Food and Agriculture Organization
of the United Nations

FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

CLETHODIM

(5*RS*)-2-{(1*EZ*)-1-[(2*E*)-3-chloroallyloxyimino]propyl}-5-[(2*RS*)-2-(ethylthio)propyl]-3-hydroxycyclohex-2-en-1-one

2017

Note. Evaluation report ONLY. The FAO specifications will be published subject to adoption of the collaboratively tested analytical methods for determination of the clethodim content in TC and EC

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 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/pest-and-pesticide-management/expert-bodies-conventions/faowho-joint-meeting-on-pesticide-specifications-jmps/pesticide-specifications/pesticide-specifications-list/en/) OR IN HARDCOPY FROM THE PLANT PROTECTION INFORMATION OFFICER.

CLETHODIM

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Recommendations

The Meeting recommended the following:

(i) the specifications proposed by Arysta LifeScience for clethodim TC and EC as amended should be adopted by FAO subject to the collaborative testing and publication of the analytical method for clethodim in the TC and EC and clarification of some open points

(ii) the evaluation report should be published

Appraisal

The Meeting considered data and supporting information submitted in 2014 by Arysta LifeScience for the development of new FAO specifications for clethodim TC and EC. A first check for completeness revealed, however, substantial gaps in the data package submitted, in relation to the requirements of the Manual on development and use of FAO and WHO specifications for pesticides (November 2010, 2nd revision of the 1st edition). The gaps include, *i.a.* the lack of collaboratively tested and published analytical methods for determination of clethodim in TC and EC formulation.

Clethodim belongs to the chemical family of the cyclohexanediones and is a selective herbicide for the post-emergent control of annual and perennial grass weeds in a variety of agricultural crops. Clethodim interacts with the plant acetyl-CoA-carboxylase, the enzyme complex responsible for the biosynthesis of lipids. Since the cell membranes are composed of phospholipids, clethodim stops new cell growth leading to the gradual death of the plant.

Clethodim has been evaluated by the FAO/WHO JMPR in 1994 for toxicology. An IPCS hazard classification of clethodim is not available.

In the 1994 JMPR toxicological evaluation, the main conclusions were (quote)

"Clethodim had slight to moderate acute oral toxicity in the rat and mouse. WHO has not classified clethodim with regard to toxic hazard.

The primary effect of treatment with clethodim after short- and long-term dietary exposure in the mouse, rat and dog was on the liver. Hepatic effects were manifest as increased liver weights and centrilobular hypertrophy. A study in rats administered clethodim at 250 mg/kg bw per day did not provide evidence for liver cytochrome P450 induction.

Clethodim was not carcinogenic when fed to mice or rats at dietary levels of up to 2500 ppm. There were no adverse effects on the rabbit fetus and no evidence of teratogenic potential at doses up to 300 mg/kg bw per day." (unquote)

A full data package for characterization of the hazard of clethodim produced by Arysta is available.

The Meeting noted, that amendments had been made to the ISO definition of the active substance (ISO 1750, July 2010) to better match the chemical definition with the actual composition of the technical material manufactured (refer to the Identity section below): the allyl group has *E* configuration but is a mixture of *E* and *Z* isomers at the ketoxim moiety, and

the carbon at position 5 is not considered as a chiral centre because of the rapid keto-enol tautomerism.

Clethodim is a clear pale yellow liquid with a melting point of -80°C (freezing temperature). The low vapour pressure indicates that clethodim is not volatile. The substance has acidic properties (pK_a 4.47) due to the enol-moiety. The water solubility is pH dependent, with increasing solubility with higher pH values. It is readily soluble in the organic solvents like xylene, dichloromethane and methanol (>200 g/L) and highly soluble in solvents like acetone, hexane, ethyl acetate (>900 g/L). The octanol/water partition coefficient (log P_{OW} = 4.2 at pH 4) is somewhat pH-dependent, with a value of 4.2 for the non-dissociated form.

Clethodim is hydrolysed in aqueous media at pH 5 with a first-order DT_{50} of 41 days, but the compound is hydrolytically stable at pH 7 and 9 (DT_{50} 398 and 307 days respectively). During exposure to natural sunlight at Richmond, California, USA (37.6°N, 122.2°W), clethodim was rapidly degraded at pH 5, 7 and 9, with effective photolysis half-lives of approx. 1.5, 4.1 and 6.0 days, respectively. The Meeting noted inconsistencies and shortcomings in some of the studies to determine the physical-chemical properties of clethodim, such as the use of the flask method of OECD 105 for determination of the water solubility of clethodim that is far above the recommended range for that method or the use of low purity clethodim (93 %) for determination of the vapour pressure. Nevertheless, the Meeting concluded that these shortcomings are not that significant that they would prevent the evaluation of the compound for development of FAO specifications for a TC and an EC.

