European Commission

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Fenoxaprop-P-ethyl

Volume 3 – B.5 (PPP) – CHA 4960

Rapporteur Member State: Austria
Co-Rapporteur Member State: Finland

Version History

When	What
2005/April	Initial DAR of the active substance. CHA 4960 was not the representative formulation
2018/March	DRAR

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B.5. METHODS OF ANALYSIS

Fenoxaprop-P-ethyl is a herbicide active substance and was included into Annex I of Directive 91/414 on 1st January 2009 (Directive 2008/66/EC).
This dossier contains exclusively data on the new representative formulation from Cheminova A/S which were not submitted at the time of the Annex I inclusion of fenoxaprop-P-ethyl under Directive 91/414/EEC and which were therefore not evaluated during the first EU review.

B.5.1. METHODS USED FOR THE GENERATION OF PRE-AUTHORISATION DATA

B.5.1.1. Analysis of the plant protection product

B.5.1.1.1. Methods for the determination of the active substance and/or variant in the plant protection product

An analytical method has been developed and validated for the determination of the active substance, fenoxaprop-P-ethyl, in CHA 4960.

The following analytical methods for the determination of the active substance in the plant protection product performed on CHA 4960 have not previously been reviewed and are provided in support of this assessment.

Reference:	**Analytical Method VAM 074-01: Determination of Cloquintocet-mexyl (CAS No. 99607-70-2) and Fenoxaprop-P-ethyl (CAS No. 66441-23-4) in EW formulation**
Author(s), year:	Hinz. B. 2006
Report/Doc. number:	VAM 074-01 (vers. 4)
Guideline(s):	--
GLP:	yes

Reference:	**Validation of analytical method VAM 074-01 for Determination of Cloquintocet-mexyl (CAS No. 99607-70-2) and Fenoxaprop-p-ethyl (CAS No. 66441-23-4) in EW Formulations**
Author(s), year:	Hinz. B. 2005
Report/Doc. number:	VAL 074-01
Guideline(s):	SANCO/3030/99
GLP:	yes

Principle of the Method:
Determination of fenoxaprop-P-ethyl (not enantioselective) and cloquintocet-mexyl in the formulated product Fenoxaprop-p-ethyl 69 g/L EW (CHA 4960) was conducted using isocratic HPLC (eluents: Hexane/THF; 90/10 % v/v), with a Phenomenex Phenosphere 5 CN 80A (150 x 4.6 mm, 5 µm) column and DAD detector. Quantitation was by external standard method at 245 nm.

Validation data are summarised in Table B.5.1.1-1

Table B.5.1.1-1: Summary of validation data

Analyte	Calibration* (linear between) [mg/L]	Levels [% w/w]	Accuracy Recovery n = 4 x 2	Levels [% w/w]	Precision Repeatability RSD [%] (n = 5)	Specificity	LOQ	Reference
Fenoxaprop-ethyl sum of R and S isomer	99 - 428 (n = 3 x 2) r^2 = 1.000	6.6	101.9	7.11	0.25 RSDr : 2.0	No interference	--	Hinz. B. 2005 VAL 074-01
				98.6	0.17 RSDr : 1.34			
Cloquintocet-mexyl	47 - 206 (n = 3 x 2) r^2 = 0.99999	3.4	102	3.41	0.16 RSDr : 2.23			
				98.0	0.61 RSDr : 1.34			

* Plot and equation is available

Conclusion

Analytical Method VAM 074-01 was used to determine fenoxaprop-P-ethyl and cloquintocet-mexyl in the formulated product fenoxaprop-P-ethyl 69 g/L EW (CHA 4960). The analytical method has been successfully validated according to guidance document SANCO 3030/99 rev. 4.

Reference:	**Analytical Method VAM 148-01: Determination of Fenoxaprop-P-ethyl (R-enantiomer) in Fenoxaprop EW formulation**
Author(s), year:	Hinz. B. 2008
Report/Doc. number:	VAM 148-01 (vers. 1)
Guideline(s):	--
GLP:	yes

Reference:	**Validation of analytical method VAM 148-01 for Determination of Fenoxaprop-p-ethyl (CAS No. 71283-80-2) in Fenoxaprop EW Formulation**
Author(s), year:	Hinz. B. 2008
Report/Doc. number:	VAL 148-01
Guideline(s):	SANCO/3030/99
GLP:	yes

Principle of the Method:

Fenoxaprop-P-ethyl is determined with HPLC using a chiral column with UV detection. In detail, formulated product (0.2 g) was dissolved in tetrahydofuran (3 mL) and chlorobutane (2 mL) and mixed, before an aliquot (200 µL) was diluted with chlorobutane (5 mL). Final determination was by isocratic elution (n-hexane: ethanol (60:40 v/v) High Performance Liquid Chromatography with Diode Array Detection (HPLC-DAD) on a Chiracel OK (250 × 4.6 mm) column with a Chircel OK (50 × 4 mm guard column). Quantification was done by external standard using peak areas at 240 nm.

