FINAL REGISTRATION REPORT

Part B

Section 5

Analytical Methods

Detailed summary of the risk assessment

Product code: CHR/H/FETEC-PART B 110 EC

Product name(s): Fenoxinn Max 110 EC, Herbos Max 110 EC

Chemical active substance:

Fenoxaprop-P-ethyl, 110 g/L

Central Zone

Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

(authorization)

Applicant: Innvigo Sp. z o.o.

Submission date: 02.2023

MS Finalisation date: 06/03/2024

Version history

When	What
05/2023	Dossier sent for evaluation
11/2023	zRMS evaluation of dRR
March 2024	Final version prepared by zRMS after Commenting period

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zRMS comments:
The text highlighted in grey was provided by the zRMS.

5 Analytical methods

5.1 Conclusion and summary of assessment

Sufficiently sensitive and selective analytical methods are available for the active substance(s) and relevant impurities in the plant protection product.
Noticed data gaps are:
- none

Sufficiently sensitive and selective analytical methods are available for all analytes included in the residue definitions. The dRR was not rewritten. The zRMS text is on grey background. For details see for example PPP related with authorization number: R - 145/2016.
Noticed data gaps are: none

Commodity/crop	Supported/ Not supported
Cereals	Supported

5.2 Methods used for the generation of pre-authorization data (KCP 5.1)

5.2.1. Analysis of the plant protection product (KCP 5.1.1)

5.2.1.1 Determination of active substance and/or variant in the plant protection product (KCP 5.1.1)

An overview on the acceptable methods and possible data gaps for analysis of fenoxaprop-P-ethyl in plant protection product is provided as follows:

Comments of zRMS: Based on the results evaluated for repeatability, recovery, linearity and specificity, precision and accuracy this method is accepted and can be used for analysing a.s. and safener in the product. The method is validated according to SANCO 3030/99 rev. 5.

Reference:	KCP 5.1
Report	Validation of analytical method for CHR/H/FETEC - PARTB 110 EC for determination of cloquintocet-mexyl and fenoxaprop-P-ethyl, Knapik, I., Study code: ICB/90/2021
Guideline(s):	Conducting of analytical method validation – own Standard Operational Procedure SPB/179
Deviations:	No
GLP:	Yes
Acceptability:	Yes

Materials and methods

Validation was carried out according to Standard Operational Procedure SPB/179. Content of cloquintocet-mexyl (Safener) at a level of 55 g/L and fenoxaprop-P-ethyl (active substance) at a level of 110 g/L in the test item was accordingly determined by gas chromatography with mass detection (GC- MS)

Equipment and materials.
- acetonitrile HPLC (VWR),
- analytical standard of cloquintocet-mexyl, batch BCCF4868 (Sigma-Aldrich),
- analytical standard of fenoxaprop-P-ethyl, batch BCCD5819 (Sigma-Aldrich),
- analytical standard of anthracene (internal standard - IS), batch BCCB5640 (Sigma-Aldrich),
- standard stock solution of cloquintocet-mexyl in acetonitrile (for calibration),
- standard stock solution of fenoxaprop-P-ethyl in acetonitrile (for calibration),
- standard stock solution of anthracene (IS) in acetonitrile,
- working standard solution of anthracene (IS) in acetonitrile,
- working standard solutions of cloquintocet-mexyl and fenoxaprop-P-ethyl in acetonitrile (for calibration),
- standard stock solution of cloquintocet-mexyl in acetonitrile (for determination recovery),
- standard stock solution of fenoxaprop-P-ethyl in acetonitrile (for determination recovery),
- analytical balance – accuracy 0.0001 g, WP/16 (Ohaus, Switzerland),
- gas chromatograph Shimadzu GC2010 with mass detection (GC-MS), WP/38 (Shimadzu, Japan),
- chromatography column ZB-5MS 30 m, I.D. = 0.25 mm, df = 0,25 µm,K/12/GC (Phenomenex),
- chromatographic vials 1.5 ml with septa buthyl/Teflon,
- volumetric flasks A class 10 mL,
- measuring syringes 10, 50, 100, 250, 500, 1000 µL.