The company produces clethodim technical material in two different plants, using the same synthetic route and based on nominally the same purity/impurity profile.

The confidential data on the manufacturing process from one of the sources of clethodim submitted by the proposer were in accordance with the information supplied to the Netherlands (NL) as EU Rapporteur Member State (RMS) or the Addendum to the Draft Assessment Report prepared in the context of the inclusion of clethodim in Annex I of Council Directive 91/414/EEC [DAR, March 2010]. Therefore, the impurities and QC limits for clethodim TC agree between the information submitted to FAO and that assessed by the NL for the first source.

The confidential data on the manufacturing process from the second source submitted by the proposer have not been assessed by the authorities in the Netherlands.

It should be noted however that evaluation of the batches submitted to the FAO from the second source confirms they are equivalent to the batches supplied to the NL for the first source, which was used as the reference source.

The Meeting was provided with commercially confidential information on the manufacturing process and 5-batch analysis data on all impurities present below or above 1 g/kg and their manufacturing limits in the TC. Mass balances ranged from 97.24 to 101.67 % (source 1) and from 98.63 to 99.16% (source 2) in the 5-batch data. The maximum limits for the impurities were supported by the batch data[2].

The analytical method for the determination of clethodim in the TC is a reverse phase HPLC with UV detection. The identity of clethodim was confirmed by retention time matching using

[2] The Meeting noted, that toluene was identified as relevant impurity in the EU inclusion directive. The issue of toluene was discussed and the Meeting concluded, that based on the hazard profile expressed as ADI of clethodim according to the 2010 JMPR evaluation, the WHO air quality guideline of toluene hazards and an exposure model this compound is not considered as relevant.

the reverse phase HPLC method and MS spectra. Impurities were determined by HPLC-UV or GC-FID analysis.

During the course of the evaluation, the company were requested and duly provided production dates for the batches analysed in the 5-batch analysis report. Given the use of a certain lower alcohol as a solvent in the synthesis of clethodim, the company were also asked to confirm whether that compound was screened for its possible presence and if required to provide confirmation of whether it is expected to be present in the final batches. To this end, the company confirmed that screening work undertaken had reported no evidence of that solvent being present in significant quantities (>1 g/kg).

It is thus highly unlikely that it would ever be present at 1% level, which is the GHS hazard classification cut-off limit for mixture components with acute toxicity and specific target organ toxicity. A statement was also submitted based on the purification procedures utilised in the synthesis of clethodim, which also provide confidence that that solvent is efficiently removed during the manufacturing process.

The company was also requested to provide structures of several impurities that were identified from the manufacturing route, which were not present in the original submission, which they duly did. Several study reports were also submitted that upon evaluation confirmed that methods of analysis for the active ingredient in the TC and the impurities are acceptably validated. Last but not least, Arysta was requested to provide some explanations regarding comments made by the RMS for Clethodim in the EU (NL) on the hydrolysis rate of clethodim, which was also promptly submitted.

The draft specification for the EC contained the limits for the relevant clauses that were essentially borrowed from the general limits in the Section 4 of the Manual and did not represent the EC quality produced by Arysta. The company was therefore requested to propose a specification based on data for a representative formulation.

In conclusion, a data package has been received i.e. physical-chem properties data, confidential data and a full toxicity package for clethodim, but due to a lack of collaboratively validated methods for determination of the content of clethodim in TC and EC and certain data gaps to support the TC and EC specifications, these specifications cannot yet be published. Nevertheless, the Meeting recommended that the evaluation report should be published.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 508/2017

USES

Clethodim is a herbicide for the post-emergent control of annual and perennial grass weeds in a variety of broadleaved agricultural crops such as alfalfa, beans and potatoes.

Clethodim belongs to the chemical family of the cyclohexanediones. Clethodim competitively binds to the acetyl-CoA-carboxylase, the enzyme responsible for the biosynthesis of lipids. Competitive binding is stronger in grasses than broadleaved crops. Depletion of fatty acids in sensitive plants leads to cessation of growth and eventual death.

