made for 72 hours post-dose.	All six animals were free of dermal irritation for the duration of the study.	5-1337 PL-95-244

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number
Rabbit males & females	eye irritation	91.8 %	Guideline OECD 405. 0.1 cc of the silthiofam was instilled into each of the 3/sex NZW rabbits. The single dose administration was followed by a 3 day observation period.	Slight to moderate conjunctival erythema were seen in all animals after one hour, which was resolved by 48 hours in all animals. There were no iridial or corneal effects.	95-1338 PL-95-243
Guinea pig	skin sensitisation	91.8 %	Guideline OECD 406. Silthiofam was used at 5% concentration for intradermal induction The test substance was used at a 100% concentration for topical induction and challenge having been moistened with 0.9% saline. Dose levels were based on a range-finding test. The area to be treated was pretreated with 10% sodium lauryl sulphate in petrolatum on the day before topical induction to provoke a mild inflammatory reaction. Topical induction and challenge applications were made 7 and 21 days after the intradermal induction, respectively.	Negative. All test and control animals were free of dermal responses 24 and 48 hours after administration of the challenge dose.	95-1327 PL-95-245

All studies were compliant with good laboratory practices and were carried in accordance with the OECD guidelines in place when the study was conducted. The acute toxicity of silthiofam following oral, percutaneous and inhalation exposure is low. Silthiofam is not a primary skin irritant or sensitiser. Silthiofam can cause slight/moderate reversible effects to the eye.

Table 4. Toxicology profile of silthiofam technical material based on repeated administration (subacute to chronic)

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number
Mouse males & females	Oral, short-term toxicity (28-day)	96.6	Guideline OECD 407. Silthiofam was administered in the feed at concentrations of 0, 10, 100, 1000 and 4000 ppm for four weeks (5 animals/sex/group).	Liver toxicity at 4000 ppm. NOAEL = 1000 ppm for both sexes corresponding to 259 (females) and 148 (males) mg/kg bw/day	MSL-14538/15332 ML-95-041
Rat males and females	Oral, short-term toxicity (28-day)	96.6%	Guideline OECD 407. Silthiofam was administered in the feed at concentrations of 0, 20, 200, 1000 and 8000 ppm for four weeks (5 animals/sex/group).	Effects at 8000 ppm included ↓body weight, ↓food consumption, ↑reticulocytes, substantial liver toxicity and possible effects on kidney and spleen. NOAEL = 1000 ppm for both sexes corresponding to 77 (females) and 73 (males) mg/kg bw/day	MSL-14537 ML-95-042
Dog males and females	Oral, range-finding study (28-day)	91.8%	No specific guideline (range-finding) Silthiofam was administered via gelatin capsule (7 days/week) at dose levels of 0, 10, 50, 150, and 250/350 mg/kg bw/day for four weeks (2/sex/group). The high dose was reduced from 350 to 250 mg/kg	High-dose (350/250) and perhaps 150 mg/kg/day were excessively toxic, as evidenced by mortality (high-dose only), clinical signs of toxicity and weight	MSL-14758 ML-95-204

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number
			bw/day after 2 (males) or 3 (females) weeks of administration because excessive toxicity was observed.	loss. Slight weight loss also seen in 50 mg/kg/day females. Increased liver weight and serum enzyme markers at 150 mg/kg/day but no histopath performed. NOAEL = 50 mg/kg bw/day for males NOAEL = 10 mg/kg bw/day for females	
Mouse, males and females	Oral, short-term toxicity (60-day)	91.8%	OECD 408. Silthiofam was administered in the feed at concentrations of 0, 50, 1000, 2500 and 5000 ppm for 60 days (10/sex/group)	Liver toxicity at 2500 and/or 5000. NOAEL = 1000 ppm in both sexes corresponding to 236 (females) and 140 (males) mg/kg bw/day	ML-95-202
Rat males and females	Oral, short-term toxicity (90-day)	91.8	Guideline OECD 408. Silthiofam was administered in the feed at concentrations of 0, 25, 250, 2500 and 5000 ppm for 90 days (10/sex/group). A satellite test system of 10 females/group was also included in this study; these rats were paired with the males from their corresponding groups for a period of up to 7 days after approximately 8	Excessive toxicity (including mortality) at 5000 ppm. Decreased weight gain at 2500 ppm. Liver toxicity at 2500 and/or 5000 ppm. Equivocal effects in kidney & spleen at 5000 ppm.	MSL-14816 ML-95-203

