FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

HALOXYFOP-P-METHYL

methyl(*R*)-2-[4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)phenoxy]propionate

FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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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.

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[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.

Since 1999 the development of FAO specifications follows the **New Procedure**, described in the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products" (FAO Plant Production and Protection Page No. 149). 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 JMPS, 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 plant protection product in accordance with chapter 4, 5 and 6 of the 5th edition of the "Manual on the development and use of FAO specifications for plant protection products".

PART TWO: **The Evaluation Report(s)** of the plant protection product reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are to be provided by the manufacturer(s) according to the requirements of Appendix A, Annex 1 or 2 of the "Manual on the development and use of FAO specifications for plant protection products" 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 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. Dates of publication of the earlier versions, if any, are identified in a footnote. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

*NOTE: publications are available on the internet at http://www.fao.org/agriculture/crops/core-themes/theme/pests/pm/jmps/en/ .

PART ONE

SPECIFICATIONS

HALOXYFOP-P-METHYL

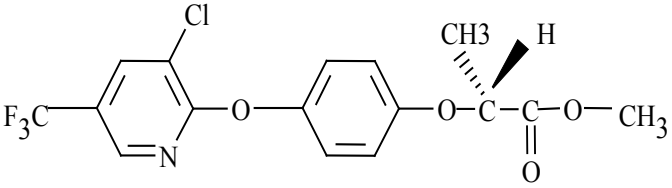
INFORMATION

ISO common name (ISO 1750 published)
Haloxyfop-P

Chemical name(s)
IUPAC
Methyl(*R*)-2-[4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)phenoxy]propionate
CA
methyl (2*R*)-2-[4-[[3-chloro-5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]propanoate

Synonyms
Haloxyfop-P methyl ester, DE-535

Structural formula



Molecular formula
$C_{16}H_{13}ClF_3NO_4$

Molecular mass
375.7

CAS Registry Number
72619-32-0

CIPAC Number
526.201

Identity tests
Retention times of *R*- and *S*-haloxyfop-methyl in enantioselective HPLC, UV- and IR-spectra

HALOXYFOP-P-METHYL TECHNICAL MATERIAL

FAO Specification 526.201/TC (May 2012*)

*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 (*526.201/2011*). 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 TC produced by other manufacturers. The evaluation report (*526.201/2011*), as PART TWO, forms an integral part of this publication*

1 Description

The material shall consist of haloxyfop-P-methyl together with related manufacturing impurities, and shall be at ambient temperatures a light amber, viscous liquid free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (526.201/TC/M/2, 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 **Haloxyfop-P methyl content** (526.201/TC/M/3, Note 1)

The haloxyfop-P-methyl content shall be declared (not less than 940 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

Note 1: The normal phase enantioselective HPLC method (CIPAC/4617) for the determination of *R*- and *S*-haloxyfop-methyl, respectively, in TC and EC was adopted by CIPAC in 2008 but is not yet published in a Handbook. Prior to its publication in Handbook N, copies of the methods may be obtained through http://www.cipac.org/cipacpub.htm

* 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/core-themes/theme/pests/pm/jmps/ps/en/

HALOXYFOP-P-METHYL EMULSIFIABLE CONCENTRATE

FAO Specification 526.201 / EC (May 2012*)

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 (526.201/2011). It should be applicable to relevant products of 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 (526.201/2011) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist of haloxyfop-P-methyl, complying with the requirements of FAO/WHO specification 526.201/TC (May 2012), in the form of an emulsifiable concentrate, dissolved in suitable solvents, together with any other necessary formulants. It shall be in the form of a stable homogeneous liquid, free from visible suspended matter and sediment, to be applied as an emulsion after dilution in water.

2 Active ingredient

2.1 Identity tests (526/EC/(M)/2 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 Haloxyfop-P-methyl content (526/EC/(M)/3 Note 1)

The haloxyfop-P-methyl content shall be declared (g/l at 20 ± 2ºC, Note 2) and, when determined, the average content measured shall not differ from that declared by more than the following tolerances:

Declared content in g/kg or g/l	Tolerance
Above 25 up to 100	± 10% of the declared content
Above 100 up to 250	± 6% of the declared content
Above 250 up to 500	± 5% of the declared content
Above 500	± 25 g/kg or g/L of the declared content

* 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/core-themes/theme/pests/pm/jmps/ps/en/

4 **Physical properties** (Note 3)

4.1 **Emulsion stability and re-emulsification** (MT 36.3, CIPAC Handbook K, p 137, 2003)

The formulation, when diluted at 30 ± 2°C with CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of stability, MT 36.3
0 h	Initial emulsification complete
0.5 h	"Cream", maximum: 2 ml
2 h	"Cream", maximum: 2 ml
	"Cream", maximum: 2 ml
24 h	"Free oil", maximum: Trace
24.5 h	Re-emulsification complete
Note: tests at 24 h are required only where results at 2 h are in doubt	"Cream", maximum: 2 ml "Free oil", maximum: Trace

4.2 **Persistent foam** (MT 47.2, CIPAC Handbook F, p 152, 1995) (Note 6)

Maximum: 40 ml after 1 min.

5 **Storage stability**

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

After storage at 0 ± 2°C for 7 days, the volume of solid and/or liquid which separates shall not be more than 0.3 ml.

