FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

FENOXAPROP-P-ETHYL

(*R*)-2-[4-(6-chlorobenzoxazol-2-yloxy)
phenoxy]propionic acid ethyl ester

FOOD AND AGRICULTURE ORGANIZATION *of* THE UNITED NATIONS

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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.

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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.

From 1999, the development of FAO specifications has followed the **New Procedure**, described in the 1st edition of "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (2002) and amended with the supplement of this manual (2006), 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 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 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 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 and WHO specifications for pesticides" 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. 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/
or in hardcopy from the Plant Protection Information Officer.

PART ONE

SPECIFICATIONS

PART ONE

FENOXAPROP-P-ETHYL

INFORMATION

ISO common name

Fenoxaprop-P (ISO 1750 published, refers to the R-enantiomer of the acid)

Variant: Fenoxaprop-P-ethyl (refers to the ethyl ester of fenoxaprop-P)

Synonyms

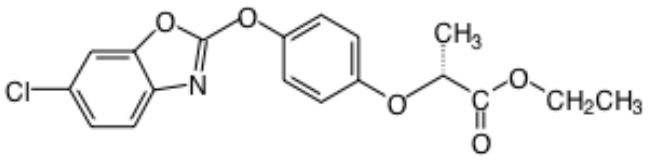
none

Chemical name(s)

IUPAC (*R*)-2-[4-(6-chlorobenzoxazol-2-yloxy)phenoxy]propionic acid ethyl ester

CA ethyl (*R*)-2-[4-[(6-chloro-2-benzoxazolyl)oxy]phenoxy]propanoate

Structural formula



Molecular formula

$C_{18}H_{16}ClNO_5$

Relative molecular mass

361.8

CAS Registry number

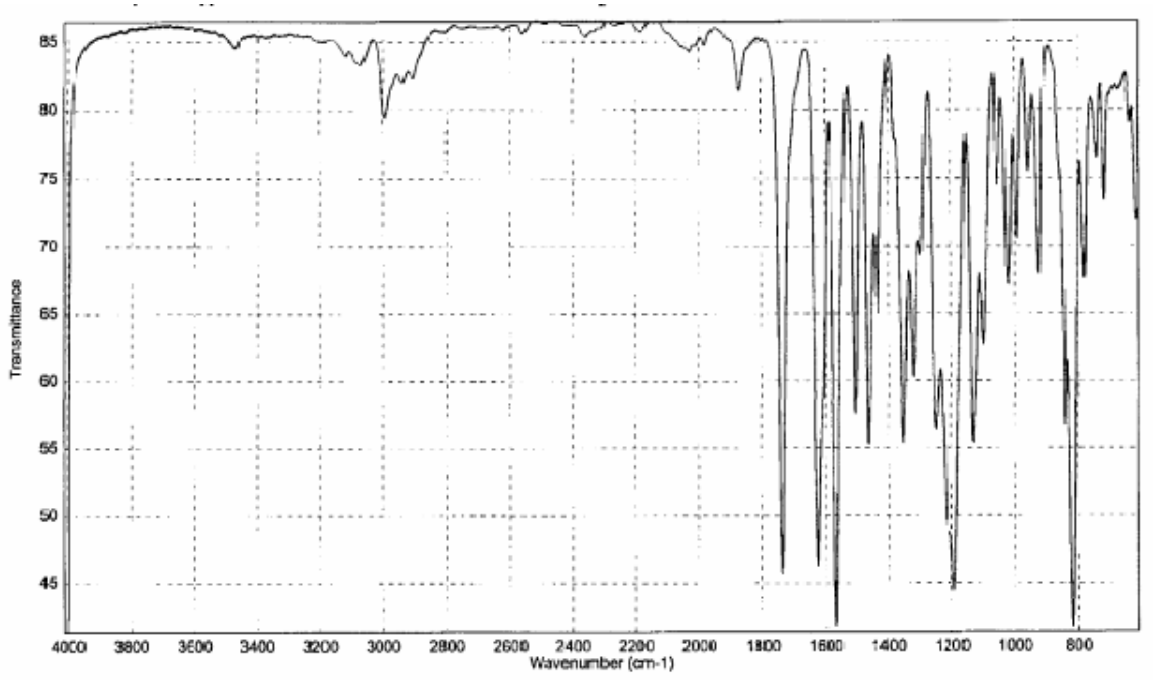
71283-80-2

CIPAC number

484.202

Identity tests

HPLC retention time, IR spectrum



FENOXAPROP-P-ETHYL TECHNICAL MATERIAL

FAO specification 484.202/TC (JUNE 2010*)

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 (484.202/2010). 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 (484.202/2010) as PART TWO forms an integral part of this publication.

1 Description

The material shall consist of fenoxaprop-P-ethyl together with related manufacturing impurities, in the form of beige to brownish crystalline solid, free from visible extraneous matter and added modifying agents.

2 Active ingredient

2.1 **Identity tests** (CIPAC 484/TC/M/3.2, Handbook M, p. 89, 2009 and CIPAC 484/TC/M/2, Handbook J, p. 52, 2000)

The active ingredient shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test (Note 1).

2.2 **Fenoxaprop-P-ethyl content** (CIPAC 484/TC/M/3.2, Handbook M, p. 89, 2009 and CIPAC 484/TC/M/3, Handbook J, p. 52, 2000)

The fenoxaprop-P-ethyl content shall be declared (not less than 920 g/kg) and, when determined, the average measured content shall not be lower than the declared minimum content.