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number
			weeks of treatment. Females in the reproduction satellite were continued on treatment through post-natal day 4.	NOAEL = 250 ppm in both sexes corresponding to 15 (males) and 18 (females) mg/kg bw/day $NOEL_{reproduction}$ = 5000 ppm in both sexes corresponding to 290 (males) and 334 (females) mg/kg bw/day	
Dog males and females	Oral, short-term toxicity (90-day)	97.4	Guideline OECD 409 Silthiofam was administered via gelatin capsule (7 days/week) at dose levels of 0, 1, 10, 50 and 125 mg/kg bw/day for 90 days (5/sex/group). The high dose was reduced from 125 to 75 mg/kg bw/day after 7 weeks of study (females only) because excessive toxicity was observed.	Excessive toxicity (including mortality) at 125/75 mg/kg/day. Liver effects at ≥50 mg/kg/day included ↑liver weights and serum enzymes but no histopathological findings. NOAEL = 10 mg/kg bw/day in both sexes	MSL-15197 ML-96-067
Dog males and females	Oral, short-term toxicity (12 month)	97.4	Guideline OECD 452. Silthiofam was administered via gelatin capsule (7 days/week) at dose levels of 0, 1, 5, 20 and 80 mg/kg bw/day for 1 year (5/sex/group).	Substantial ↓weight gain and some evidence of liver toxicity at 80 mg/k/day. Slight reduction in some serum electrolytes at	MSL-15574 ML-97-043

Species	Test	Purity % Note	Guideline, duration, doses and conditions	Result	Study number
				≥20 mg/kg/day was considered treatment-related but not adverse since there were no other correlated findings. NOAEL(males) = 20 mg/kg bw/day	
Rats males and females	Percutaneous, short-term toxicity (21 days)	97.7	Guideline OECD 410 Silthiofam was administered dermally using occluded procedures. The test item was applied each morning 5 days/week for 3 weeks to a sterile gauze wrap, moistened with 0.9% saline and applied to an area of skin approximately 25-35 cm^2 on the back of each rat. An occlusive wrapping was applied. The application period each day was 6 hours. The dose levels were 0, 100, 300 and 1000 mg/kg bw/day (8 animals/sex/group)	Slight ↑liver weight in 1000 mg/kg/day males was considered treatment related but not adverse due to lack of associated clinical chemistry or histopath findings. Increased spleen weights in 300 and 1000 mg/kg/day males also not considered to be adverse due to lack of correlated findings. NOAEL = 1000 mg/kg bw/day	MSL-15527 ML-97-206

Table 5. Mutagenicity profile of silthiofam technical material based on *in vitro* and *in vivo* tests

Species	Test	Purity % Note[1]	Guideline, duration, doses and conditions	Result	Study number
Salmonella bacterial cells	*In-vitro* gene mutation (Ames test)	96.6	Guideline OECD 471 Silthiofam was evaluated in plate incorporation and liquid pre-incubation assays using bacterial strains TA98, TA100, TA102, TA1535 and TA1537 in presence and absence of an exogenous metabolic activation system. The concentrations of the test substance were 0, 0.015, 0.05, 0.15, 0.5 and 1.5 mg/plate.	Negative	MSL-14335 ML-95-057
Chinese hamster ovary cells	*In vitro* HGPRT assay	97.5	Guideline OECD 476 Silthiofam was evaluated in 2 experiments with Chinese hamster ovary cells. An initial experiment was conducted at concentrations of 0, 62.5, 125, 250 and 500 µg/ml test substance in absence (0%) and presence of metabolic activation system (1, 5 and 10%).. A confirmatory study was conducted at the same concentrations in presence and absence of a 1% exogenous metabolic activation system.	Negative	MSL-14936 ML-96-144
Human lymphocytes	*In-vitro* cytogenetic study	96.6	Guideline OECD 473 Silthiofam was evaluated in two experiments with cultured whole blood human lymphocytes in presence and absence of an exogenous metabolic activation system. An initial experiment was conducted at concentrations of	Negative	HL-95-159

[1] Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

Species	Test	Purity % Note[1]	Guideline, duration, doses and conditions	Result	Study number
			0, 50.5, 101, 201, 401, 601 and 801 µg/ml ± S9. Lymphocytes were incubated for 3.5 hours with silthiofam and harvested at 22 hours. A confirmatory study was conducted using the same concentrations in presence of metabolic activation and at concentrations of 0, 3.18, 6.35, 12.7, 25.3, 50.5 and 101 µg/ml in the absence of metabolic activation (3 hour incubation followed by harvest at 22 and 45.9 hours)		
Mouse	*In vivo* Mouse micronucleus	97.4	Guideline OECD 474 Silthiofam was administered as a single oral (gavage) dose in corn oil at levels of 0, 500, 1000 and 2000 mg/kg bw (10 CD-1® male mice/group). Bone marrow cells were harvested 24 and 48 hours (5 mice/group/time-point) after dose administration.	Negative .	MSL-14933 ML-96-143