Validation - Results and discussions

Table 5.2-1: Methods suitable for the determination of fenoxaprop-P-ethyl and cloquintocet-mexyl in plant protection product CHR/H/FETEC-PART B 110 EC

	fenoxaprop-P-ethyl	**cloquintocet-mexyl**
Author(s), year		
Principle of method	GC- MS	GC- MS
Linearity (linear between mg/L / % range of the declared content) (correlation coefficient,	In order to check the linearity of cloquintocet-mexyl, calibration curve was prepared using standard solutions with concentrations contained in Table 5. A graph of the ratio of peak area of cloquintocet-mexyl to the area internal standard was plotted against the ratio of cloquintocet-mexyl concentration to the internal standard concentration. The resulting curve is linear in the tested concentrations. Linearity range of cloquintocet-mexyl is from 1.034 to 310.08 µg/mL. Correlation coefficient R2 is 0.997346 (Figure 4) and the linear regression is described by equation: $f(x)=0.418371 \cdot x - 0.088559$.	In order to check the linearity of fenoxaprop-P-ethyl, calibration curve was prepared using standard solutions with concentrations contained in Table 5. A graph of the ratio of peak area of fenoxaprop-P-ethyl to the area internal standard was plotted against the ratio of fenoxaprop-P-ethyl concentration to the internal standard concentration. The resulting curve is linear in the tested concentrations. Linearity range of fenoxaprop-P-ethyl is from 1.059 to 317.64 µg/mL. Correlation coefficient R2 is 0.996257 (Figure 5) and the linear regression is described by equation: $f(x)=0.191923 \cdot x - 0.051926$.

<table>
<tr><th></th><th>fenoxaprop-P-ethyl</th><th>cloquintocet-mexyl</th></tr>
<tr><td>ex-pressed as r)</td><td></td><td></td></tr>
<tr><td>Preci-sion – Repeat-ability Mean n = 5 (%RSD)</td><td>Linearity : R^2 = 0.996257
<table>
<tr><th>Validation level</th><th>Active ingredient</th><th>Precision [%]</th><th>Horwitz ratio</th><th>Recovery [%]</th><th>Standard addition [%]</th></tr>
<tr><td>100% without standard addition</td><td>fenoxaprop-P-ethyl</td><td>0.44</td><td>0.23</td><td>-</td><td>-</td></tr>
<tr><td>100% with standard addition (20-30%)</td><td>fenoxaprop-P-ethyl</td><td>-</td><td>-</td><td>97.52-102.54</td><td>24.97</td></tr>
<tr><td>LOQ</td><td>fenoxaprop-P-ethyl</td><td>2.04</td><td>0.77</td><td>93.4 (average)</td><td>-</td></tr>
<tr><td>ULOQ</td><td>fenoxaprop-P-ethyl</td><td>1.25</td><td>0.64</td><td>93.8 (average)</td><td>-</td></tr>
</table></td><td>Linearity : R^2 = 0.997346
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<tr><td>100% without standard addition</td><td>cloquintocet-mexyl</td><td>1.81</td><td>0.87</td><td>-</td><td>-</td></tr>
<tr><td>100% with standard addition (20-30%)</td><td>cloquintocet-mexyl</td><td>-</td><td>-</td><td>90.44-105.30</td><td>24.71</td></tr>
<tr><td>LOQ</td><td>cloquintocet-mexyl</td><td>1.33</td><td>0.50</td><td>96.7 (average)</td><td>-</td></tr>
<tr><td>ULOQ</td><td>cloquintocet-mexyl</td><td>1.30</td><td>0.66</td><td>99.0 (average)</td><td>-</td></tr>
</table></td></tr>
<tr><td>Accu-racy n = 5 (% Re-covery)</td><td>
<table>
<tr><th>Validation level</th><th>Active ingredient</th><th>Precision [%]</th><th>Horwitz ratio</th><th>Recovery [%]</th><th>Standard addition [%]</th></tr>
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</table></td></tr>
<tr><td>Inter-ference/ Speci-ficity</td><td colspan="2">Specificity of the method was evaluated based on the analysis of chromatograms for placebo against samples of the test item and standards. (Figure 12). On the basis of the placebo analysis of the tested substances were not detected. Analysis showed no overlapping of determined substances signal with the signals of matrix components under method conditions, hence method specificity criterion is fulfilled. Specificity and selectivity of validated method for cloquintocet-mexyl and fenoxaprop-P-ethyl determination was assessed at the point of optimizing conditions of analysis, by obtaining parameters for the best ingredients separation while maintaining interference impact at its lowest. The compounds were identified by the presence of specific fragmentation ions and determine by the target ions for each analyte. The method was set up in the way the percentage ratio between value of the main ion to identified reference ions doesn't exceed 30% value of the error from the mass spectrum. Ions have been selected by NIST 11 library.</td></tr>
<tr><td>Com-ment</td><td></td><td></td></tr>
</table>

Conclusion

It was confirmed that the method is specific. There were no peaks from placebo interfering with determined compounds. The validation parameters (specificity, linearity, instrument precision, repeatability and accuracy) are within the acceptance range and fulfil EU requirements given in SANCO /3030 /99 rev.5

5.2.1.2 Description of analytical methods for the determination of relevant impurities (KCP 5.1.1)

Not relevant.