IDENTITY OF THE ACTIVE INGREDIENT

ISO common name Clethodim (ISO 1750, published)

Chemical name(s)

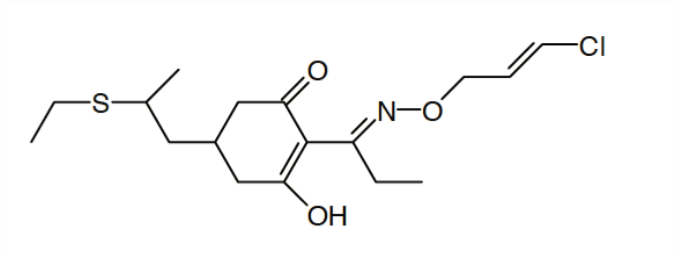
IUPAC (5*RS*)-2-{(1*EZ*)-1-[(2*E*)-3-chloroallyloxyimino]propyl}-5-[(2*RS*)-2-(ethylthio)propyl]-3-hydroxycyclohex-2-en-1-one

CA 2-[1-[[[(*2E*)-3-chloro-2-propen-1-yl]oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one

Synonym

RE 45601 -

Structural formula



Molecular formula

$C_{17}H_{26}ClNO_3S$

Molecular mass

359.92

CAS Registry number

99129-21-2

CIPAC number

508

Identity tests

HPLC-UV, UV-Vis, IR, MS and NMR

Table 1: Physical-chemical properties of pure clethodim

Parameter	Value(s) and conditions	Purity % Note[3]	Method reference (and technique if the reference gives more than one)	Study number
Vapour pressure	2.1 x 10^{-6} Pa at 20°C 4.9 x 10^{-6} Pa at 25°C	93	OECD 104 (vapour pressure balance method)	[201] 20050645.01
Vapour pressure (estimated)	1.35 x 10^{-8} Pa at 25°C	Not applicable	Modified Grain estimation method within EPI Suite	[202] PML 2003-C148
Melting point.	-80 °C (freezing temperature)	98.3	EEC A1 (DSC Method)	[202] PML 2003-C148
Temperature of decomposition	133°C Test was performed under normal atmosphere conditions. Clethodim decomposes from approximately 406±0.5 K (133±0.5°C) at 100.52 kPa	98.5	EEC A2,	[203] 2699/0001
Solubility in water	0.0530 g/l at 20°C at pH 4 5.45 g/l at 20°C at pH 7 58.9 g/l at 20°C at pH 9 30 g/l at 20°C at pH 10	98.3	EEC A6 and OECD 105 (flask method).	[204] 03J0007c and [205] A46034
Octanol/water partition coefficient	log P_{OW} = 4.14 at pH 7 log P_{OW} = 4.22 pH 9 log P_{OW} = 4.2 (4.176) for the non-dissociated form of clethodim. Measurements at different pH values are used to calculate the Log P_{ow} from the non-dissociated clethodim at pH 5, 7 and 9. This is acceptable	99.0	EPA 63.11 (Equivalent to EEC Method A.8).	[206] 8828545 (Beltran 2005 position paper)

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

Hydrolysis characteristics	Propyl label Half-life = 28 days at 25 °C at pH 5 Half-life = 300 days at 25 °C at pH 7 Half-life = 310 days at 25°C at pH 9 Allyl label Half-life = 54 days at 25 °C at pH 5 Half-life = 499 days at 25 °C at pH 7 Propyl-label: the major hydrolysis product oxazole RE-47365 (maximum levels recorded after 32 days: 50.5, 6.8 and 4.9% at pH 5, 7 and 9, respectively). Allyl-label, the major hydrolysis product was chloroallyl alcohol (RE-46261; maximum levels recorded after 30 days were 30.7 and 4.3% at pH 5 and 7, respectively).	a) [4,6-ring-^{14}C] clethodim Specific activity: 56 mCi/mM, radiopurity: 98% b) [Allyl-2-^{14}C] clethodim Specific activity: 40.3 mCi/mM, radio-purity: 98%	EPA 161.2 (Equivalent to EEC Method C.7 or OECD 111)	[207] MEF 0013/8703 899
Photolysis characteristics	Clethodim, at pH 5, 7 and 9, respectively: degradation half-lives in irradiated solutions 1.5, 6.4 and 9.3 days; corresponding effective photolysis half-lives of 1.7, 6.8 and 9.6 days. Enhanced rate of photolysis in sensitized irradiated solutions (1% acetone), with effective photolysis half-lives of 0.94, 1.2 and 0.52 days. Sunlight at Richmond, California, USA (37.6°N, 122.2°W), 4.8-31.3 kW/cm^2 mean daily sunlight intensity. Effective photolysis half-lives were calculated as ln(2)/$k_{photolysis}$, where $k_{photolysis} = k_{irradiated} - k_{dark}$	1) [4,6-ring-14C] clethodim Specific activity: 56 mCi/mM, radio-purity: 98%	EPA 161.2	[208] MEF 0024