Validation data are summarised in Table B.5.1.1-2

Table B.5.1.1-2: Summary of validation data

Analyte	Calibration* (linear between) [mg/L]	Levels 80-120% nominal [% w/w]	Accuracy Recovery	Level [% w/w]	Precision Repeatability RSD [%] (n = 5)	Specificity	LOQ	Reference
Fenoxaprop-ethyl R isomer	58 - 178 (n = 6) r^2 = 0.99994	5.6	102 (n = 2)	7.3	0.33 RSDr : 2.0	No interference	--	Hinz. B. 2005 VAL 148-01
		6.7	103 (n = 4)					
		8.0	102 (n = 2)					

* Plot and equation is available

Conclusion

Analytical Method VAM 074-01 was used to determine fenoxaprop-P-ethyl enantioselective in the formulated product CHA 4960. The analytical method has been successfully validated according to guidance document SANCO 3030/99 rev. 4.

Applicability of existing CIPAC methods

CIPAC method 484/EW/M/-, CIPAC Handbook J, page 51, for the determination of fenoxaprop-P-ethyl in emulsion, oil in water (EW) formulations, is applicable.

B.5.1.1.2. Methods for determination of relevant impurities identified in the technical material or which may be formed during manufacture of the plant protection product or from degradation of the plant protection product during storage

Not applicable as there are no relevant impurities in fenoxaprop-P-ethyl technical material which are formed during manufacture of the Plant Protection Product or from degradation during storage stability.

B.5.1.1.3. Methods for the determination of relevant co-formulants or components of co-formulants, where required by the national competent authorities

The analytical method described under (a) above allows the determination of cloquintocet-mexyl. The method is fully validated. There are no other relevant co-formulants or components of co-formulants in the composition of this Plant Protection Product.

B.5.1.2. Methods for the determination of residues

Following guidance from SANCO/12592/2012 “Template Assessment Report” and SANCO/10181/2013 cross reference as appropriate is made to the Supplementary Dossier of the active substance fenoxaprop-P-ethyl. All data and evaluations regarding the active substance fenoxaprop-P-ethyl are provided in Part CA B.5.

B.5.1.2.1. Methods in soil, water, sediment, air and any additional matrices used in support of environmental fate studies

No additional methods of analysis for the support of environmental fate studies were developed. Please refer to Part CA B.5.

B.5.1.2.2. Methods in soil, water and any additional matrices in support of efficacy studies

No additional methods of analysis for the support of efficacy studies were developed. No detailed study package of efficacy is submitted or is foreseen for evaluation during renewal of approval.

B.5.1.2.3. Methods in feed, body fluids and tissues, air and any additional matrices used in support of toxicological studies

No additional methods of analysis for the support of operator, worker, resident and bystander exposure studies were developed. Please refer to Volume 3 Part CA B.5.

B.5.1.2.4. Methods in or on plants, plant products, processed food commodities, food of plant and animal origin, feed and any additional matrices used in support of residues studies

No additional methods of analysis for the support of dietary exposure- and human safety studies were developed. Please refer to Volume 3 Part CA B.5.

B.5.1.2.5. Methods in soil, water, sediment, feed and any additional matrices used in support of ecotoxicology studies

Reference:	**Acute Toxicity of Fenoxaprop-P-ethyl 69 g/L EW to Rainbow Trout (*Oncorhynchus mykiss*) in a 96-hour Semi Static Test.**
Author(s), year:	[redacted] (2005)
Report/Doc. number:	Project 24783230 / 98 FPE
Guideline(s):	Not stated. However, the method design and validation meet the requirements of SANCO/3029/99 rev.4.
GLP:	yes

Principle of the method

Samples of Fenoxaprop-P-ethyl 69 g/L EW , CHA 4960 were shaken with n-hexane. The organic extracts were dried with Na_2SO_4 which was washed afterwards with n-hexane. The combined organic phases were evaporated and redissolved in mobile phase (55% acetonitrile / 45% pure water pH 3)
The quantification of the active ingredient fenoxaprop-P-ethyl was performed using isocratic liquid chromatography (HPLC-UV-Vis) at 200 nm. Column: Ultrasep ES RP 18e Pharm (125 x 3 mm)

Validation

Limit of quantification
0.028 mg fenoxaprop-P-ethyl /L
0.014 mg cloquintocet-mexyl /L

Linearity
The calibration range was measured between 0.1 to 10 mg/L (n = 9) with a regression coefficient of 0.9998 (fenoxaprop-P-ethyl and cloquintocet-mexyl).