Note 1 The IR spectrum provides a suitable additional method to determine identity of fenoxaprop-ethyl. A reference spectrum of fenoxaprop-P-ethyl is given on page 4 of this document. However, in order to assess the enantiomeric purity of the material, the quantitative identity test based on enantioselective HPLC and published in CIPAC Handbook M has to be used.

* 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/.

FENOXAPROP-P-ETHYL EMULSIFIABLE CONCENTRATE

FAO Specification 484.202/EC (JUNE 2010*)

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 (484.202/2010). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated source. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation report (484.202/2010), as PART TWO, forms an integral part of this publication.

1 Description

The material shall consist of technical fenoxaprop-P-ethyl, complying with the requirements of FAO specification 484.202/TC (JUNE 2010), dissolved in suitable solvents, together with any other necessary formulants. It shall be in the form of a stable homogeneous liquid of beige to brownish colour, free from visible suspended matter and sediment, to be applied as an emulsion after dilution in water.

2 Active ingredient

2.1 **Identity tests** (CIPAC 484/EC/M/2, Handbook M, p. 92, 2009 and Handbook J, p. 52, 2000)

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 **Fenoxaprop-P-ethyl content** (CIPAC 484/EC/3.1, Handbook M, p. 92, 2009)

The fenoxaprop-P-ethyl content shall be declared (g/kg or g/l at 20 ± 2ºC, Note 1) 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 at 20 ± 2°C	Tolerance
up to 25	± 15% of the declared content
above 25 up to 100	± 10% of the declared content
above 100 up to 250	± 6% of the declared content
Note: In each range the upper limit is included	

* 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/.

3 Physical properties

3.1 **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
0 h	Initial emulsification complete
0.5 h	"Cream", maximum: 2 ml "Free oil", maximum: trace
2.0 h	"Cream", maximum: 2 ml "Free oil", maximum: 1 mL
24 h	Re-emulsification complete
24.5 h	"Cream", maximum: 2 ml "Free oil", maximum: trace
Note: tests after 24 h are required only where results at 2 h are in doubt	

3.2 **Persistent foam** (MT 47.2, CIPAC Handbook F, p.152, 1995) (Note 2)

Maximum: 40 ml after 1 min.

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 volume of solid and/or liquid which separates shall not be more than 0.3 ml.

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

After storage at 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 3) and the formulation shall continue to comply with the clause for:

- emulsion stability and re-emulsification (3.1).

Note 1 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 2 The mass of the sample to be used in the test should be specified at the highest rate of use recommended by the supplier. The test is to be conducted in CIPAC standard water D.

Note 3 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

FENOXAPROP-P-ETHYL EMULSION, OIL IN WATER

FAO Specification 484.202/EW (JUNE 2010*)

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 (484.202/2010). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TC from the evaluated source. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TC from other sources. The evaluation report (484.202/2010), as PART TWO, forms an integral part of this publication.

1 Description

The formulation shall consist of an emulsion of technical fenoxaprop-P-ethyl, complying with the requirements of FAO specification 484.202/TC (JUNE 2010), in an aqueous phase together with suitable formulants and be of white to beige colour. After gentle agitation, the formulation shall be homogeneous (Note 1) and suitable for dilution in water.

2 Active ingredient

2.1 **Identity tests** (CIPAC 484/EW/M/2.2, Handbook J, p. 58, 2000 and CIPAC 484/EW/M/3.2, Handbook M, p. 92, 2009)

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 **Fenoxaprop-P-ethyl content** (CIPAC 484/EW/M, Handbook J, p. 58, 2000)

The fenoxaprop-P-ethyl content shall be declared (g/kg or 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 at 20 ± 2°C	Tolerance
above 25 up to 100	± 10 % of the declared content
above 100 up to 250	± 6 % of the declared content
Note: In each range the upper limit is included	

3 Physical properties

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

* 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/.

pH range (1 % aqueous dilution): 6.5 to 8.5.

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

Maximum "residue": 9 %.
Maximum rinsed residue: 0.5 %

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

The formulation, when diluted at 30 ± 2°C (Note 3) with CIPAC Standard Waters A and D, shall comply with the following:

Time after dilution	Limits of stability
0 h	Initial emulsification complete
0.5 h	"Cream", maximum: 2 ml "Free oil", maximum: trace
2.0 h	"Cream", maximum: 2 ml "Free oil", maximum: 1 mL
24 h	Re-emulsification complete
24.5 h	"Cream", maximum: 2 ml "Free oil", maximum: trace
Note: tests after 24 h are required only where results at 2 h are in doubt	

3.4 **Persistent foam** (MT 47.2, CIPAC Handbook F, p.152, 1995) (Note 4)

Maximum: 60 ml after 1 min.

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, no separation of particulate or oily matter shall be visible after gentle agitation.

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

After storage 54 ± 2°C for 14 days, the determined average active ingredient content must not be lower than 95% relative to the determined average content found before storage (Note 5) and the formulation shall continue to comply with the clauses for:

- pH range (3.1),
- emulsion stability and re-emulsification (3.3).

Note 1 All physical and chemical tests listed in this specification are to be performed with a laboratory sample taken after the recommended homogenization procedure.