5.2 **Stability at elevated temperature** (MT 46.3, CIPAC Handbook J, p 128, 2000)

After storage at 54 ± 2°C for 14 days (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 clause for:

- emulsion stability and re-emulsification (4.1)

Note 1: The normal phase enantioselective HPLC method (CIPAC/4617) for the determination of *R*- and *S*-haloxyfop-methyl, respectively, in TC and EC was adopted by CIPAC in 2008 but is not yet published in a Handbook. Prior to its publication in Handbook N, copies of the methods may be obtained through http://www.cipac.org/cipacpub.htm

Note 2 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 3 Flash point may be an important safety characteristic in some cases but the risks are dependent upon both climate and the specific use, so FAO/WHO specifications cannot provide global specifications for this characteristic. In all cases strict adherence to national requirements is essential.

Note 4 The mass of sample to be used in the test should correspond to the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 5 Unless other temperatures and/or times are specified. Refer to Section 4.6.2 of this Manual for alternative storage conditions.

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

PART TWO

EVALUATION REPORTS

HALOXYFOP-P-METHYL

2011 FAO/WHO evaluation report based on submission of information from

HALOXYFOP-P-METHYL

FAO/WHO EVALUATION REPORT 526.201/2011

Recommendations

The meeting recommended that:

(i) the specifications for haloxyfop-P-methyl TC and EC, proposed by Dow AgroSciences, as amended, should be adopted by FAO.

Appraisal

The Meeting considered data submitted in 2007 by Dow AgroSciences, for the development of new FAO specifications for haloxyfop-P-methyl TC and EC. The data and proposed specifications submitted were in accordance with the requirements of the revised 1st edition of the Manual on development and use of FAO and WHO specifications for pesticides (FAO/WHO Manual, 2006) and supported the draft specifications.

The haloxyfop-molecule carries an asymmetrically substituted carbon atom at C_2 and therefore exists as two enantiomers. The compound was initially developed and introduced into the market as a racemate with equimolar ratio of the *R*- and *S*-enantiomers. Later, the enantiopure compound designated as haloxyfop-P-methyl replaced the racemic compound. The P (from plus, the direction of rotation of polarized light) stands for the technical material having a large excess of the *R*-enantiomer (equal or higher 940 g/kg of the *R*-enantiomer). This enantiomer carries the desired herbicidal activity – inhibition of fatty acid synthesis by competitive binding to the Acetyl-CoA-carboxylase in grasses.

Haloxyfop-P-methyl is not under patent.

The FAO/WHO JMPR in 2009 and WHO/IPCS in 2006 evaluated haloxyfop and haloxyfop-P. Some of the main conclusions of the 2006 JMPR evaluation for the toxicology for the absorption/distribution/metabolism and excretion studies (ADME) were:

- Irrespective of whether haloxyfop or haloxyfop-R methyl ester was administered, haloxyfop was the only substance detected in the plasma.

- *S*-isomeric form(s) of haloxyfop underwent rapid and almost complete inversion to *R*-form(s) in rats, and it was assumed that this also occurred in other species.

For that reason, toxicity studies on racemic haloxyfop could be used to bridge for some endpoints for haloxyfop-P-methyl. As the common metabolite is always haloxyfop and the S-enantiomer was rapidly converted to the R-form, the Meeting considered these arguments as robust justification to bridge from racemic haloxyfop-methyl to haloxyfop-P-methyl concerning hazard data.

Haloxyfop-P-methyl was re-evaluated by the European Commission as part of the EU review of existing active substances for inclusion in the former Annex I of the Council Directive 91/414/EEC, currently EU Regulation 540/2011.

Haloxyfop-P-methyl belongs to the family of aryloxyphenoxyproponic acid herbicides and has a low volatility (vapour pressure: 2.6×10^{-5} P at 20°C). It is slightly soluble in water; the solubility is somewhat influenced by pH in the range between 5 and 9. Its octanol/water partition coefficient (log P_{ow}=4.0) shows that the molecule is lipophilic, with a theoretical potential for bioaccumulation. In practice, the ester is rapidly cleaved in the environment liberating the free acid that shows a much lower lipophilicity. Haloxyfop-P-methyl is hydrolytically stable at pH 4.

The main formulation type available is emulsifiable concentrate**,** EC.

The Meeting was provided with commercially confidential information on the manufacturing process and five batch analysis data on impurities present at or above 1g/kg and their manufacturing limits in the TC. Mass balances ranged from 993-1001 g/kg in the five batch data. None of the manufacturing impurities considered is, on the basis of information available, of toxicological or environmental concern. The impurities and their QC limits in the manufacturing specifications were similar to the haloxyfop-P-methyl impurity profile provided to the Australian authorities for registration purposes.

The analytical methods for the identification and quantification of haloxyfop-P-methyl in TC and EC formulations were collaboratively validated by CIPAC and in the meantime adopted as full CIPAC method. Prior to its publication in Handbook N presumably in 2012, copies of the method are available through the CIPAC prepublishment scheme.

The quantification method is based on a normal phase HPLC separation of *R*- and *S*-haloxyfop-P-methyl with a chiral phase column using UV detection at 280 nm and external standardization. The column (a Chiralcel OK column) provides baseline separation of the *R*- (first eluting) and *S*-enantiomer (second eluting) respectively. Identity tests are based on comparison of the UV- and IR-spectra with those of authentic standards.

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

The data provided for the technical material supports the specification for the TC as proposed. There are no relevant impurities in the technical material, and impurities present at or above 1 g/kg in the TC are analysed by GC-FID using external standard calibration.

In considering the specification for emulsifiable concentrate (EC) formulation, the meeting concluded that the pH clause in the draft specification is unnecessary. With respect to the limit for persistent foam, the meeting noted that the maximum value of 60 ml is high. The company clarified that, although they produce a wide range of products globally with a range of persistent foam, the value of 40 ml is more appropriate, a value accepted by the Meeting.