Comments of zRMS: Not applicable. There is no relevant impurity of the a.s. to be tested in the formulation.

5.2.1.3 Description of analytical methods for the determination of formulants (KCP 5.1.1)

Not required.

5.2.1.4 Applicability of existing CIPAC methods (KCP 5.1.1)

Not required.

5.2.2 Methods for the determination of residues (KCP 5.1.2)

An overview on the acceptable methods and possible data gaps for analysis of residues of fenoxaprop-P-ethyl for the generation of pre-authorization data is given in the following table. For the detailed evaluation of additional studies it is referred to Appendix 2.

Table 5.2-2: Validated methods for the generation of pre-authorization data

Component of residue definition: Fenoxaprop-P-ethyl and metabolites				
Matrix type	**Method type**	**Method LOQ**	**Principle of method (i.e. GC-MS or HPLC-UV)**	**Author(s), year / missing / EU agreed**
Plants, plant products	Primary	0.01 mg/kg	GC-MS	Kaune A. (2003)
	Confirmatory (if required)	0.01 mg/kg	GC-MS	Rosati D., (2003a)
Soil	Primary	0.01 mg/kg	HPLC-UV	Clayton B., Parkes R.L. (1993a) Neuss B. (2005)
	Confirmatory (if required)	0.02 mg/kg	HPLC-UV	Clayton B., Parkes R.L. (1993a) Neuss B. (2005)
Water	Primary	0.1 mg/kg	HPLC-UV	Neuss B. (2000a) Neuss B. (2000b)
	Confirmatory (if required)	1.0 mg/kg	HPLC-UV	Neuss B. (2000a) Neuss B. (2000b)
Air	Primary	5.05 µg a.i. m3	HPLC-UV	Reichert N. (1994a) Glaenzel A. (2005)
	Confirmatory (if required)	Not required		

5.3 Methods for post-authorization control and monitoring purposes (KCP 5.2)

Data provided on Annex I inclusion is sufficient for post-authorizations methods. All data is described in EU approved documents.

5.3.1. Analysis of the plant protection product (KCP 5.2)

Analytical methods for the determination of the active substance and relevant impurities in the plant protection product shall be submitted, unless the applicant shows that these methods already submitted in accordance with the requirements set out in point 5.2.1 can be applied.

5.3.2. Description of analytical methods for the determination of residues fenoxaprop-P-ethyl (KCP 5.2)

5.3.1.1 Overview of residue definitions and levels for which compliance is required

Compared to the residue definition proposed in the Draft Assessment Report (incl. its addenda) the current legal residue definition is identical.

Table 5.3-1: Relevant residue definitions for monitoring/enforcement and levels for which compliance is required

Matrix	Residue definition	LOQ	Relevant residue limit	Reference for MRL/level Remarks
Plant, high protein/high starch content (dry commodities)	Fenoxaprop-P-ethyl	0.01 mg/kg	0.05 mg/kg (proposed MRL in grain for Fenoxaprop-P-ethyl together with metabolites expressed as Fenoxaprop- P-ethyl)	Kaune A. (2003a) Neuss B., (2005)
Muscle	-	Not required	-	No analytical method is evaluated as no MRLs and no residue definition for food of animal origin is proposed
Milk				
Eggs				
Fat				
Liver, kidney				
Soil (Ecotoxicology)	Fenoxaprop-P-ethyl and metabolites	0.01 mg/kg	0.05 mg/kg (general upper limit according SANCO 825/00)	Clayton B., Parkes R.L. (1993a) Neuss B. (2005)
Drinking water (Human toxicology)	Fenoxaprop-P-ethyl and metabolites	0.1 µg/L	0.1 Sg/L (EU drinking water limit)	general limit for drinking water
Surface water (Ecotoxicology)	Fenoxaprop-P-ethyl and metabolites	1 µg/L	0.19 mg/L (Bluegill sunfish) 34.2 mg/L (Green alga) 6.6 mg/L (Waterflea)	
Air	Fenoxaprop-P-ethyl	5.05 µg/m^3	1.9 µg/m3	AOEL sys