Before sampling to verify the formulation quality, the commercial container must be inspected carefully. On standing, emulsions may develop a concentration gradient which could even result in the appearance of a clear liquid on the top (sedimentation of the emulsion) or on the bottom (creaming up of the emulsion). Therefore, before sampling, the formulation must be homogenized according to the instructions given by the manufacturer or, in the absence of such instructions, by gentle shaking of the commercial container (for example, by inverting the closed container several times). Large containers must be opened and stirred adequately.

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 The formulation should be tested at the highest and lowest rates of use recommended by the supplier.

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

Note 5 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

FENOXAPROP-P-ETHYL

FENOXAPROP-P-ETHYL

FAO/WHO EVALUATION REPORT 484.202/2010

Recommendations

The meeting recommended that:

(i) the specifications for fenoxaprop-P-ethyl TC, EC and EW, proposed by Bayer CropScience, as amended, should be adopted by FAO.

(ii) The specification for fenoxaprop-P-ethyl OD formulations, proposed by Bayer CropScience, should not be adopted by FAO.

Appraisal

Data for fenoxaprop-P-ethyl were submitted by Bayer CropScience in support of new FAO specifications in 2006, together with certain amendments in 2007, for evaluation in 2007.

Fenoxaprop-P-ethyl is no longer under patent in most of the countries where it is registered, though it is still under patent in the USA (until 2010) and Argentina (until 2012). Fenoxaprop-P-ethyl has not been evaluated by the FAO/WHO JMPR and WHO/IPCS. It has been evaluated by US EPA ((EPA 2008), currently under registration review) and by the EU (EU 2008). As a consequence of the EU review, which specifically addressed the fenoxaprop-P-ethyl variant, it was included in the Annex I of Directive 91/414/EEC on 01.01.2009.

Fenoxaprop-P-ethyl is an odourless white solid which melts at 86.5°C. It has a low vapour pressure and water solubility. It is soluble in most organic solvents, although least soluble in *n*-hexane. The octanol/water partition coefficient (log P_{OW} = 4.58) indicates a potential for bioaccumulation. However, the ethyl ester is rapidly hydrolysed *in vivo* (plants, animals, soil and water) liberating fenoxaprop-acid, which has a much higher water solubility and is still herbicidally active.

The Meeting was provided with commercially confidential information of the manufacturing process for fenoxaprop-P-ethyl, the manufacturing specifications for the TC and 5-batch analytical data on the purity and impurities ≥1 g/kg. Mass balances were high (98.9-99.5%) and there were no unidentified impurities. The data were identical to those submitted for registration in Europe (Rapporteur Member State: Austria). The Meeting agreed that none of the impurities should be designated as relevant in specifications.

In addition to the biologically active fenoxaprop-P-ethyl (R-enantiomer) the TC also contains the S-enantiomer (fenoxaprop-M-ethyl), which does not carry herbicidal activity and is regarded as a non relevant impurity. The total amount of fenoxaprop-ethyl in the TC is about 960 g/kg, with an R to S enantiomeric ratio of typically 98 to 2.

The analytical methods for determination of fenoxaprop-P-ethyl in the TC, EW, EC and OD are full CIPAC methods, published in 2000 (TC, EW) and 2009 (EC, OD). The content ("chemical purity") of fenoxaprop-P-ethyl is determined by normal phase

HPLC on a silica column, using UV detection at 227 nm and external standardization. The enantiomeric purity of fenoxaprop-P-ethyl is determined by HPLC on an enantioselective column (a permethylated beta-cyclodextrin bonded on silica gel used in normal phase mode), using UV detection at 237 nm and external standardisation. Identity tests are based on thin layer chromatography, enantioselective HPLC and IR spectroscopy, respectively.

The Meeting considered the proposed specifications which, with the exception of that for OD, were generally in accordance with the requirements of the Manual (FAO/WHO 2006).

TC. The specification was accepted as proposed.

EC. The Meeting requested specification limits for emulsion stability after 2 h, as required in CIPAC MT 36.3.

EW. The Meeting requested specification limits for emulsion stability after 2 h, as required in CIPAC MT 36.3.

The Meeting questioned the proposed high limit for pourability and the need for the guideline maximum limit (60 ml) for persistent foam of EW formulations. The manufacturer provided additional QC and registration data, showing that the values were necessary and that the limits were not considered to pose unacceptable problems for users and the Meeting accepted the limits.

The Meeting noticed that it should be clearly stated in the specification for which concentration the pH range is valid (undiluted formulation or for a dilution of 1%, as either determination is possible according to CIPAC MT 75.3).

The Meeting also questioned the suitability of the upper limit for pH range, noting that hydrolysis of fenoxaprop-P-ethyl is rapid at pH 9 (half-life = 0.6 days), which is close to the upper specified limit. However, due to the low solubility in water, it can be assumed that fenoxaprop-P-ethyl is well protected in the oil phase.

OD. The Meeting noted that OD formulations containing fenoxaprop-P-ethyl are mixed formulations in which fenoxaprop-P-ethyl is present as a solution in the oil phase while one or more other active ingredients which are sparingly soluble in the oil phase is/are present in dispersed particulate form. Therefore, the definition of an OD formulation is not met by fenoxaprop-P-ethyl. In consequence, the Meeting concluded that an OD specification could not be applied to fenoxaprop-P-ethyl but suggested that OD specifications could be developed for active ingredients present as particulates in OD formulations containing fenoxaprop-P-ethyl.