Photolysis characteristics	Clethodim, at pH 5, 7 and 9, respectively: degradation half-lives in irradiated solutions 1.4, 4.1 and 5.4 days; corresponding effective photolysis half-lives of 1.5, 4.1 and 6.0 days. Enhanced rate of photolysis in sensitized irradiated solutions (1% acetone), with effective photolysis half-lives of 0.20, 0.61 and 0.33 days. Degradation products >5% at pH 5, 7 and 9, respectively, in non-sensitized irradiated samples: CO_2 (max. 2.8, 24.8 and 5.6%). Clethodim sulfoxide (max. 10.8, 14.2 and 7.4%). Chloroallyl alcohol (max. 12.2, 31.3 and 24.5%). 3-Chloropropenal (max. 31.3, 21.8~~33.5~~ and 10.5~~15.7~~%). Chloroallyl alcohol and 3-chloropropenal appeared to be stable under the test conditions. Conditions: sterile buffers, 25±1°C, exposure to natural sunlight at Richmond, California, USA (37.6°N, 122.2°W), 8.7-31.3 kW/cm^2 mean daily sunlight intensity. Effective photolysis half-lives were calculated as $\ln(2)/k_{photolysis}$, where $k_{photolysis} = k_{irradiated} - k_{dark}$	2) [Allyl-2-14C] clethodim Specific activity: 40.3 mCi/mM, radiopurity:98%	EPA 161.2	[209] MEF 0025
Dissociation characteristics	pKa = 4.47 at 20°C	98.5	OECD 112 (titration method).	[206] 8828545
Solubility in organic solvents	247 g/l xylene at 25 °C 246 g/l 1,2 dichloroethane at 25 °C 244 g/l methanol at 25 °C 950 g/l acetone at 25 °C 931 g/l hexane at 25 °C 934 g/l ethyl acetate at 25 °C 907 g/l dimethylformamide at 25 °C	93.0% (for materials used in study 03J0006c). Purity of material used in 8828545 is unclear from the study report.	EPA 63.8 and OECD 105 (Shake Flask Method)	[206] 8828545 and [210] 03J0006c

Table 2. Chemical composition and properties of clethodim technical material (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 97.24 to 101.67 % (source 1) and from 98.63 to 99,16% (source 2).
Declared minimum clethodim content	930 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 (performed on pure, not technical grade material).	-80 °C decomposes from approximately 133°C	98.3-98.5%	EEC As and EEC A2	[202] PML 2003-C148
Solubility in organic solvents	247 g/l xylene at 25 °C 246 g/l 1,2 dichloroethane at 25 °C 244 g/l methanol at 25 °C 950 g/l acetone at 25 °C 931 g/l hexane at 25 °C 934 g/l ethyl acetate at 25 °C 907 g/l dimethylformamide at 25 °C	93.0% (for materials used in study 03J0006c). Purity of material used in 8828545 is unclear from the study report.	EPA 63.8 and OECD 105 (Shake Flask Method)	[206] 8828545 and [210] 03J0006c

FORMULATIONS AND CO-FORMULATED ACTIVE INGREDIENTS

The main formulation types available are emulsifiable concentrates (EC). These formulations are registered and sold in many countries throughout the world. Clethodim may be co-formulated with other broad-leaf and some grass herbicides and various bio-stimulants.

METHODS OF ANALYSIS AND TESTING

The analytical method for the determination of clethodim in the TC is a reverse phase HPLC with UV detection. The identity of clethodim was confirmed by retention time matching using the reverse phase HPLC method and MS spectra. Impurities were determined by HPLC-UV or GC-FID analysis.

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE CONTENT OF ACTIVE INGREDIENT

The active ingredient content is expressed as clethodim.

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 clethodim having impurity profiles similar to those referred to in the table above.