Matrix	Residue definition	LOQ	Relevant residue limit	Reference for MRL/level Remarks
	and metabolites		(based on an AOELsystemic of 0.0064 mg/kg b.w./d proposed by RMS AE F088406)	0.014 mg/kg bw/d
Tissue (meat or liver)	-	Not required	-	As the active substance is not classified as toxic or very toxic, no analytical method for Fenoxaprop-P-ethyl in human body fluids and tissues is submitted.
Body fluids		Not required	-	

5.3.1.2 Description of analytical methods for the determination of residues in plant matrices (KCP 5.2)

An overview on the acceptable methods and possible data gaps for analysis of fenoxaprop-P-ethyl in plant matrices is given in the following tables. For the detailed evaluation of additional studies it is referred to Appendix 2.

Table 5.3-2: Validated methods for food and feed of plant origin (required for all matrix types, "difficult" matrix only when indicated by intended GAP)

Component of residue definition: fenoxaprop-P-ethyl				
Matrix type	**Method type**	**Method LOQ**	**Principle of method (i.e. GC-MS or HPLC-UV)**	**Author(s), year / missing / EU agreed**
High protein/high starch content (dry)	Primary	0.01 mg/kg	GC/MS	Kaune A. (2003a)
	ILV	0.01 mg/kg	GC/MS	Rosati D., (2003a)
	Confirmatory (if required)	Not required		

For any special comments or remarkable points concerning the analytical methods for the determination of residues in plant matrices, please refer to Appendix 2.

Table 5.3-3: Statement on extraction efficiency

	Method for products of plant origin
Not required, because:	Residues below LOQ

5.3.1.3 Description of analytical methods for the determination of residues in animal

matrices (KCP 5.2)

No analytical method is evaluated as no MRLs and no residue definition for food of animal origin is proposed.

5.3.1.4 Description of methods for the analysis of soil (KCP 5.2)

An overview on the acceptable methods and possible data gaps for analysis of fenoxaprop-P-ethyl in soil is given in the following tables.

Table 5.3-4: Validated methods for soil (if appropriate)

Component of residue definition: fenoxaprop-P-ethyl, fenoxaprop-P and chlorobenzoxazolone			
Method type	**Method LOQ**	**Principle of method (*i.e.* GC-MS or HPLC-UV)**	**Author(s), year / missing**
Primary	0.01 mg/kg	HPLC-UV	Clayton B., Parkes R.L. (1993a) Neuss B. (2005)
Confirmatory	0.02 mg/kg	HPLC-UV	Clayton B., Parkes R.L. (1993a) Neuss B. (2005)

For any special comments or remarkable points concerning the analytical methods for soil please refer to Appendix 2.

5.3.1.5 Description of methods for the analysis of water (KCP 5.2)

An overview on the acceptable methods and possible data gaps for analysis of fenoxaprop-P-ethyl in surface and drinking water is given in the following tables.

Table 5.3-5: Validated methods for water (if appropriate)

Component of residue definition: fenoxaprop-P-ethyl, fenoxaprop-P and chlorobenzoxazolone				
Matrix type	**Method type**	**Method LOQ**	**Principle of method (i.e. GC-MS or HPLC-UV)**	**Author(s), year / missing**
Drinking water	Primary	0.1 µg/L	HPLC-UV	Neuss B. (2000a) Neuss B. (2005)
	Confirmatory	0.1 µg/L	HPLC-UV	Neuss B. (2000a) Neuss B. (2005)
Surface water	Primary	1.0 µg/L	HPLC-UV	Neuss B. (2000a) Neuss B. (2005)
	Confirmatory	1.0 µg/L	HPLC-UV	Neuss B. (2000a) Neuss B. (2005)

For any special comments or remarkable points concerning the analytical methods for water please refer to Appendix 2.

No independent laboratory validation for drinking water in EU approved documents is available.

5.3.1.6 Description of methods for the analysis of air (KCP 5.2)

An overview on the acceptable methods and possible data gaps for analysis of fenoxaprop-P-ethyl in air is given in the following tables.

Table 5.3-6: Validated methods for air (if appropriate)

Component of residue definition: fenoxaprop-P-ethyl and fenoxaprop-P			
Method type	**Method LOQ**	**Principle of method (i.e. GC-MS or HPLC-UV)**	**Author(s), year / missing**
Primary	5.05 a.i. µg/m^3	HPLC-UV	Reichert N. (1994a) Glaenzel A. (2005)
Confirmatory	Not required		

For any special comments or remarkable points concerning the analytical methods for air it is referred to Appendix 2.