The Meeting noted that the CIPAC numbering system for active ingredients had been modified a couple of years ago to make it more consistent and transparent, especially for those active ingredients that may exist as variants, e.g. as a methyl ester. This is also the case for haloxyfop-P-methyl. The ISO common name refers to the free acid with a note, that “when this substance is used as an ester or a salt, its identity should be stated, for example haloxyfop-P-etotyl, haloxyfop-P-methyl“. The CIPAC code for haloxyfop-P (as acid) is 526, and the variant methyl ester is covered by the suffix 201. Therefore, the complete CIPAC code is 526.201 for haloxyfop-P-methyl. Some elder CIPAC documents like that of the haloxyfop-P-methyl method still refer to 526 only instead of 526.201, which is the correct CIPAC code also used in these specifications.

SUPPORTING INFORMATION
FOR
EVALUATION REPORT 526.201/2011

USES

Haloxyfop-P-methyl is a selective herbicide controlling annual and perennial grasses in dicotyledoneous crops like sugar beet, canola and vegetables. After uptake by plants, the methylester is rapidly hydrolysed to yield haloxyfop, which is the active moiety. In grasses, haloxyfop-P acts by competitively binding to the Acetyl-CoA-carboxylase (ACCase) that catalyzes the biosynthesis of fatty acid.

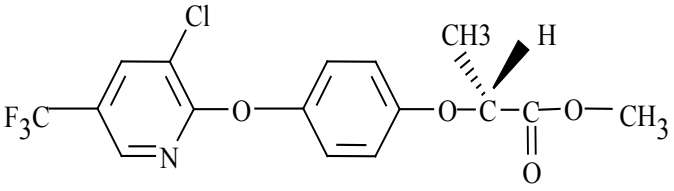
IDENTITY OF THE ACTIVE INGREDIENT

ISO common name (ISO 1750 published)
Haloxyfop-P

Chemical names
IUPAC methyl(R)-2-[4-(3-chloro-5-trifluoromethyl-2-pyridyloxy)phenoxy]propionate
CA propanoic acid, 2-[4-[[3-chloro-5-(trifluoromethyl)-2-pyridinyl]oxy]phenoxy]-, methyl ester,

Synonyms
Haloxyfop-P methyl ester, DE-535

Structural formula



Molecular formula
$C_{16}H_{13}ClF_3NO_4$

Molecular mass
375.7

CAS Registry Number
72619-32-0

CIPAC Number
526.201

Identity tests
Retention times of R- and S-haloxyfop-methyl in enantioselective HPLC, UV- and IR-spectra

Table 1: Physico-chemical properties of pure haloxyfop-P-methyl

Parameter	Value(s) and conditions		Purity %	Method reference (and technique if the reference gives more than one)	Report Reference
Vapour pressure	2.6 x 10^{-5} P at 20°C 5.5 x 10^{-5} P at 25°C		99.3	EEC Method A4	GHE-P-4060
Melting point, boiling point and/or temperature of decomposition	Melting point: not applicable Boiling point: > 280°C (estimated value > 437°C) Decomposition temperature: not required as boiling point has been determined		99.3	EEC Method A2	GHE-P-2140
Solubility in water, (test performed at 20°C)	pH	Solubility mg/L	99.3	EEC Method A2	GHE-P-4060
	Purified water	9.08 mg/l			
	pH 5 buffer	6.93 mg/l			
	pH 7 buffer	7.86 mg/l			
	pH 9 buffer	Due to known rapid hydrolysis of the material at this pH, no test was performed.			
Octanol/water partition coefficient, (test performed at 20°C)	Log K_{ow} = 4.00 Equivalent K_{ow} 9890 The pK_a value has not been determined due to the low solubility in water, and therefore the effect of pH on the partition coefficient has not been determined		99.3	EEC Method A8	GHE-P-4060
Hydrolysis characteristics, (test performed at 20°C)	pH	Hydrolysis half live	96.5	EEC Method C7 and OECD 111	GH-C-5364
	4	stable			
	7	43 days			
	9	0.63 days			
	Natural water	3 days			
Photolysis characteristics	DE-535, sterile buffer	20 days	97.5	SETAC Part 1, Section 10.1	GH-C-5353

At summer sunlight 40°N, 24-hour exposure, pH 5 buffered HPLC-grade water.	Natural water	2 days			
Dissociation characteristics	Not determined for haloxyfop-P-methyl due to the low water solubility		n/a	None	None
Solubility in organic solvents	Miscible up to 50 % w/w at 20 °C in: acetone, cyclohexanone, dichloromethane, ethanol, ethylacetate, hexane, isopropanol, methanol, toluene, xylene		n/a	none	GH-C 2162

Table 2. Chemical composition and properties of haloxyfop-P-methyl 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 ranged from 99.3 – 100.1 %
Declared minimum haloxyfop-P-methyl content	940 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
Boiling temperature range of the TC and/or TK	Boiling point > 280°C

HAZARD SUMMARY

Haloxyfop has been evaluated by the WHO/IPCS in 1995 and by FAO/WHO JMPR in 2009. The meeting concluded that it is not genotoxic as it has been adequately tested for genotoxicity in a range of tests *in vivo* and *in vitro*.
Haloxyfop has been evaluated by the FAO/WHO JMPR in 2006 and 2009. The Meeting set an acceptable daily intake (ADI) of 0-0.0007 mg/kg bw and an ARfD of 0.08 mg/kg bw in 2006, for racemic haloxyfop, haloxyfop-*R* and their methyl-esters.