SUPPORTING INFORMATION

FOR

EVALUATION REPORT 484.202/2007

Uses

Fenoxaprop-P-ethyl is the herbicidally active *R*-enantiomer of the racemic substance fenoxaprop-ethyl. It is an aryloxyphenoxypropionate herbicide, used for post-emergence control of annual grass weeds, from the two-leaf stage up to full tillering, in spring and winter wheat, spring and winter barley, rice, turf and various broadleaf crops. The mode of action and reason for its selectivity is by inhibition of the Acetyl-CoA-carboxylase in grasses, the enzyme catalyzing the first step in the *de novo* synthesis of fatty acids. The depletion of fatty acids supply blocks the production of phospholipids essential in the cell growth of sensitive plants. Incorporation of a safener to improve the selectivity is required for uses in cereals and rice, as these crops also belong to the family of grasses.

Identity of the active ingredient

ISO common name

Fenoxaprop-P (ISO 1750 published, refers to the *R*-enantiomer of the acid)

Variant: Fenoxaprop-P-ethyl (the ethyl ester of fenoxaprop-P)

Synonyms

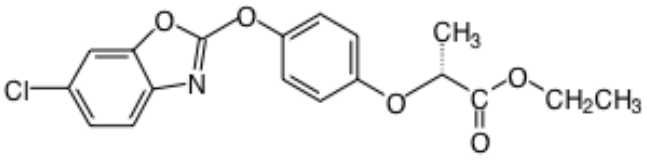
none

Chemical name(s)

IUPAC (*R*)-2-[4-(6-chlorobenzoxazol-2-yloxy)phenoxy]propionic acid ethyl ester

CA ethyl (*R*)-2-[4-[(6-chloro-2-benzoxazolyl)oxy]phenoxy]propanoate

Structural formula



Molecular formula

$C_{18}H_{16}ClNO_5$

Relative molecular mass

361.8

CAS Registry number

71283-80-2

CIPAC number

484.202

Identity tests

HPLC retention time, TLC, IR spectrum

Physico-chemical properties of fenoxaprop-P-ethyl

Table 1. Physico-chemical properties of pure fenoxaprop-P-ethyl

Parameter	Value(s) and conditions	Purity %, chemical/ optical	Method	Reference
Vapour pressure	5.3×10^{-7} Pa at 20°C (extrapolated from measurements at 70-110°C)	99.0/98.7	OECD 104, vapour pressure balance	M-125880-01-1
Melting point	86.5°C	99.7/99.5	EEC A1	M-187345-01-1
Decomposition temperature	>260°C	~93%	EEC A1	M-117569-01-1, M-120377-01-1
Solubility in water	0.7×10^{-3} g/l at 20°C [pH 5.8], no pH influence	99.0/98.7	OECD 105, column elution method	M-117981-01-1, M-126592-01-1
Octanol/water partition coefficient	log P_{OW} = 4.58 at 30°C	98.9/98.4	OECD 117	M-138162-01-1
Hydrolysis characteristics	Half-life at 25°C: 2.8 days at pH 4 19.2 days at pH 5 23.2 days at pH 7 0.6 days at pH 9	99.5 (racemate) >98.7 (radiochemical)	OECD 111	M-215094-01-1
Photolysis characteristics	Photolysis in sterile buffer (pH 5, 0.33 mg a.i./l): sun test II (3.05x sunlight intensity): DT_{50} = 210.5 h DT_{90} = 699.2 h sun test III (2.84x sunlight intensity): DT_{50} = 259.4 h DT_{90} = 861.7 h Estimated half-live (June, at 52 ° North, sea level), assuming 12 h sunlight per day: sun test II: 53.5 d sun test III 61.4 d	98 (radiochemical)	EPA 161-2	M-132306-02-1
Dissociation characteristics	Does not dissociate	-	-	

Table 2. Chemical composition and properties of technical fenoxaprop-P-ethyl (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 98.9-99.5% and no unidentified impurities were reported.
Declared minimum fenoxaprop-P-ethyl content	920 g/kg
Relevant impurities ≥1 g/kg and maximum limits for them	None
Relevant impurities <1 g/kg and maximum limits for them:	None
Stabilizers or other additives and maximum limits for them:	None
Melting or boiling temperature range of the TC	Melting point: 80-84°C (reference M-117985-01-1) Method: CIPAC MT 2

Hazard summary

Fenoxaprop-P-ethyl has not been classified according to hazard by WHO (WHO 2004), it has not been evaluated by IPCS or FAO/WHO JMPR, but it has been evaluated for registration by the EU (EU 2008) and is currently under registration review by US EPA (EPA 2008).

Formulations and co-formulated active ingredients

Fenoxaprop-P-ethyl EC and EW for use on cereals contain mefenpyr-diethyl as a safener, whereas the EC and EW for use on broad-leaved crops (mainly soybeans), turf or rice do not contain the safener. Fenoxaprop-P-ethyl may also be co-formulated with diclofop-methyl or isoxadifen-ethyl.

Methods of analysis and testing

The analytical methods for the active ingredient (including identity tests) are CIPAC methods (CIPAC Handbook J, 2000). The chemical purity of fenoxaprop-P-ethyl is determined by normal phase HPLC, using UV detection at 227 nm and external standardization. The enantiomeric purity of fenoxaprop-P-ethyl is determined by liquid chromatography on an enantioselective stationary phase using UV detection at 237 nm and external standardization. The methods have also been validated for analysis of the EC and OD formulations (CIPAC Handbook M, 2009).

Methods for the determination of impurities are based on reversed-phase HPLC, with gradient elution and UV detection at 230 nm.