5.3.1.7 Description of methods for the analysis of body fluids and tissues (KCP 5.2)

As the active substance is not classified as toxic or very toxic, no analytical method for Fenoxaprop-P-ethyl in human body fluids and tissues is submitted.

5.3.1.8 Other studies/ information

Not required.

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner
KCP 5.1./01	Knapik, I.	2022	Validation of analytical method for CHR/H/FETEC - PARTB 110 EC for determination of cloquintocet-mexyl and fenoxaprop-P-ethyl Study code: ICB/90/2021 ICB Pharma 10 Lema Street 43-600, Jaworzno POLAND GLP Unpublished	N	Chemirol

List of data submitted or referred to by the applicant and relied on, but already evaluated at EU peer review

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner
KCP 5/01	Kaune A.	2003a	Description and validation of an analytical method to determine AE F046360, AE F088406 and AE F054014 in cereal shoot, straw and grain. Bayer CropScience GmbH, DEU; Residues and Human Exposure, Frankfurt Document No: C027353 GLP / GEP Yes Unpublished	N	BCS

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner
KCP 5/02	Rosati D.	2003a	Independent laboratory validation of analytical method AM01/02 for the determination of residue in wheat grain of AE F046360 and its metabolites AE F088406 and AE F054014. Document No: C029562 GLP / GEP Yes Unpublished	N	BCS
KCP 5/03	Clayton B., Parkes R.L.	1993a	Method validation for determinationation in soil, water and application cards of Fenoxaprop-P-ethyl and its metabolites, Fenoxaprop-P-acid and benzoxazolone Generated by: EN-CAS; Document No: A51877 GLP / GEP Yes unpublished	N	BCS
KCP 5/04	Neuss B.	1999i	Enforcement method for water by HPLC-UV/VIS AE F046360 and its metabolites AE F088406 and AE F054014 Fenoxaprop-P-ethyl Code: AE F046360 Generated by: Hoechst Schering AgrEvo GmbH; Rueckstaende und Verbrauchersicherheit, Frankfurt Document No: C005936 GLP / GEP No Unpublished	N	BCS
KCP 5/05	Neuss B.	2000a	Validation of method EM F10/99-0 AE F046360 and its metabolites AE F088406 and AE F054014 Fenoxaprop-P-ethyl, Code: AE F046360 Generated by: Aventis CropScience GmbH, DEU; Residues and Human Exposure, Frankfurt Document No: C008304 GLP / GEP Yes Unpublished	N	BCS
KCP 5/06	Reichert N.	1994a	Development and validation of a method in air for determining, Fenoxaprop-Pethyl, Code: Hoe 046360 Generated by: Res.Consult.Comp., DEU;	N	BCS

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner
			Document No: A56140 GLP / GEP Yes Unpublished		
KCP 5/07	Glaenzel A.	2005	Methodenentwicklung und –Validierung zur Bestimmung von Fenoxaprop-Pethyl (HOE 046360) in Luft Addendumto final report Code: AE F046360 Generated by: RCC Ltd., Itingen, CHE Docum nt No: C046678 GLP / GEP: Yes Unpublished	N	BCS

Appendix 2 Detailed evaluation of submitted analytical methods

A 2.1 Analytical methods for fenoxaprop-P-ethyl

A 2.1.1 Methods used for the generation of pre-authorization data (KCP 5.1)

No new or additional studies have been submitted

A 2.1.2 Methods for post-authorization control and monitoring purposes (KCP 5.2)

A 2.1.2.1 Description of analytical methods for the determination of residues in plant matrices (KCP 5.2)

No new or additional studies have been submitted

A 2.1.2.2 Description of analytical methods for the determination of residues in animal matrices (KCP 5.2)

No new or additional studies have been submitted

A 2.1.2.3 Description of Methods for the Analysis of Soil (KCP 5.2)

No new or additional studies have been submitted

A 2.1.2.4 Description of Methods for the Analysis of Water (KCP 5.2)

No new or additional studies have been submitted

A 2.1.2.5 Description of Methods for the Analysis of Air (KCP 5.2)

No new or additional studies have been submitted

A 2.1.2.6 Description of Methods for the Analysis of Body Fluids and Tissues (KCP 5.2)

No new or additional studies have been submitted

A 2.1.2.7 A.2.A.9 Other Studies/ Information

No new or additional studies have been submitted