FORMULATIONS

The main formulation types available are emulsifiable concentrates (EC), for agricultural use only. Haloxyfop-P methyl is not co-formulated with other pesticides. These formulations are registered and sold in many countries throughout the world.

METHODS OF ANALYSIS AND TESTING

Haloxyfop-P-methyl is determined according to CIPAC Method available under the CIPAC prepublishment scheme by HPLC using a normal phase enantioselective column (Chiralcel OK) and UV detection. The method provides baseline separation of *R*- and *S*- haloxyfop-P-methyl, respectively. Quantification is performed using external standard method. The methods for determination of impurities have been validated and are based on GC using a flame ionisation detector, on a dimethylpolysiloxane stationary phase with 5 % phenyl groups (Ultra 2) capillary column.
Test methods for determination of physico-chemical properties of the technical active ingredient were OECD, while those for the formulations were CIPAC, as indicated in the specifications.

CONTAINERS AND PACKAGING

No special requirements for containers and packaging have been identified.

EXPRESSION OF THE ACTIVE INGREDIENT

Haloxyfop-P-methyl is expressed as the ester or acid, depending on country requirements.

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 haloxyfop-P-methyl 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.

(iii) The data relate to more than one form of the a.i. The active substance hydrolyses to the acid on ingestion, and the *S*-enantiomer is converted to the *R*-enantiomer. Therefore, the majority of the sub-chronic and chronic toxicity studies have been conducted on racemic haloxyfop (a 50:50 ratio of *R*- and *S*-enantiomers) or racemic haloxyfop methyl ester. This was the original form of the active substance developed in the 1980's; as only the *R*-enantiomer has biogical activity, Dow AgroSciences replaced the racemic mixture with the resolved isomer in the 1990's. Several toxicology studies have been conducted to demonstrate the toxicological equivalence of the ester to the acid, and the resolved isomer to the racemic material. These studies have been evaluated in the WHO evaluations.

Table 3. Toxicology profile of the haloxyfop-P-methyl technical material, based on acute toxicity, irritation and sensitization.

Species	**Purity, %**	**Test**	**Duration and conditions or guideline adopted**	**Result for haloxyfop-P-methyl unless stated**	**Report Reference**
Rat, both sexes	98.6	Acute oral LD_{50}	OECD Guideline No. 401 Acute Oral Toxicity, 1987 Dosage : 0,100, 500, 1000 mg/kg bw	LD_{50} = 300 mg/kg bw in males LD_{50} = 623 mg/kg bw in females	HET DR-0217-5704-001A
Rat, both sexes	Not stated	Acute oral LD_{50}	OECD Guideline No. 401 Acute Oral Toxicity, 1987 Dosage : 0,250, 300(M), 400(M), 500, 1000, 2000 mg/kg bw (M)= Male only	Haloxyfop methyl ester LD_{50} = 337 mg/kg bw in males LD_{50} = 545 mg/kgbw in females	HET K-131381-(5)
Mouse, both sexes	98.6	Acute oral LD_{50}	OECD Guideline No. 401 Acute Oral Toxicity, 1987 Dosage : 0, 100, 500, 1000 mg/kg bw	LD_{50} = 707 mg/kg bw	HET DR-0217-5704-001G
Rat, both sexes	98.6	Acute dermal LD_{50}	OECD Guideline No. 402 Acute Dermal Toxicity, 1987 Dosage : 2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	HET DR-0217-5704-001D
Rabbit, both sexes	Not stated t	Acute dermal LD_{50}	OECD Guideline No. 402 Acute Dermal Toxicity, 1987 Dosage : 2500, 5000 mg/kg bw	Haloxyfop methyl ester LD_{50} > 5000 mg/kg bw	HET K-131381-(5)
None	N/A	inhalation		Haloxyfop-P-methyl does not have properties that require an inhalation study to be carried out	None
Rabbit, both sexes	98.6	skin irritation	OECD Guideline No. 404 Acute Dermal Irritation/Corrosion, 1987 Dosage : 0.5ml	No irritation	HET DR-0217-5704-001B
Rabbit, both sexes	98.6	eye irritation	EC Method Number B.5. Acute toxicity (eye irritation), 1992 Dosage : 100mg	No irritation	HET DR-0217-5704-001C
Guinea pig, male	Not stated	Skin sensitisation	EC test guideline (Method No. B.6. Skin sensitisation, 1996	No sensitisation	GHE-T 1154

Species	Purity, %	Test	Duration and conditions or guideline adopted	Result for haloxyfop-P-methyl unless stated	Report Reference
	in report		Magnussen and Kligman test Dosage : 25%, 50% 75% in vehicle (peanut oil)		
Guinea pig, female	98.6	Skin sensitisation	Buehler Dosage : 0.4ml	No sensitisation	HET DR-0217-5704-001E

Table 4. Toxicology profile of technical haloxyfop or haloxyfop-P-methyl based on repeated administration (subacute to chronic)