Table 6. Ecotoxicology profile of silthiofam technical material

Species	Test	Purity % Note[1]	Guideline, duration, doses and conditions	Result [(isomer/form)]	Study number
Rainbow trout *Oncorhynchus mykiss*	Acute toxicity	91.8	Guideline OECD 203 Fish were exposed to silthiofam at nominal measured concentrations of 3.2, 5.3, 8.4, 13 and 16 mg a.s./L under static conditions for a period of 96 h. Twenty fish were allocated to each group, divided into 2 replicates/dose level. Animals were fasted during acclimation and test periods.	LC_{50} = 14 mg a.s./L NOEC = 3.2 mg a.s./L	WL-95-276
Bluegill fish *Lepomis macrochirus*	Acute toxicity	91.8	Guideline OECD 203 Fish were exposed to silthiofam at nominal measured concentrations of 2.4, 3.7, 6.0, 8.4 and 12 mg a.s./L under static conditions for a period of 96 h. Twenty fish were allocated to each group, divided into 2 replicates/dose level. Animals were fasted during acclimation and test periods.	LC_{50} = 11 mg a.s./L NOEC = 3.7 mg a.s./L	WL-95-280
Water flea *Daphnia magna*	Acute toxicity	91.8	Guideline OECD 202 Daphnids were exposed to silthiofam at measured concentrations of 2.9, 4.9, 7.8, 13 and 20 mg a.s./L. Test system was static, test duration was 48h.	EC_{50} = 14 mg a.s./L NOEC = 4.9 mg a.s./L	WL-95-275

[1] Note: Purity is the content of pure active ingredient in the technical material, expressed as a percentage.

			Twenty neonate daphnia (<24h old) per group were divided into two replicated per dose level. Animals were fasted during the test period.		
Water flea *Daphnia magna*	Chronic toxicity	99.67	Guideline OECD 211 Young daphnids (<24hours old) were exposed under semi-static conditions for 21 days to measured concentrations of 0.23, 0.47, 0.96, 1.8 and 3.7 mg a.s./L. Each group consisted of 10 replicate test chambers containing one daphnid. Test solutions were renewed three times/week (except weekends). Daphnids were fed once daily during the test.	NOEC = 0.47 mg a.s./L	139A-258
Freshwater alga *Selenastrum capricornutum*	Effect on growth, static water	97.7	Guideline OECD 201 Freshwater algae (approximately 3000 cells/ml at test start) were exposed for 5 days to silthiofam at measured concentrations of 1.1, 2.3, 4.6, 9.0 and 19 mg a.s./L). There were three replicates.	72hr E_rC50 = 13 mg a.s./L 72hr E_bC50 = 8.6 mg a.s./L	WL-97-167
Earthworm *Eisenia foetida*	Acute toxicity	97.5	Guideline OECD 207 Adult earthworms with clitellum were exposed to silthiofam in soil at nominal concentrations of 0, 6.25, 12.5, 25, 50, 100 and 200 mg a.s./kg dry soil. Forty worms were allocated to each group, divided	LC_{50} = 133 mg a.s/kg dry soil NOEC = 12.5 mg/kg dry soil	WL-95-196

			into 4 replicates/dose level. Test duration was 14 days with a 24h acclimation period. Animals were not fed during testing.		
Japanese quail *Coturnix Japonica*	acute toxicity	97.5	FIFRA Chapter 71-1 Silthiofam was administered orally by gelatine capsule to 7-week old Japanese quail (10 birds/treatment, 5/sex) at single doses of 0, 175, 292, 486, 810, 1350, 2250 mg/kg feed. Dosing was followed by subsequent observation period of 14 days. Average room temperature was 18.3 ± 2.6°C and relative humidity 26 ±6%.	LD50> 2250 mg a.s./kg feed NOEL = 175 mg a.s./kg feed	WL-94-351
Northern bobwhite *Colinus virginianus*	short-term toxicity	91.8	Guideline OECD 205 Birds (10 days old) were exposed to silthiofam in feed during 5 days at measured concentrations of 0, 542, 1020, 1760, 3190 and 5670 ppm, followed by a 3-day observation period. Ten birds (immature, undifferentiated by sex) were allocated to each dose level, with 4 control groups. The acclimatation period was 10 days (from hatching). Ambient temperature was 38 ± 1°C in the brooding compartment and 22.9 ± 1.2 °C in the test room. Relative humidity was 31 ± 11%.	LC50 = >5670 mg/kg feed NOEL = >5670 mg/kg feed	WL-95-277