Specificity
Control data are reported to be <LOD.

Recovery (Accuracy) - Precision

Fenoxaprop-P-ethyl [mg/L]	Recovery rate [%]	RSD [%]	n
0.028	99	10	6
0.071	98	2.5	6
0.71	96	5	6

Cloquintocet-mexyl [mg/L]	Recovery rate [%]	RSD [%]	n
0.014	95	6	6
0.034	118	8	6
0.34	122	12	6

Conclusion

Although mean recoveries for cloquintocet-mexyl are outside the range of 70-110% the analytical method is fit for purpose covering the LOQs mentioned.

Reference:	**Revised Final Report No. 1 Acute Toxicity of Fenoxaprop-P-ethyl 69 g/L EW to *Daphnia magna* in a Semi Static 48-hour Immobilization Test**
Author(s), year:	Grade R., Wydra V. (2005)
Report/Doc. number:	Project 24782220 / 97 FPE
Guideline(s):	Not stated. However, the method design and validation meet the requirements of SANCO/3029/99 rev.4.
GLP:	yes

Principle of the method

Samples of Fenoxaprop-P-ethyl 69 g/L EW , CHA 4960 were shaken with n-hexane. The organic extracts were dried with Na_2SO_4 which was washed afterwards with n-hexane. The combined organic phases were evaporated and redissolved in mobile phase (55% acetonitrile / 45% pure water pH 3)
The quantification of the active ingredient fenoxaprop-P-ethyl and cloquintocet-mexyl was performed using isocratic liquid chromatography (HPLC-UV-Vis) at 200 nm. Column: Ultrasep ES RP 18e Pharm (125 x 3 mm)

Validation

Limit of quantification
0.028 mg fenoxaprop-P-ethyl /L
0.014 mg cloquintocet-mexyl /L

Linearity
The calibration range was measured between 0.1 to 10 mg/L (n = 9) with a regression coefficient of 0.9996 for fenoxaprop-P-ethyl and 0.9994 for cloquintocet-mexyl.

Specificity
Control data are reported to be <LOD.

Recovery (Accuracy) - Precision

Fenoxaprop-P-ethyl [mg/L]	Recovery rate [%]	RSD [%]	n
0.028	97	9	8
0.071	97	4	8
0.34	107	15	8

Cloquintocet-mexyl [mg/L]	Recovery rate [%]	RSD [%]	n
0.014	105	23	8
0.034	108	19	8
0.34	107	12	8

Conclusion

Although %RSD for cloquintocet-mexyl for the level at the LOQ is slightly higher than 20% the analytical method is fit for purpose covering the LOQs mentioned.

Reference:	**Influence of Fenoxaprop-P-ethyl 69 g/L EW to *Daphnia magna* in a Reproduction Test**
Author(s), year:	Kley A., Wydra V. (2010)
Report/Doc. number:	37571221 / 314 FPE
Guideline(s):	Not stated. However, the method design and validation meet the requirements of SANCO/3029/99 rev.4
GLP:	yes

This method describes the determination of Fenoxaprop-p-ethyl, Fop-acid and Chloquintocet-mexyl in test water from *Daphina magna* in a reproduction test by HPLC-MS/MS in support of an aquatic toxicity study.

Principle of the method

Water samples were stabilised by adjusting the pH to 3 with hydrochloric acid. Thereafter the samples were subjected to solid phase extraction using a C18 cartridge conditioned with acetonitrile and pure water (1:2, v:v). An aliquot dried and re-dissolved in acetonitrile before analysis by means of HPLC-MS/MS in the ESI positive mode, monitoring the mass transitions 362→288 for Fenoxaprop-P-ethyl, 334→288 for FOP-acid and 336→238 for Cloquintocet-mexyl.
Columns:
FOP-acid: Column: Luna 3µ C18 (2) 50 x 3 mm
Fenoxaprop-P-ethyl and **c**loquintocet-mexyl: PerfectSil 120 ODS-2 125 x 3 mm.

Validation
Limit of quantification
0.0014 mg/L FOP-acid
0.0021 mg fenoxaprop-P-ethyl /L

Linearity
Linearity was tested by injecting 5 to 8 analytical standards in the range of 0.0025 mg/L to 0.2 mg/L and plotting the response against the concentration. The correlation coefficient was r^2>0.999 for all analytes.