Test methods for determination of physico-chemical properties of the pure and technical grade active ingredient were OECD, EPA, EC, while those for the formulations were CIPAC, as indicated in the specifications.

Physical properties

The physical properties, the methods for testing them and the limits proposed for the EC and EW formulations comply with the requirements of the FAO/WHO manual (FAO/WHO 2006) [M-360693-02-1].

Containers and packaging

No special requirements for containers and packaging have been identified.

Expression of the active ingredient

The active ingredient is expressed as fenoxaprop-P-ethyl.

ANNEX 1

HAZARD SUMMARY PROVIDED BY THE PROPOSER

Note: the proposer provided written confirmation that the toxicological data included in the following summary were derived from fenoxaprop-P-ethyl having impurity profiles similar to those referred to in Table 2, above.

Table A. Toxicology profile of fenoxaprop-P-ethyl technical material, based on acute toxicity, irritation and sensitization

Species	Test	Duration and conditions	Result	Reference
Rat, Wistar (m,f)	Acute oral	OECD 401; 2000, 3150, 4000, 5000 mg/kg bw; purity 90.0%	LD_{50} within the range 3150-4000 mg/kg bw	M-135864-01-1
Mouse, NMRI (m,f)	Acute oral	OECD 401; 5000 mg/kg bw; purity ~95.6%, inactive enantiomer <1%	LD_{50} >5000 mg/kg bw	M-118995-01-1
Rat, Wistar (m,f)	Acute dermal	OECD 402; 2000 mg/kg bw; purity 90.0%	LD_{50} >2000 mg/kg bw	M-117843-01-1
Rat, Wistar (m,f)	Acute inhalation	OECD 403; 1224 mg/L; purity 90.0%	LC_{50} >1224 mg/m^3*	M-130946-01-1
Rabbit, NZ White	Skin irritation	OECD 404; purity ~95.6%, inactive enantiomer <1%	Non-irritant	M-117880-01-1
Rabbit, NZ White	Eye irritation	OECD 405; purity ~95.6%, inactive enantiomer <1%	Non-irritant	M-117842-01-1
Guinea pig, Pirbright White (f)	Skin sensitization	OECD 406 (Magnussun & Kligman); purity ~95.6%, inactive enantiomer <1%	Sensitizer	M-118976-01-1
Guinea pig, Pirbright White (f)	Skin sensitization	OECD 406 (Buehler test); purity ~95.6%, inactive enantiomer <1%	Inconclusive	M-117860-01-1
Guinea pig, Pirbright White (f)	Skin sensitization	OECD 406 (Buehler test); purity ~95.6%, inactive enantiomer <1%	Non-sensitizer	M-135807-01-1

* Highest concentration achievable.

None of the tests of acute toxicity resulted in irreversible damage to health.

Table B. Toxicology profile of fenoxaprop-P-ethyl technical material, based on repeated administration (sub-acute to chronic)

Species	Test	Duration and conditions	Result	Reference
Rat, Wistar (m,f)	Oral (feeding)	OECD 407 (4-week); 0, 20, 80, 320, 1280, 5120 ppm; purity ~95.6%, inactive enantiomer <1%	NOAEL = 6 mg/kg bw/d LOEL = 26 mg/kg bw/d	M-118344-01-1
Rat, Wistar (m,f)	Oral (feeding)	OECD 407 (13-week); 0, 10, 80, 640 ppm; purity ~95.6%, inactive enantiomer <1%	NOAEL = 0.7 mg/kg bw/d LOEL = 5.8 mg/kg bw/d	M-118342-01-1
Mouse, NMRI (m,f)	Oral (feeding)	OECD 407 (4-week); 0, 20, 80, 320, 1280 ppm; purity ~95.6%, inactive enantiomer <1%	NOAEL = 14 mg/kg bw/d LOEL = 56 mg/kg bw/d	M-118334-01-1
Mouse, NMRI (m,f)	Oral (feeding)	OECD 407 (13-week); 0, 20, 80, 320, 1280 ppm; purity ~95.6%, inactive enantiomer <1%	NOAEL = 1.4 mg/kg bw/d LOEL = 11.9 mg/kg bw/d	M-118343-01-1
Dog, Beagle (m,f)	Oral (feeding)	OECD 407 (4-week); 0, 80, 320, 1280 ppm; purity ~95.6%, inactive enantiomer <1%	NOAEL = 56 mg/kg bw/d (highest dose tested)[1]	M-118335-01-1
Dog, Beagle (m,f)	Oral (feeding)	OECD 408 (13-week); 0, 80, 400, 2000 ppm; purity ~95.6%, inactive enantiomer <1%	NOAEL = 15.6 mg/kg bw/d LOEL = 77.7 mg/kg bw/d	M-118393-01-1
Rat, Wistar (m,f)	Inhalation	OECD 412, 40 d; 0, 15, 70, 300 mg/m^3; purity ~95.6%, inactive enantiomer <1%	NOAEL = 70 mg/m^3 LOEL = 300 mg/m^3	M-123650-01-1
Rat, Wistar (m,f)	Dermal	OECD 410, 30 d; 0, 10, 20, 100, 500 mg/kg bw/d; purity ~95.6%, inactive enantiomer <1%	NOAEL = 100 mg/kg bw/d LOEL = 500 mg/kg bw/d	M-123662-01-2
Rat, Wistar (m,f)	Oral (feeding), chronic, carcinogenicity	OECD 453 with interim sacrifices and full histopathological examination at 6, 12, 24, 28 months; 0, 5, 30, 180 ppm; purity 94% (racemic mixture)[2]	NOAEL = 1.6 mg/kg bw/d LOEL = 9.1 mg/kg bw/d Not carcinogenic	M-110046-01-1

[1] Study of limited value due to the small number of animals tested.