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

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

Species	Test	Purity % Note[4]	Guideline, duration, doses and conditions	Result	Study number
Rat, female	oral	83.3	Guideline: EPA 81.1 and OECD 401 Duration: 14 days observation after dosing Dose: single dose of 0.8 to 2.5 g/kg bw by oral gavage	LD_{50} = 1630 mg/kg bw (males) LD_{50} = 1360 mg/kg bw (females)	[301] S-2498
Rabbit, male and female	dermal	83.3	Guideline: EPA 81.2 and OECD 402 Duration: 14 days observation after dosing Dose: single dose of 5.0 or 2.0 g/kg bw applied to clipped intact skin site	LD_{50} = >4167 mg/kg bw both sexes	[302] CEHC 2510
Rat, male and female	inhalation	83.3	Guideline: EPA 81.3 and OECD 403 Duration: 4 hours exposure followed by 14-day observation period Dose: single whole body exposure 3.9 mg/L	LC_{50} = >3.25 mg/L	[303] CEHC 2513
Rabbit, male	skin irritation	93.4	Guideline: EEC B4 and OECD 404 Duration: 4 hours application followed by observation for up to 9 days Dose: single 0.5 mL undiluted dose applied to clipped skin site	Irritating (classified R38 in EU)	[304] 29389 TAL

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

Species	Test	Purity % Note[4]	Guideline, duration, doses and conditions	Result	Study number
Rabbit, male	eye irritation	83.3	Guideline: EPA 81.4 Duration: 3-day observation after application Dose: single 0.1 mL undiluted dose applied to one eye of each rabbit	Non-irritant	[305] CEHC 2511
Guinea pig, female	skin sensitisation (maximisation M&K test)	92.4	Guideline: EEC B6 Duration: Intradermal induction, followed one week late by topical induction (48 hours) and then challenge 2 weeks later Dose: 50% dilution for intradermal induction, 75% for topical induction and 50% for challenge	Sensitizer (classified R43 in EU)	[306] A42210

Table 4: Toxicology profile of the Clethodim technical material based on repeated administration (subacute to chronic)

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
Mouse	oral	83.3	Guideline: EPA 82.1 Duration: 4 weeks Doses: 0, 100, 250, 625, 1500, 4000 ppm mixed in feed for 4 weeks	NOAEL = 625 ppm (74.4 mg/kg bw/d)[6]	[307] 2107-140
Rat	oral	83.4	Guideline: EPA 83.1 Duration: 5 weeks Doses: 0, 200, 1000, 4000, 8000 ppm mixed in feed for 5 weeks	NOAEL = 200 ppm (12.5 mg/kg bw/d)	[308] SOCAL 2457
Rat	oral	84.0	Guideline: EPA 82.1 Duration: 13 weeks Doses: 0, 50, 500, 2500, 5000 ppm mixed in feed for 13 weeks	NOAEL = 25 mg/kg bw/d	[309] SOCAL 2501
Dog	oral	83.3	Guideline: EPA 82.1 Duration: 90 days Doses: 0, 1, 25, 75, 125 mg/kg bw/day in gelatine capsule	NOAEL = 21 mg/kg bw/d	[310] 85-2999

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

[6] Based on standard conversion factor in the mouse of 7 ppm = 1 mg/kg bw/d

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
Dog	oral	83.3	Guideline: EPA 82.1 Duration: 1 year Doses: 0, 1, 75, 200/300[7] mg/kg bw/day in gelatine capsule	NOAEL = 0.83 mg/kg bw/d (Overall NOAEL in 90-day and 1 year studies = 25 mg/kg bw/d)	[311] 2107-153
Rat	dermal	83.3	Guideline: EPA 82.4 Duration: 4 weeks Doses: 0, 10, 1000 mg/kg bw/d 5 days per week	NOAEL = 83 mg/kg bw/d	[312] CEHC 2552
Rat	oral	83.3	Guideline: EPA 83.5 Duration: 2 years (1 year interim kill) Doses: 0, 5, 20, 500, 2500 ppm mixed in feed for 1-2 years	Not oncogenic Chronic NOAEL = 500 ppm 16 mg/kg bw/d	[313] SOCAL 2500
Mouse	oral	83.3	Guideline: EPA 83.5 Duration: 18 months Doses: 0, 20, 200, 1000 ppm mixed in feed for 18 months	Not oncogenic Chronic NOAEL = 200 ppm (30 mg/kg bw/d[13])	[314] 2107-145