Species	Purity, %	Test and dose levels (mg/kg bw/day unless stated)	Duration and conditions or guideline adopted	Result racemic haloxyfop (acid) unless otherwise stated	Report Reference
Rat, both sexes	99	16 week oral 0, 0.002, 0.02, 0.2 or 2	EC Guideline 87/302/EEC	NOAEL = 0.02 mg/kg bw/d LOEL = 0.2 mg/kg bw/d	HET K-131381-(4)
Rat, both sexes	99.4	16 week oral 0, 0.065, 0.2 or 2	OECD 408	Haloxyfop-P-methyl NOAEL = 0.065 mg/kg bw/d LOEL = 0.2 mg/kg bw/d	DR-0298-5651-001
Rat, both sexes	99	37 week oral 0, 0.002, 0.02, 0.2 or 2	EC Guideline 87/302/EEC	NOAEL = 0.02 mg/kg bw/d LOEL = 2.0 mg/kg bw/d	HET K-131381-(4)
Mouse, both sexes	96	13 week oral 0, 0.002, 0.02, 0.2 or 2	EC guideline 87/302/EEC	NOAEL = 0.2 mg/kg bw/d LOEL = 2.0 mg/kg bw/d	HET K-131381-(3)
Mouse, both sexes	96	36 week oral 0, 0.002, 0.02, 0.2 or 2	EC guideline 87/302/EEC	NOAEL = 0.02 mg/kg bw/d LOEL = 2.0 mg/kg bw/d	HET K-131381-(3)

Species	Purity, %	Test and dose levels (mg/kg bw/day unless stated)	Duration and conditions or guideline adopted	Result racemic haloxyfop (acid) unless otherwise stated	Report Reference
Dog, both sexes	99.8	13 week oral 0, 2, 5 or 20	EC guideline 87/302/EEC	NOAEL = 2.0 mg/kg bw/d LOEL = 5.0 mg/kg bw/d	HET K-131381-056
Dog, both sexes	99.6	52 week oral 0, 0.05, 0.5 or 5	EC guideline 87/302/EEC	NOAEL = 0.5 mg/kg bw/d LOEL = 5.0 mg/kg bw/d	TXT: K-131381-(17)
Monkey, both sexes	99.8	13 week oral 0, 2, 10 or 30	EC guideline 87/302/EEC	NOAEL = 2.0 mg/kg bw/d LOEL = 10.0 mg/kg bw/d	HET K-131381-058 (T-1242)
Rat, both sexes	99.6	2-year 0, 0.01, 0.03, 0.065 or 0.1 in males. 0, 0.01, 0.03, 0.065 or 1.0 in females.	EC guideline 87/302/EEC	NOAEL = 0.065 mg/kg bw/d LOEL = 0.1 mg/kg bw/d males 1.0 mg/kg bw/d females	HET K-131381-(18B)
Mouse, both sexes	99.6	2-year 0, 0.03, 0.065 or 0.6 mg/kg bw/day.	EC Guideline 87/302/EEC	NOAEL = 0.065 mg/kg bw/d LOEL = 0.6 mg/kg bw/d	HET K-131381-(22)
Rat/F-344, both sexes	99.6	3 generation reproduction 0, 0.005, 0.05, or 1.0	EC Guideline 87/302/EEC	NOAEL = 0.05 mg/kg bw/d LOEL = 1.0 mg/kg bw/d	HET K-131381-012
Rat/CD, both sexes	99.4	2 generation reproduction 0, 0.01, 0.065 or 1.0	EC Guideline 87/302/EEC	NOAEL = 0.065 mg/kg bw/d LOEL = 1.0 mg/kg bw/d	K-131381-039

Species	Purity, %	Test and dose levels (mg/kg bw/day unless stated)	Duration and conditions or guideline adopted	Result racemic haloxyfop (acid) unless otherwise stated	Report Reference
Rat, female	99.7	Teratogenicity 0, 0.1, 1 or 7.5	EC Guideline 87/302/EEC	Dam NOAEL = 1.0 mg/kg bw/d LOEL = 7.5 mg/kg bw/d Litter NOAEL = 1.0 mg/kg bw/d LOEL = 7.5 mg/kg bw/d	HET K-131381-(28)
Rabbit, female	99.7	Teratogenicity 0, 1, 7.5 or 20.0	EC Guideline 87/302/EEC	Dam NOAEL = 7.5 mg/kg bw/d LOEL = 15 mg/kg bw/d Litter NOAEL = 15 mg/kg bw/d LOEL = 20 mg/kg bw/d	HET K-131381-(28)
	99.6	0, 3, 7.5 or 15.0			HET K-131381-(042)

***Table* 5. Mutagenicity profile of technical haloxyfop or haloxyfop-P-methyl based on in vitro and in vivo tests**

Species	**Purity, %**	**Test**	**Conditions**	**Result racemic haloxyfop (acid) unless stated**	**Report Reference**
S.typhimurium TA 98, 100, 1535 & 1538	99	Ames	OECD 471	2000μg/plate – negative	HET-K-131381 (6)
S.typhimurium TA 98, 100, 1535 & 1538	99.4	Ames	OECD 471	Haloxyfop-P-methyl 1580μg/plate – negative	TXT:DR-0298-5651-003
Human	99.4	*In vitro* chromosome aberration	OECD 473	500μg/ml – negative	DET 821; 86/DCS006/515
Rat	99.4	*In vitro* chromosome aberration	OECD 473	Haloxyfop-P-methyl 5000μg/ml – negative	TXT:DR-0298-5651-005
Chinese hamster ovary cells	Not stated in report	*In vitro* CHO/HGPRT	87/302/EEC	2000μg/ml – negative	HET-K-131381-(21)
Rat hepatocyte	99	*In vitro* unscheduled DNA synthesis	87/302/EEC	0.3 x 10^{-3} M - negative	HET-K-131381-(7)
Rat hepatocyte	99.4	*In vitro* unscheduled DNA synthesis	OECD 482	Haloxyfop-P 500μg/ml – negative	TXT: DR-0298-5651-004
Rat Polychromatic erythrocytes	99.6	*In vivo* rat micronucleus	OECD 474	300mg/kg – negative	TXT: K-131381-(27)