Mallard duck *Anas platyrhynchos*	Short term toxicity	91.8	Guideline OECD 205 Birds (10 days old) were exposed to silthiofam in feed during 5 days at measured concentrations of 0, 504, 957, 1630, 3070 and 5400 ppm, followed by a 3-day observation period. Ten birds (undifferentiated by sex) were allocated to each group, with 3 control groups. The acclimatation period was 8 days. Ambient temperature was 30 ± 1°C in the brooding compartment and 21.7 ± 0.8 °C in the test room. Relative humidity was 55 ± 10%.	LC50 = >5400 mg/kg feed NOEL = >3070 mg/kg feed	WL-95-274
Northern bobwhite *Colinus virginianus*	Sub-chroic and reproduction	97.7	Guideline OECD 206 Groups of 32 young adult birds (16/sex) (22-week old) were exposed for 20 weeks to silthiofam in feed at nominal concentrations of 0, 100, 500 and 2500 ppm. The acclimatation period was 3 weeks. Ambient temperature was 37.5°C in the incubation compartment and 19.6 ± 2.3 °C in the test room (adults). Relative humidity was 56% in the incubation compartment and 50 ± 16% in the test room.	NOEL = 2500 mg/kg feed	WL-97-183

Hazard Summary

Silthiofam has not been evaluated by the WHO IPCS or by the FAO/WHO JMPR. The IPCS hazard classification of silthiofam is not available.

ANNEX 2
REFERENCES

Study number	Author(s)	Year	Study Title Company Source (where different from company) TC or Pure a.i. GLP / GEP status Published or not
291353		2000	Determination of the melting temperature of MON65500 Pure a.i. GLP/GEP (Y/N): Y Published (Y/N): N
291386		2000	Determination of the vapour pressure of MON65500 Pure a.i. GLP/GEP (Y/N): Y Published (Y/N): N
291432		2000	Determination of the water solubility of MON 65500 Pure a.i. GLP/GEP (Y/N): Y Published (Y/N): N
291454		2000	Determination of the solubility of MON 65500 in 6 organic solvents Pure a.i. GLP/GEP (Y/N): Y Published (Y/N): N
291443		2000	Determination of the partition coefficient (n-octanol/water) of MON 65500 Pure a.i. GLP/GEP (Y/N): Y Published (Y/N): N
64/55-1015		1996	(^{14}C)-MON 65500: Hydrolytic Stability Pure a.i. GLP/GEP (Y/N): Y Published (Y/N) : N
64/71		1998	Determination of the Direct Phototransformation of MON 65500 in water Pure a.i. GLP/GEP (Y/N): Y Published (Y/N) : N
64/46 – 104		1995	MON65500 : Determination of the physio-chemical properties TC GLP/GEP (Y/N): Y Published (Y/N) : N
PL-95-241		1996	Acute oral toxicity study in rats with MON 65500 TC GLP/GEP (Y/N): Y Published (Y/N): N
PL-95-242		1996	Acute dermal toxicity study in rats with MON 65500 TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-14866 (ML-96-158)		1996	Acute inhalation study of MON 65500 TC Report: GLP/GEP (Y/N): Y Published (Y/N): N

PL-95-244	1996	Primary dermal irritation study in rabbits with MON 65500 TC GLP/GEP (Y/N): Y Published (Y/N): N
PL-95-243	1996	Primary eye irritation study in rabbits with MON 65500 TC GLP/GEP (Y/N): Y Published (Y/N): N
PL-95-245	1996	Guinea pig maximization test with MON 65500 TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-14538/15332 (ML-95-041)	1996	4-week range-finding feeding study of MON 65500 in CD-1 mice TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-14537 (ML-95-042)	1996	4-week range-finding feeding study of MON 65500 in CD-1 rats TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-14758 (ML-95-204)	1996	Range-finding study of MON 65500 administered orally to beagle dogs TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-15251 (ML-95-202)	1997	Sixty-day feeding study of MON 65500 in CD-1 mice TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-14816 (ML-95-203)	1996	Three-month feeding study of MON 65500 in Sprague-Dawley rat with pilot reproduction phase TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-15197 (ML-96-067)	1997	Three-month feeding study of MON 65500 administered by capsule to beagle dogs TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-15574 (ML-97-043)	1998	One-Year study of MON 65500 administered by capsule to beagle dogs TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-15527 (ML-97-206)	1998	Range-finding and twenty-one day dermal study of MON 65500 in rats TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-14335 (ML-95-057)	1995	Ames/Salmonella mutagenicity assay of MON 65500 TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-14936 (ML-96-144)	1996	CHO/HGPRT gene mutation assay of MON 65500 TC GLP/GEP (Y/N): Y Published (Y/N): N