[2] Long-term studies and reproduction study (2-generation) were conducted with the racemic mixture, AE F033171, based on the fact that fenoxaprop-P-ethyl and racemic fenoxaprop-ethyl showed similar toxicity profile in sub-acute and sub-chronic toxicity studies.

Table B. Toxicology profile of fenoxaprop-P-ethyl technical material, based on repeated administration (sub-acute to chronic)

Species	Test	Duration and conditions	Result	Reference
Mouse, NMRI (m,f)	Oral (feeding), carcinogenicity	OECD 451, 24 months with interim sacrifice at 12 months; 0, 40, 115, 320 ppm; purity 96.8% (racemic mixture)[1]	NOAEL = 5.7 mg/kg bw/d LOEL = 16.6 mg/kg bw/d Increased incidence of hepatocellular tumours due to peroxisome proliferation (rodent-specific)	M-141216-01-1
Dog, Beagle (m,f)	Oral (feeding)	OECD 452 (2 year); 0, 3, 15, 75 ppm; purity 94% (racemic mixture)[1]	NOAEL = 0.9 mg/kg bw/d LOEL = 4.6 mg/kg bw/d	M-109895-02-1
Rat, Wistar (m,f)	Oral (feeding), 2-generation reproduction	USEPA 83-3; 0, 5, 30, 180 ppm; purity 97.2% (racemic mixture)[1]	NOAEL (parent) = 2.5 mg/kg bw/d NOAEL (pup development) = 5 mg/kg bw/d NOAEL (reproduction) = 15 mg/kg bw/d (highest dose tested) No impairment of fertility or reproductive performance	M-112616-02-1
Rat, Wistar	Oral (gavage), developmental toxicity	OECD 414 (May 1981); 0, 10, 32, 100 mg/kg bw/d; purity >99%[2]	NOAEL (dams) = 32 mg/kg bw/d NOAEL (pups) = 10 mg/kg bw/d Not teratogenic	M-114591-01-1
Rat, Wistar	Oral (gavage), embryotoxicity, post-natal development toxicity	OECD 414 (May 1981) with 21-d post-natal development period; 0, 10, 32, 100 mg/kg bw/d; purity ~95.6%, inactive enantiomer <1%	NOAEL (dams) = 32 mg/kg bw/d NOAEL (offspring) = 100 mg/kg bw/d	M-117538-01-1
Rabbit, Himalayan	Oral (gavage), developmental toxicity	OECD 414 (May 1981); 0, 10, 32, 100 mg/kg bw/d; purity >99%[2]	NOAEL (dams) = 32 mg/kg bw/d NOAEL (pups) = 100 mg/kg bw/d Not teratogenic	M-113735-01-2

Fenoxaprop-P-ethyl belongs to a class of compounds known to interfere with lipid metabolism in rodents, leading to enhanced lipid turnover and peroxisome proliferation in liver cells. Therefore, main effects observed after repeated administration included changes in clinical chemistry (lipid metabolism and liver enzymes) of liver and kidney, the main target organs. Liver tumours in mice were linked to peroxisome proliferation and thus seen as rodent-specific. There was no indication of any neurotoxic effect in any of the studies conducted with fenoxaprop-P-ethyl.

[1] Long-term studies and reproduction study (2-generation) were conducted with the racemic mixture, AE F033171, based on the fact that fenoxaprop-P-ethyl and racemic fenoxaprop-ethyl showed similar toxicity profile in sub-acute and sub-chronic toxicity studies.

[2] Only chemical purity determined. Content of the *S*-enantiomer believed to be <4%.

Table C. Mutagenicity profile of fenoxaprop-P-ethyl technical material, based on *in vitro* and *in vivo* tests

Species	Test	Duration and conditions	Result	Reference
S. typhimurium TA98, TA 100, TA 1535, TA 1537*; E. coli* WP2uvrA	*In vitro* mutagenicity (Ames test); OECD 471 & 472	0, 4, 20, 100, 500, 2500, 5000 µg/plate (in DMSO), ± S9 mix; purity 88.7%	Negative ±S9	M-133836-01-1
Schizosaccharomyces plombe P1	*In vitro* forward mutation; no guideline available	0, 2.5, 5, 10, 20, 40 µg/ml (in DMSO), ± S9 mix; purity ~95.6%, inactive enantiomer <1%	Negative ±S9	M-114840-01-1
Chinese hamster V79 cells	*In vitro* gene mutation; OECD 476	0, 6.25, 12.5, 25, 50, 100 µg/ml (in DMSO), ± S9 mix; purity ~95.6%, inactive enantiomer <1%	Negative ±S9	M-114841-01-1
Human lymphocytes	*In vitro* chromosome aberration; OECD 473	0, 50, 79, 125 µg/ml (in DMSO), ± S9 mix; purity ~95.6%, inactive enantiomer <1%	Negative ±S9	M-117024-01-1
Saccharomyces cerevisiae D4	*In vitro* mitotic gene conversion; EEC directive 79/83, Annex V, part B	0, 1.25, 2.5, 5, 10, 20 µg/ml (in DMSO), ± S9 mix; purity ~95.6%, inactive enantiomer <1%	Negative ±S9	M-114842-01-1
Primary rat hepatocytes	*In vitro* unscheduled DNA synthesis; OECD 482	0, 2.51, 5.02, 5, 10, 25.1, 50.2, 100, 201, 301 µg/ml (in DMSO); purity ~95.6%, inactive enantiomer <1%	Negative	M-115662-01-1
Mammalian cell line (A549)	*In vitro* unscheduled DNA synthesis; OECD 482	0, 0.1, 0.3, 10, 30, 100 µg/ml (in DMSO), ± S9 mix; purity 88.7%	Negative ±S9	M-134646-01-1
Mouse, NMRI	*In vivo* micronucleus test in bone marrow; OECD 474	0, 1000, 2000 and 4000 mg/kg bw in sesame oil; purity ~95.6%, inactive enantiomer <1%	Negative	M-115073-01-1