Table 6. Ecotoxicology profile of the technical haloxyfop-P-methyl

Species	Purity, %	Test	Duration and conditions	Result Haloxyfop-P-methyl unless otherwise stated	Report Reference
Rainbow trout (*Oncorhynchus mykiss*)	98.4	Acute toxicity	OECD 203 Dosage : 0, 93,156, 259, 432, 720,1200 µg/L	96-hour LC_{50} = 460 **µ**g/L	DECO HET DR-0217-5704-017
Rainbow trout (*Oncorhynchus mykiss*)	99.0	Acute toxicity	OECD 203 Dosage : 0,5, 9, 15, 28, 50 mg/L	Haloxyfop-P 96-hour LC_{50} = >50 mg/L	GHE-P-1943; RCC 215313
Lepomis macrochirus	98.4	Acute toxicity	OECD 203 Dosage : 0, 35, 58, 113, 175, 292, 487 µg/L	96-hour LC_{50} = 88.4 µg/L	DECO HET DR-0217-5704-020; Study ID: 991231
Rainbow trout (*Oncorhynchus mykiss*)	96.4	Chronic toxicity	OECD 204 Dosage : 0, 2, 7, 20, 70, 200, 700 µg/L	28-day LC_{50} = 236.9 µg/L NOEC = 5.2 **µ**g/L	GHE-T-673 Study ID: 295/51-1018
Fathead minnow (*Pimephales promelas*)	100	Fish Early Life Stages	OECD 210 Dosage : 0, 1.0, 2.2, 4.6, 10.0 mg/L	Haloxyfop-P 28-day LC_{50} = 3.6 **m**g/L NOEC = 0.86 **m**g/L	GHE-T-843 DWC 885/973687
Rainbow trout	>99	Bioaccumulation	OECD 305E Dosage : 0,5, 5 mg/L	Haloxyfop-P BCF = 24.8	GHE-T-200 215278
Daphnia magna	98.4	Acute toxicity	OECD 202 (part 1) Dosage : 0, 1.6, 2.6, 4.3, 7.2, 12, 20 mg/L	48 hour EC_{50} = >12.3 mg/l	DECO HET DR-0217-5704-018 991231
Daphnia magna	99.5	Acute toxicity	OECD 202 (part 1) Dosage : 0, 100 mg/L	Haloxyfop-P 48 hour EC_{50} = >100 mg/l	GHE-T-836 DWC883/973310
Daphnia magna	96.4	Chronic toxicity	OECD 202 (part II) Dosage : 0, 0.06, 0.2, 0.6, 2, 6 mg/L	NOEC = 0.509 mg/l	GHE-T-642 Study ID: 295/50-1018
Daphnia magna	100	Chronic toxicity	OECD 202 (part II) Dosage : 0, 0.32, 1, 3.2, 10, 32 mg/L	Haloxyfop-P NOEC = 9.6 mg/l	GHE-T-939: DWC 884/992250

Species	Purity, %	Test	Duration and conditions	Result Haloxyfop-P-methyl unless otherwise stated		Report Reference
Scenedesmus subspicatus (green alga)	98.7	effect on growth, static water	OECD 201 Dosage : 0, 3.1, 6.3, 12.5, 25, 50, 100 mg/L	Haloxyfop-P		DECO HET DR-0298-5651-025 011042
				96-hour E_rC_{50} (growth rate)	> 94.9 mg/L	
				96-hour E_bC_{50} (biomass)	50.0 mg/L	
				96-hour cell density EC_{50}	56.6 mg/L	
				72 and 96-hour NOEC	28.9 mg/L	
Navicula pelliculosa (diatom)	98.4	effect on growth, static water	U.S. EPA FIFRA 123-2 Dosage : 0.365, 0.731, 1.46, 2.92, 5.85 and 11.7 mg/L	120-hour EC_{50} (growth)	2.55 mg/L	DECO HET DR-0217-5704-015: 991216
				120-hour E_bC_{50} (areas under growth curve)	1.72 mg/L	
				120-hour E_rC_{50} (growth rate)	5.37 mg/L	
				120-hour NOEC	1.10 mg/L	
Chironomus riparius (midge larva)	>98.6	28-day toxicity	Streloke, M. and Kopp, H. 'Long term toxicity test with *Chironomus riparius*: Development and validation of a new test system', BBA (1995). Dosage : 0, 0.1, 0.32, 1,0, 3.2, 10 mg/L	28-day EC_{50} (emergence)	> 10 mg/L	GHE-T-1096DOS 063/994330
				28-day NOEC (emergence)	3.2 mg/L	
				28-day EC_{50} (development rate)	> 10 mg/L	
				NOEC (development rate)	3.2 mg/L	
Lemna minor (duck weed)	96.8	Growth inhibition test	U.S. EPA, Subdivision J, 122-2 and 123-3 and OECD Draft 'Duckweed, static growth inhibition test (1981) Dosage : 0, 0.07, 0.22, 0.7, 2.2, 7 mg/L	14-day EC_{50}	3.1 mg/L	GHE-T-876: DWC 909/982103
				14-day NOEC	0.054 mg/L	
Lemna minor (duck weed)	100	Growth inhibition test	U.S. EPA, Subdivision J, 122-2 and 123-3 and OECD Draft 'Duckweed, static growth inhibition test (1981) Dosage : 0, 0.5, 1.6, 5, 16, 50 mg/L	Haloxyfop-P 14-day EC_{50} 14-day NOEC	 3.1 mg/L 0.054 mg/L	GHE-T-875 DWC 908/982300