[7] Increased from 200 to 300 mg/kg bw/d from week 8

Species	Test	Purity % Note[5]	Guideline, duration, doses and conditions	Result	Study number
Rat	oral	83.3	Guideline: EPA 83.4 Duration: Continuously through two generations (pre-mating periods 63-77 days) Doses: 0, 5, 20, 500, 2500 ppm mixed in feed (pre-mating, mating, gestation and lactation)	Reproductive NOAEL = ≥ 2500 ppm (≥ 133.7 mg/kg bw/d) Offspring NOAEL = ≥ 2500 ppm (≥ 160 mg/kg bw/d) Parental NOAEL = 500 ppm (26.7 mg/kg bw/d)	[315] S-2778
Rat	oral	83.3	Guideline: EPA 83.3 Duration: dosing from gestation days 6-15 Doses: 0, 10, 100, 350, 700 mg/kg bw/d by oral gavage	Not teratogenic. Maternal and developmental NOAEL = 83.3 mg/kg bw/d	[316] 86-3042
Rabbit	oral	83.3	Guideline: EPA 83.3 Duration: Dosing from gestation days 7-19 Doses: 0, 25, 100, 300 mg/kg bw/d by oral gavage	Not teratogenic. Maternal NOAEL = 25 mg/kg bw/d Developmental NOAEL = 300 mg/kg bw/d	[317] 303-007

Table 5: Mutagenicity profile of the clethodim technical material based on *in vitro* and *in vivo* tests

Species	Test	Purity % Note[8]	Guideline, duration, doses and conditions	Result	Study number
Salmonella typhimurium TA98, TA100, TA1535 and TA1537	*In vitro* bacterial mutagenicity	83.3	Guideline: EPA 84.2 and OECD 471 Doses: 0.1-10 mg/plate	Negative ± metabolic activation (S9)	[318] SOCAL 2505
Salmonella typhimurium TA98, TA100, TA1535 and TA1537, and *Escherichia coli* WP2 uvrA	*In vitro* bacterial mutagenicity	83.3	Guideline: EPA 84.2 and OECD 471, 472 Doses: 0.1-10 mg/plate	Negative ± metabolic activation (S9)	[319] SOCAL 2555
CHO (Chinese hamster ovary cells)	*In vitro* mammalian cell mutagenicity (HGPRT)	92.7	Guideline: OECD 476 Doses: 0-500 µg/mL	Negative ± metabolic activation (S9)	[320] 19395
CHO (Chinese hamster ovary cells)	*In vitro* chromosome aberration	83.3	Guideline: EPA 84.2 and OECD 473 Doses: 0.027-1.20 µg/mL	Positive minus metabolic activation (S9) Negative + metabolic activation (S9)	[321] T4529.337
CHO (Chinese hamster ovary cells)	*In vitro* chromosome aberration	96.1	Guideline: EPA 84.2 Doses: 0.03-1.20 µg/mL	Negative ± metabolic activation (S9)	[322] T4927.337

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

Species	Test	Purity % Note[8]	Guideline, duration, doses and conditions	Result	Study number
Rat	*In vivo* bone marrow chromosome aberration	83.3	Guideline: EPA 84.2 Doses: single dose of 150, 500 or 1500 mg/kg bw by oral gavage	Negative	[323] T5072.105
Mouse	*In vivo/in vitro* unscheduled DNA synthesis (UDS)	83.3	Guideline: EPA 84.4 and OECD 482 Doses: single dose of 100, 1000 or 5000 mg/kg bw by oral gavage	Negative	[324] S-2762