Table D. Ecotoxicology profile of fenoxaprop-P-ethyl technical material

Species	Test	Duration and conditions	Result	Reference
Oncorrhynchus mykiss (rainbow trout)	Acute toxicity (dynamic)	OECD 203; 96 h; purity 88.1%	LC_{50} = 0.39 mg/l	M-183992-01-1
Lepomis macrochirus (bluegill sunfish)	Acute toxicity (dynamic)	OECD 203; 96 h; purity 88.1%	LC_{50} = 0.19 mg/l	M-184457-01-1
Daphnia magna (water flea)	Acute toxicity (semi-static)	OECD 202; 48 h; purity 88.1%	EC_{50} = >1.06 µg/l	M-147888-01-1
Pseudokirchneriella subcapitata (green alga) [a]	Effect on growth (static)	OECD 201; 72 h; purity 97.4%	EC_{50} = 0.54 mg/l	M-129715-03-1
Eisenia foetida (earthworm)	Acute toxicity (artificial soil)	OECD 207; 14 d; purity 97.2%	LC_{50} >1000 mg/kg dry soil	M-121462-01-1
Apis mellifera (honey bee)	Acute toxicity (contact)	OECD 214; 48 h; purity 96.2%	LD_{50} >200 µg/bee	M-194261-01-1
Apis mellifera (honey bee)	Acute toxicity (oral)	OECD 213; 48 h; purity 96.2%	LD_{50} >199 µg/bee	M-194261-01-1
Coturnix coturnix (Japanese quail)	Acute toxicity (oral)	USEPA FIFRA 71-1; purity 95.6%	LD_{50} ~2000 mg/kg bw	M-118746-01-1
Anas platyrhynchos (mallard duck)	Acute toxicity (oral)	USEPA FIFRA 71-1; purity 95.6%	LD_{50} >2000 mg/kg bw	M-118214-01-1
Coturnix coturnix (Japanese quail)	Acute toxicity (5 d dietary)	OECD 205; purity 95.6%	LC_{50} >5000 mg/kg diet	M-118509-01-1
Anas platyrhynchos (mallard duck)	Acute toxicity (5 d dietary)	OECD 205; purity 95.6%	LC_{50} >5000 mg/kg diet	M-118216-01-1

[a] Previous name (used in the report): *Selenastrum capricornutum*

On an acute basis, Fenoxaprop-P-ethyl is considered to be very toxic to aquatic organisms (fish and green algae).

ANNEX 2. References

Bayer CropScience AGREDOC number or other reference	Year and title of report or publication details
M-109895-02-1	1987. Toxicological testing by repeated oral administration to Beagle dogs for 2 years of Hoe 33171.
M-110046-01-1	1985. Combined chronic toxicity and carcinogenicity study in rats (24 and 28 month feeding studies) (summary) and evaluation of the results; Hoe 33171.
M-112616-02-1	1987. Multiple generation study in rats (report part I) on Hoe 033171 substance, technical grade.
M-113735-01-2	2006. Embryotoxicity in Himalayan rabbits following oral administration Hoe 046360.
M-114591-01-1	1985. Embryotoxicity in Wistar rats following oral administration Hoe 046360 active ingredient technical.
M-114840-01-1	1986. Forward mutation in Schizosaccharomyces plombe P1 Hoe 046360 substance, technical.
M-114841-01-1	1986. Gene mutation in Chinese hamster V79 Cells Hoe 046360 substance, technical.
M-114842-01-1	1986. Mitotic gene conversion in S. cerevisiae D4 test substance: Hoe 046360 substance, technical.
M-115073-01-1	1986. Micronucleus test in male and female NMRI mice after oral administration Hoe 046360 substance, technical.
M-115662-01-1	1986. Rat primary hepatocyte unscheduled DNA synthesis assay of Hoe 046360 substance, technical.
M-117024-01-1	1987. Chromosome aberrations in human lymphocytes cultured in vitro Hoe 046360 substance, technical.
M-117538-01-1	1987. Embryotoxicity and effects on post-natal development in Wistar rats oral administration Hoe 046360 active ingredient
M-117569-01-1	1987. Decomposition point of Hoe 046360 substance, technical.
M-117842-01-1	1985. Primary eye irritation in the rabbit Hoe 046360 active ingredient.
M-117843-01-1	1985. Acute dermal toxicity in the male and female Wistar rat Hoe 046360 active ingredient
M-117860-01-1	1986. Sensitizing properties in the Pirbright-White guinea pig according to the technique of Buehler Hoe 046360 active ingredient technical.
M-117880-01-1	1985. Primary dermal irritation in the rabbit Hoe 046360 active ingredient technical.
M-117981-01-1	1987. Solubility in water.
M-117985-01-1	1987. Melting point of Hoe 046360 substance, technical.
M-118214-01-1	1986. Acute oral toxicity in the male and female mallard duck (Anas platyrhynchos) Hoe 046360 active ingredient.
M-118216-01-1	1986. 8-day dietary LC50 test in the mallard duck (Anas platyrhynchos) Hoe 046360 active ingredient technical.
M-118334-01-1	1987. Repeated-dose oral toxicity: 28-day feeding study in mice Hoe 046360 technical.
M-118335-01-1	1987. Repeated-dose oral toxicity: 28-day feeding study in dogs Hoe 046360 technical.
M-118342-01-1	1987. Sub-chronic oral toxicity 13-week feeding study in rats Hoe 046360 technical.
M-118343-01-1	1987. Sub-chronic oral toxicity 13-week feeding study in mice Hoe 046360 technical.
M-118344-01-1	1987. Repeated-dose oral toxicity: 28-day feeding study in rats Hoe 046360 technical.
M-118393-01-1	1987. Sub-chronic oral toxicity 13-week feeding study in beagle dogs Hoe 046360 technical.