Species	**Purity, %**	**Test**	**Duration and conditions**	**Result Haloxyfop-P-methyl unless otherwise stated**	**Report Reference**
Earthworm	98.6	Acute toxicity	OECD 207 Dosage: 0, 316, 552, 986, 1775, 3157 mg/kg dry soil	LC_{50} = 1343 mg/kg dry soil	GHE-T-968: CEMR-1064
Apis mellifera (honey bee)	99.3	Acute oral toxicity	U.K. PSPS Working Document D3 Dosage : 0, 100 µg/bee	LD_{50} = >100 µg/bee	GHE-P-1947 DWC 528/881432
Apis mellifera (honey bee)	99.3	Acute contact toxicity	EPPO 170, U.K. PSD Working Document 7/3 and U.S. EPA Subdivision L, 141-1 Dosage : 0, 100 mg/bee	LC_{50} = >100 µg/bee	GHE-P-1947 DWC 528/881432
Bobwhite quail	99.3	Acute toxicity	SETAC (1995). Dosage : 0, 500, 1000, 200 mg/kg	LD_{50} = 1159 mg/kg bw	GHE-P-1942 DWC 529/89694
Bobwhite quail	98.0	Acute toxicity	SETAC (1995). Dosage : 0, 198, 296, 444, 667, 1000 mg as/kg bw	Haloxyfop-P LD_{50} = 414 mg/kg bw	GHE-T-971 DOS 043/994387
Bobwhite quail	98.0	Short-term toxicity	OECD 205 Dosage : 0, 158, 313, 625, 1250, 2500, 5000 mg/kg	Haloxyfop-P LC_{50} = >5000 mg/kg diet	GHE-T-1079 DOS 054/994386
Bobwhite quail	98.7	Reproduction	OECD 206 Dosage : 0, 100, 200, 400, 800 mg/kg	Haloxyfop-P NOEC = 210 mg/kg diet	DECO HET DR-0298-5651-024 12550.4100

Annex 2

References

Physico-chemical properties of the technical active substance haloxyfop-P-methyl

Study number	Author(s)	year	Study title. All studies Dow AgroSciences.
GH-C 2162		1989	Solubility of XRD-535 Methyl Ester in Organic Solvents
GH-C 5353		2002	Aqueous Photolysis of DE-535 and DE-535-acid in pH 5 Buffer and Natural Water Under Xenon Light
GH-C-5364		2002	Hydrolysis of ^{14}C Haloxyfop-*R* Methyl Ester in Natural Water and Buffered Water as a Function of pH
GHE-P-2140		April 1990	XRD 535 Methyl ester: Determination of physico-chemical properties
GHE-P-4060		1995b	DE 535 (Ester) Pure: Determination of Physico-chemical Properties

Mammalian toxicology (as assessed by WHO in 2006)

Study number	Author(s)	year	Study title. All studies after 1986 conducted under GLP. All studies by Dow AgroSciences unless otherwise specified
HET DR-0217-5704-001A		1989a	XRD-535 METHYL ESTER: Acute Oral Toxicity Study in Fischer 344 Rats.
HET K-131381-(5)		1980	DOWCO 453 Acute Toxicological Properties and Industrial Handling Hazards
HET DR-0217-5704-001G		1989b	XRD-535 METHYL ESTER: Acute Oral Toxicity Study in B6C3F1 Mice
HET DR-0217-5704-001D		1989	XRD-535 METHYL ESTER: Acute Dermal Toxicity Study in Fischer 344 Rats
HET DR-0217-5704-001B		1989a	XRD-535 METHYL ESTER: Primary Dermal Irritation Study in New Zealand White Rabbits
HET DR-0217-5704-001C		March 1989b	XRD-535 METHYL ESTER: Primary Eye Irritation Study in New Zealand White Rabbits
GHE-T 1154		1994	Haloxyfop-R Methyl Ester Technical: Magnusson and Kligman Maximisation Study in the Guinea Pig
HET DR-0217-5704-001E		1989c	XRD-535 METHYL ESTER: Dermal Sensitization Potential in the Hartley Albino Guinea Pig

Study number	Author(s)	year	Study title. All studies after 1986 conducted under GLP. All studies by Dow AgroSciences unless otherwise specified
HET K-131381-(4)		1982	DOWCO 453: Results of 16 and 37-Week Dietary Toxicity Studies in Fischer 344 Rats
TXT: DR-0298-5651-001		1989	XRD-535 Herbicide: Subchronic Rat Dietary Toxicity and Recovery Study
HET K-131381-(3)		J 1982	DOWCO 453: Results of 13 and 36-Week Dietary Toxicity Studies in B6C3F1 Mice
HET K-131381-056		1987	DOWCO 453 Herbicide: 13-Week Dietary Toxicity Study in Beagle Dogs
TXT: K-131381-(17)		1984	DOWCO 453 Herbicide: Results of a 12-Month Dietary Toxicity Study in Beagle Dogs
HET K-131381-058 (T-1242)		1987	Haloxyfop: 13-Week Oral Toxicity Study in Cynomolgus Monkeys
HET K-131381 (18B)		1984	DOWCO 453: 2-Year Chronic Toxicity – Oncogenicity Study in CDF Fischer 344 Rats
HET K-131381 (22)		1985	DOWCO 453: 2-Year Dietary Chronic Toxicity – Oncogenicity Study in B6C3F1 Mice
HET K-131381-012		1985	DOWCO 453: Three-Generation Dietary Reproduction Study in Fischer 344 Rats