Specificity
Analysis of control samples resulted in no detectable apparent residues at the characteristic retention times of the analytes. It can therefore be concluded that few, if any, apparent residues or false positive values would arise.

Recovery (Accuracy) – Precision

Matrix	Fortification level (µg/L) [(a)]	Average recovery (%)	Relative standard deviation (%)	Number of tests
Water	**Fenoxaprop-p-ethyl**			
	2.145	80	11.3	12
	21.35	82	5.6	12
	213.8	61	5.9	12
	Overall	74	15.2	36
	FOP-acid			
	1.388	114	8.3	6
	13.88	102	4.9	6
	138.8	100	4.2	6
	Overall	105	18	18
	Cloquintocet-mexyl			
	1.026	18	100	12
	10.26	28	39.2	12
	104.1	45	13.3	12
	Overall	30	36.0	36

Conclusion

Analytical method 314 FPE is sufficiently validated for fenoxaprop-P-ethyl and FOP-acid covering the LOQs mentioned.. This does not apply to cloquintocet-mexyl due to poor recoveries (18 to 45%).

Reference:	**Toxicity of Fenoxaprop-P-ethyl 69 g/L EW to *Desmodesmus subspicatus* in an Algal Growth Inhibition Test**
Author(s), year:	Pawlowski S., Wydra V. (2005)
Report/Doc. number:	24781210 / 96 FPE
Guideline(s):	Not stated. However, the method design and validation meet the requirements of SANCO/3029/99 rev.4.
GLP:	yes

Principle of the method

Residues of medium samples were extracted with n-hexane for 2 minutes. The extracts were dried with Na_2SO_4 and washed with n-hexane. The organic phase was evaporated to dryness and re-dissolved in acetonitrile:water (55:45, v:v) before analysis by means of HPLC-UV-VIS at a detection wave length of 200 nm. Column: Ultrasep ES RP 18e Pharm (125 x 3 mm)

Validation

Limit of quantification
0.007 mg/L fenoxaprop-P-ethyl
0.034 mg/L cloquintocet-mexyl as it is sufficiently validated. The revealed LOQ of 0.014 mg/L by the notifier is taken from study Grade R., Wydra V. (2016) which is evaluated above. This approach is not acceptable as the compositions of the test waters used in the studies are different.

Linearity
Linearity was tested by injecting 9 analytical standards in the range of 0.1 mg/L to 10 mg/L and plotting the response against the concentration. The correlation coefficient was r^2>0.997 for both analytes.

Specificity
Analysis of control samples resulted in no detectable apparent residues at the characteristic retention times of the analytes. It can therefore be concluded that few, if any, apparent residues or false positive values would arise.

Recovery (Accuracy) – Precision

Matrix	Fortification level (mg/L) [(a)]	Average recovery (%)	Relative standard deviation (%)	Number of tests
Algae growth medium Water	**Fenoxaprop-p-ethyl**			
	0.007	94	5.1	4
	0.071	92	6.6	4
	0.711	96	2.7	4
	Overall	94	4.9	12
	Cloquintocet-mexyl			
	0.003	36	88.7	4
	0.034	72	10.7	4
	0.341	108	9.0	4
	Overall	72	49.4	12

a Fortifications were performed with analyte reference standard solutions

Conclusion

Analytical method 96 FPE is sufficiently validated for fenoxaprop-P-ethyl and cloquintocet-mexyl covering the LOQs mentioned.

Reference:	**Toxicity of Fenoxaprop-P-ethyl 69 g/L EW to the Aquatic Plant *Lemna gibba* in a Semi Static Growth Inhibition Test**
Author(s), year:	Pawlowski, S.; Wydra V. (2005)
Report/Doc. number:	24780240 / 154 FPE
Guideline(s):	Not stated. However, the method design and validation meet the requirements of SANCO/3029/99 rev.4.
GLP:	Yes

This method describes the determination of Fenoxaprop-p-ethyl and Chloquintocet-mexyl in test water from aquatic toxicity tests by GC-ECD in support of several aquatic toxicity studies to *Lemna gibba*.

Principle of the method

The samples were subjected to solid phase extraction using a C18 cartridge conditioned with acetonitrile and pure water (1:2, v:v). An aliquot was dried and re-dissolved in acetonitrile before analysis by means of GC-ECD.