Table 6: Ecotoxicology profile of clethodim technical material

Species	Test	Purity % Note[9]	Guideline, duration, doses and conditions	Result Clethodim	Study number
Bobwhite quail	acute oral toxicity	82.0	Guideline: EPA 71-1 Duration: 14 day Dose: single dose 500-2000 mg/kg bw by gavage tube	LD_{50} = >1640 mg/kg bw	[401] 162-165
Bobwhite quail	Dietary toxicity	83.3	Guideline: EPA 71-2 Duration: 5 day feeding Dose: nominal dose 600, 1290, 2750 and 6000 ppm. No mortality at highest dose tested	LD_{50} > 6000 ppm	[402] 162-166
Mallard duck	Dietary toxicity	83.0	Guideline: EPA 71-1 Duration: 5 day in feed followed by 3 days untreated feed Dose: 600-6000 mg/kg feed	NOEC = 1805 mg/kg feed, based on a reduction of body weight gain and feed consumption at 4938 mg/kg. LC 50 >4938 mg/kg feed (>851 mg/kg bw/day)	[403] 162-167
Bobwhite quail	Subchronic toxicity and reproduction	83.3	Guideline: EPT 70-4 Duration: 22 weeks in feed Dose: 0-1000 mg/kg in corn oil	NOEL = 17 mg/kg bw/day	[403]162-176 and 162-183
Salmo gairdneri (rainbow trout - Oncorhynchis mykiss)	Acute toxicity	83.3	Guideline: EPA 72-1 Duration 96 hr acute toxicity study Dose: nominal concentrations- 10, 18, 32, 56 and 100 mg a.s/L.	Mortality 96 hr LC_{50} = 25 mg a.s./L based on mean measured concentration	[404] S-2838

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

Species	Test	Purity % Note[9]	Guideline, duration, doses and conditions	Result Clethodim	Study number
Bluegill sunfish	Acute toxicity	83.3	Guideline: EPA 72-1 Duration 96 hour acute toxicity study Dose: nominal concentrations- 10, 18,32,56 and 100 mg/L	Mortality 96 hr LC_{50} = > 100 mg a.s./L based on nominal concentration - but mean measured concentration at the highest concentration was 33 mg a.s/L. Based on mean measured conc LC_{50} >33 mg a.s/L	[405] S-2839
Oncorhynchis mykiss	Chronic toxicity	93.0	Guideline: OECD 204 Conditions: chronic toxicity study under flow through conditions, Dose: mean measured concentrations were 0.41, 0.79, 1.9, 3.9, 9.0, 17 and 40 mg a.s/L.	NOEC = 3.9 mg a.s./L based on mean measured concentrations	[406] 97223/01-ACOm
Daphnia magna	Acute toxicity	83.3	Guideline: EPA 72-2, Duration: 48 hour Conditions: test conditions: 200 ml aged well water; 10 animals per concentration in duplo. Dose: nominal concentrations: 6.0, 12, 25, 50 and 100 mg/L. Water: pH 7.9-8.5, DO 8.0-8.8 mg/L, temp. 20°C, hardness (as $CaCO_3$) 240-280 mg/L. Light period 16 h, 540-750 lx. Concentrations 6.0-100 mg/L	Immobility EC_{50} > 100 mg a.s./L based on nominal concentrations	[407] S-2835
Daphnia magna	Chronic toxicity	92.4	Guideline: OECD No 202 Duration: 21 day exposure. Dose: six test concentrations between 0.87 - 150 mg/L.	21 day EC_{50} 90 mg a.s/L based on nominal concentrations	[408] 95027/01-ARDm

Species	Test	Purity % Note[9]	Guideline, duration, doses and conditions	Result Clethodim	Study number
			Conditions: semi static study with change of medium 3 times a week.		
Selenastrum capricornutum	Algal growth inhibition	92.4	Guideline: OECD No 201. Dose: Five test concentrations ranged from 34.6, 51.9, 77.8, 116.7 and 175 mg/L	E_bC_{50} 32.5 mg a.s/L based on measured concentration	[409] 95027/01- AASs
Lemna gibba	Acute toxicity	82.4	Guideline: EPA guideline 123-2. Duration: 14 day Conditions: static toxicity study Dose: mean measured concentrations tested: 0.022, 0.053, 0.37, 0.79, 1.7, 4.0 and 8.4 mg/L	Fronds Number EC_{50} = 1.34 mg a.s./L based on measured concentration	[410] ABC: 38621
Lemna gibba	Acute toxicity	91.1	Guideline: EPA guideline 123-2 Duration: 14 day static toxicity study Dose: mean measured concentrations tested: 0.05, 0.11, 0.26, 1.18, 2.05, 4.09 and 4.88 mg/L	Fronds Number EC_{50} = 4.09 mg a.s./L based on measured concentration	[411] S 3308
Apis mellifera (honey bee)	Acute oral toxicity	87.9	Guideline: EPA 141-1.	LD_{50} = >100 µg a.s./bee	[412] 439
Apis mellifera (honey bee)	Acute contact toxicity	87.9	Guideline: EPA 141-1	LD_{50} = >100 µg a.s./bee	[412] 439

ANNEX 2

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