HL-95-159	1995	MON65500 *In vitro* Cytogenetic study with Human Lymphocytes for the Detection of Induced Clastogenic effects. TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-14933	1996	Mouse bone marrow micronucleus assay of MON 65500 TC (ML-96-143) GLP/GEP (Y/N): Y Published (Y/N): N
SR-2001-127	2002	Evaluation of MON 65500 in the unscheduled DNA synthesis (UDS) assay using Sprague-Dawley rats TC GLP/GEP (Y/N) : Y Published (Y/N) : N
MSL-15585 (ML-96-126)	1998	Oncogenicity study of MON 65500 administered in feed to CD-1 mice for 18 months TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-15713 (ML-96-35)	1998	Combined chronic toxicity /oncogenicity study of MON 65500 administered in feed to CD rats for 24 months TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL-15554 (ML-96-159)	1998	Two-generation reproduction study of MON 65500 administered in the diet to CD rats TC GLP/GEP (Y/N): Y Published (Y/N): N
WI-95-240	1996	A developmental toxicity study of MON 65500 in rats WIL Research Laboratories TC GLP/GEP (Y/N): Y Published (Y/N): N
WI-95-239	1997	A dose range-finding developmental toxicity study of MON 65500 in rabbits TC GLP/GEP (Y/N): Y Published (Y/N): N
WI-96-105	1997	A developmental toxicity study of MON 65500 in rabbits TC GLP/GEP (Y/N): Y Published (Y/N): N
WL-94-351	1995	MON 65500: An acute oral toxicity study with the Japanese Quail TC GLP/GEP (Y/N): Y Published (Y/N): N
WL-95-277	1996	MON 65500: A dietary LC50 study with the Northern Bobwhite TC GLP/GEP (Y/N): Y Published (Y/N): N
WL-95-274	1996	MON 65500: A dietary LC50 study with the mallard TC GLP/GEP (Y/N): Y Published (Y/N): N

WL-97-183	1998	MON 65500: A reproduction study with the Northern Bobwhite TC GLP/GEP (Y/N): Y Published (Y/N): N
WL-95-276	1996	MON 65500: A 96-hour static acute toxicity test with the rainbow trout (*Oncorhynchus mykiss*) TC GLP/GEP (Y/N): Y Published (Y/N): N
WL-95-280	1996	MON 65500: A 96-hour static acute toxicity test with the Bluegill (*Lepomis macrochirus*) TC GLP/GEP (Y/N): Y Published (Y/N): N
WL-95-275	1996	MON 65500: A 48-hour static acute toxicity test with the cladoceran (*Daphnia magna*) TC GLP/GEP (Y/N): Y Published (Y/N): N
WL-2000-93	2000	MON 65500: A semi-static life-cycle toxicity test with the cladoceran (*Daphnia magna*). TC GLP/GEP (Y/N): Y Published (Y/N): N
WL-97-167	1998	MON 65500: A five-day toxicity test with the freshwater algae (*Selenastrum capricornutum*) TC GLP/GEP (Y/N): Y Published (Y/N): N
WL-95-196	1996	MON 65500: An acute toxicity study with the earthworm in an artificial soil substrate TC GLP/GEP (Y/N): Y Published (Y/N): N
MSL0023947	2012	Physico-chemical properties and storage stability of MON 65557; analysis of fresh test item, after 18 weeks at 30°C and after 1 and 2 years at 20°C. CRA-W Report No.: 22085 Monsanto Company Report No.: GLP/GEP (Y/N): Y Published (Y/N): N
CIPAC/5004/m	2015	The analytical laboratory method for the determination of the identity and assay of Silthiofam (code 635). Monsanto Company GLP/GEP (Y/N): N Published (Y/N): Y
CIPAC/5005/R	2015	The full scale collaborative study on the determination of Silthiofam (code 635) in Silthiofam TC and FS by HPLC. Monsanto Company GLP/GEP (Y/N): N Published (Y/N): Y