Bayer CropScience AGREDOC number or other reference	Year and title of report or publication details
M-118509-01-1	1986. 8-day dietary LC50 test in the Japanese quail (Coturnix coturnix japonica) Hoe 046360 active ingredient technical.
M-118746-01-1	1987. Acute oral toxicity in the male and female Japanese quail (Coturnix coturnix japonica) Hoe 046360 active ingredient technical.
M-118976-01-1	1986. Sensitizing properties in the Pirbright-White guinea pig in a Maximisation test Hoe 046360 active ingredient technical.
M-118995-01-1	1985. Acute oral toxicity in the male and female NMRI mouse Hoe 046360 active ingredient technical.
M-120377-01-1	1988. Boiling point of Hoe 046360 substance, pure.
M-121462-01-1	1989. Effect to Eisenia fetida (earthworm) in a 14 day artificial soil test (method OECD) Hoe 046360 substance, technical.
M-123650-01-1	1989. Subchronic inhalation toxicity (28 applications within 40 days) in male and female Wistar rats Hoe 046360 substance, technical.
M-123662-01-2	1988. Subchronic dermal toxicity (21 treatments in 30 days) in the Wistar rat Hoe 046360 active ingredient.
M-125880-01-1	1987. Vapour pressure of Hoe 046360 substance, pure.
M-126592-01-1	1990. Solubility in water (addendum to report CP 050/87) Code: Hoe 046360.
M-129715-03-1	1991. Effect to Selenastrum capricornutum (green alga) in an algal assay bottle test (method EPA) Fenoxaprop-P-ethyl substance, technical.
M-130946-01-1	1991. Acute aerosol inhalation toxicity in the male and female SPF Wistar rat 4-hour LC50 Fenoxaprop-P-ethyl substance, technical.
M-135807-01-1	1992. Sensitizing properties in the Pirbright-White guinea pig according to the technique of Buehler Fenoxaprop-P-ethyl substance technical.
M-135864-01-1	1992. Acute oral toxicity in the male and female Wistar rat Fenoxaprop-P-ethyl substance, technical.
M-138162-01-1	1992. Determination of the partition coefficient n-octanol/water by HPLC (according to OECD Guideline #117) Hoe 046360.
M-132306-02-1	1993. Photodegradation in surface water, sterile buffer and distilled water of Fenoxaprop-P-ethyl Hoe 046360-14C.
M-133836-01-1	1994. Mutagenic potential in strains of Salmonella typhimurium (Ames test) and Escherichia coli Hoe 046360 substance, technical
M-134646-01-1	1995. Detection in the unscheduled DNA synthesis test in mammalian cells in vitro Hoe 046360 substance, technical.
M-141216-01-1	1996. Carcinogenicity study in mice Fenoxaprop-ethyl substance, technical.
M-147888-01-1	1998. 48 hour acute toxicity to Daphnia magna, in a static renewal system Fenoxaprop-P-ethyl technical.
M-183992-01-1	1999. The 96 hour acute toxicity to the rainbow trout, Oncorhynchus mykiss, in a flow through system Fenoxaprop-P-ethyl technical.
M-184457-01-1	1999. The 96 hour acute toxicity to the bluegill sunfish, Lepomis macrochirus, in a flow through system Fenoxaprop-P-ethyl technical.
M-187345-01-1	1999. Melting point / melting range Fenoxaprop-P-ethyl substance, pure.
M-194261-01-1	2000. Toxicity to the honeybee Apis mellifera L. (laboratory) according to EPPO Guideline No. 170 (1992).
M-215094-01-1	2002. (14C)-fenoxaprop-ethyl: Hydrolysis at five different pH values.
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M-360693-01-1	Manual on the development and use of FAO and WHO specifications for pesticides, March 2006 revision of the 1st edition. FAO, Rome, March 2006; WHO, Geneva, March 2006 (internet publications).
EPA 2008	2008. Fenoxaprop-p-ethyl Final Work Plan (FWP) Registration review February 2008. Available at http://www.epa.gov/oppsrrd1/registration_review/fenoxaprop/index.htm
WHO 2004	The WHO recommended classification of pesticides by hazard and guidelines to classification 2004. WHO, Geneva, 2005.