Study number	Author(s)	year	Study title. All studies after 1986 conducted under GLP. All studies by Dow AgroSciences unless otherwise specified
HET K-131381-039		1985	DOWCO 453: Two-Generation Dietary Reproduction Study in Sprague-Dawley Rats
HET K-131381-(28)		1983	DOWCO 453 Sodium Salt: Oral Teratology Study in Rats and Rabbits
HET K-131381-(042)		1985	Haloxyfop: Oral Teratology Study in Rabbits (Repeat study)
HET-K-131381 (6)		1981	Evaluation of DOWCO* 453 Herbicide in the Ames' Salmonella/Mammalian Microsome Mutagenicity Assay
TXT:DR-0298-5651-003		1989	Evaluation of XRD-535 in the Ames Salmonella/Mammalian-Microsome Bacterial Mutagenicity Assay
DET 821		1986	In Vitro Assessment of the Clastogenic Activity of DOWCO* 453 in Cultured Human Lymphocytes
TXT:DR-0298-5651-005		1989	Evaluation of XRD-535 in an *In-Vitro* Chromosomal Aberration Assay Utilizing Rat Lymphocytes
HET-K-131381-(21)		1982	Mutagenicity Evaluation f XRD-0453 (DOWCO* 453) in the CHO/HGPRT Forward Mutation Assay
HET-K-131381-(7)		1980	The Evaluation of DOWCO* 453 Herbicide in the Rat Hepatocyte Unscheduled DNA Synthesis Assay

Study number	Author(s)	year	Study title. All studies after 1986 conducted under GLP. All studies by Dow AgroSciences unless otherwise specified
TXT:DR-0298-5651-004		1989	Evaluation of XRD-535 in the Rat Hepatocyte Unscheduled DNA Synthesis (UDS) Assay.
TXT:K-131381-(27)		1982	Evaluation of DOWCO* 453 Herbicide in the Rat Bone Marrow Micronucleus Test.

Ecotoxicology of haloxyfop-P methyl ester and the major degradates, haloxyfop-P acid

Study number	Author(s)	year	Study title. All studies after 1986 conducted under GLP. All studies to Dow AgroSciences.
DECO HET DR-0217-5704-017		1999a	DE-535 (Haloxyfop-R Methyl Ester): An Acute Toxicity Study with the Rainbow Trout, *Onchorhynchus mykiss* Walbaum
GHE-P-1943		1989	XRD-535 Acid: 96-Hour Acute Toxicity Study (LC_{50}) in the Rainbow Trout
DECO HET DR-0217-5704-020		1999b	DE-535 (Haloxyfop-R Methyl Ester): An Acute Toxicity Study with the Bluegill Sunfish, *Lepomis macrochirus* Rafinesque
GHE-T-673		1996	Haloxyfop-R methyl ester (XRD-535): 28 day prolonged toxicity test to *Oncorhynchus mykiss*
GHE-T-843		1997	Haloxyfop-R Acid: Fish Early Life Stage Toxicity for Fathead Minnow
GHE-T-200		1990a	Accumulation and Elimination of ^{14}C-labelled XRD 535 (Acid) by Rainbow Trout in a dynamic flow-through system
DECO HET DR-0217-5704-018		1999	DE-535 (Haloxyfop-R Methyl Ester): An Acute Toxicity Study with the Daphnia, *Daphnia magna* Straus
GHE-T-836		1997	Haloxyfop-R Acid: Acute Toxicity to *Daphnia magna*

Study number	Author(s)	year	Study title. All studies after 1986 conducted under GLP. All studies to Dow AgroSciences.
GHE-T-642		1996	Haloxyfop-R Methyl Ester (XRD-535): *Daphnia magna* Reproduction Study
GHE-T-939		1999	Haloxyfop-R Acid: Prolonged Toxicity for *Daphnia magna*
DECO HET DR-0298-5651-025		2001	Haloxyfop ®: Growth inhibition test with the freshwater green alga, *Selenastrum capricornutum*, PRINTZ
DECO HET DR-0217-5704-015		1999	Effects of DE-535 (Haloxyfop-R Methyl Ester) on the Growth of the Freshwater Diatom, *Navicula pelliculosa*
GHE-T-876		1998a	Haloxyfop-R Methyl Ester: Higher Plant (*Lemna*) Growth Inhibition Test
GHE-T-875		1998b	Haloxyfop-R : Higher Plant (*Lemna*) Growth Inhibition Test
GHE-T-1096		2001	Haloxyfop-R Methyl Ester: Toxicity to the sediment dwelling phase of the Midge *Chironomus Riparius*
GHE-T-968		1999	The Acute Toxicity of DE-535 to the Earthworm, *Eisenia foetida*
GHE-P-1947		1989	The Acute Contact and Oral Toxicity to Honey Bees of Technical XRD-535
GHE-P-1942		1989	Acute Oral Toxicity (LD_{50}) of XRD-535 Methyl Ester Technical to the Bobwhite Quail

Study number	Author(s)	year	Study title. All studies after 1986 conducted under GLP. All studies to Dow AgroSciences.
GHE-T-971		1999	Haloxyfop Acid (R-Isomer): Acute Oral Toxicity (LD_{50}) to the Bobwhite Quail
GHE-T-1079		1999	Haloxyfop Acid (R-Isomer): Dietary Toxicity (LD_{50}) to the Bobwhite Quail
DECO HET DR-0298-5651-024	.	2001	Haloxyfop ® – Reproductive Toxicity Test with the Northern Bobwhite Quail *(Colinus virginianus)*