Validation

Limit of quantification
0.0007 mg/L for fenoxaprop-p-ethyl

Linearity
Linearity was tested in the range of 0.01 mg/L to 1 mg/L for fenoxaprop-p-ethyl (n = 5) and 0.02 to 1 mg/L (n = 8) for cloquintocet-mexyl and plotting the response against the concentration. The correlation coefficient was r^2>0.994 for both analytes.

Specificity
Analysis of control samples resulted in no detectable apparent residues at the characteristic retention times of the analytes. It can therefore be concluded that few, if any, apparent residues or false positive values would arise.

Recovery (Accuracy) – Precision

Matrix	Fortification level (mg/L) [(a)]	Average recovery (%)	Relative standard deviation (%)	Number of tests
Algae growth medium Water	**Fenoxaprop-p-ethyl**			
	0.0007	105	5.9	4
	0.0021	89	7.5	8
	0.021	90	11.4	10
	0.711	87	7.3	8
	Overall	91	10.4	30
	Cloquintocet-mexyl			
	0.01	55	13.5	10
	0.341	67	17.9	8
	Overall	60	18.6	18

Conclusion

Analytical method 154 FPE is sufficiently validated for fenoxaprop-P-ethyl covering the LOQ mentioned. Validation of cloquintocet-mexyl is not according to guidance document SANCO 3029/99 due to poor recoveries.

B.5.1.2.6. Methods in water, buffer solutions, organic solvents and any additional matrices resulting from the physical and chemical properties tests

No additional methods of analysis for the support of physical-chemical studies were developed. Please refer to Volume 3 Part CA B.5

B.5.2. METHODS FOR POST-APPROVAL CONTROL AND MONITORING PURPOSES

Following guidance from SANCO/12592/2012 "Template Assessment Report" and SANCO/10181/2013 cross reference as appropriate is made to the Supplementary Dossier of the active substance fenoxaprop-P-ethyl. All data and evaluations regarding the active substance fenoxaprop-P-ethyl are provided in Volume 3 Part CA B.5.

B.5.2.1. Methods for the determination of residues in or on plants, plant products, processed food commodities, food and feed of plant and animal origin

No additional methods of analysis for the determination of residues in or on plants, plant products, processed food commodities, food and feed of plant and animal origin were developed. Please refer to Volume 3 Part CA B.5.

B.5.2.2. Methods for the determination of residues in soil

No additional methods of analysis for the determination of residues in soil were developed. Please refer to Volume 3 Part CA B.5.

B.5.2.3. Methods for the determination of residues in water

No additional methods of analysis for the determination of residues in water were developed. Please refer to Volume 3 Part CA B.5.

B.5.2.4. Methods for the determination of residues in air, unless the applicant shows that exposure of operators, workers, residents or bystanders is negligible

No additional methods of analysis for the determination of residues in air were developed. Please refer to Volume 3 Part CA B.5.

B.5.2.5. Methods for the determination of residues in body fluids and tissues

No additional methods of analysis for the determination of residues in body fluids and tissues were developed. Please refer to Volume 3 Part CA B.5

B.5.3. REFERENCES RELIED ON

Annex point / reference number	Author(s)	Year	Title Source Company name, Report No., Date, GLP status, published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner
KCP 5.1.1/01	Hinz B.	2006	Analytical Method VAM 074-01. Determination of Cloquintocet-mexyl (CAS No. 99607-70-2) and Fenoxaprop-P-ethyl (CAS No. 66441-23-4) in EW Formulations. Cheminova Agro A/S, Study No. VAM 074-01 GLP, Unpublished	N	Y	New representative formulation	CHE
KCP 5.1.1/02	Hinz B.	2005	Validation of analytical method VAM 074-01 for Determination of Cloquintocet-mexyl (CAS No. 99607-70-2) and Fenoxaprop-P-ethyl (CAS No. 66441-23-4) in EW Formulations incl. Amendments 1, 2, 3 Cheminova Agro A/S, Study No. VAL 074-01 GLP, Unpublished	N	Y	New representative formulation	CHE
KCP 5.1.1/03	Hinz B.	2008	Analytical Method VAM 148-01: Determination of Fenoxaprop-P-ethyl (R-enatiomer) in Fenoxaprop EW formulation Cheminova A/S study No: VAM 148-01 GLP, Unpublished	N	Y	New representative formulation	CHE
KCP 5.1.1/04	Hinz B.	2008	Validation of analytical method VAM 148-01 for determination of Fenoxaprop-P-ethyl (CAS No. 71283-80-2) in Fenoxaprop EW formulation Cheminova A/S study No: VAL 148-01 GLP, Unpublished	N	Y	New representative formulation	CHE