

European Commission



**Renewal Assessment Report prepared according to the Commission
Regulation (EU) N° 1107/2009**

Mecoprop-P **Volume 3 – B.7 (AS)**

Rapporteur Member State : United Kingdom
Co-Rapporteur Member State : Ireland

Version History

When	What
31/03/2016	Initial Renewal Assessment Report (RAR)

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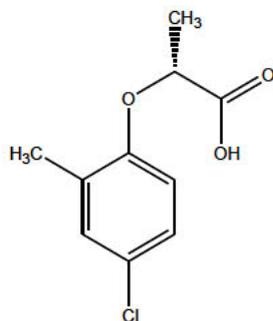
Summary notes for Renewal Assessment Report

Throughout this document, the original DAR written by Denmark, is referred to as the DAR (Draft Assessment Report) and this evaluation, written by the UK, is referred to as the RAR (Renewal Assessment Report). Studies that were evaluated in the DAR ('in the framework of the peer review under Directive 91/414/EEC) have not been re-evaluated. For some studies the evaluation presented in the DAR has been reproduced here for convenience and if necessary, additional information included for clarity. Studies which are introduced with the following information box (extract) are original DAR studies, i.e.

Previous evaluation:	In DAR for original approval
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Studies introduced in the format below are new for the RAR.

Report:	Annex point, Author. (date)
Title	
Guidelines:	
GLP:	
Deviations	
Previous evaluation:	Submitted for purposes of renewal.

Mecoprop-P

Mecoprop-P ((R)- 2-(4-chloro-2-methylphenoxy)propanoic acid, IUPAC) is a herbicide auxin type systemic herbicide which is absorbed via leaves and translocated in the plant basi- and acropetally. Technical mecoprop-P is a single enantiomer (R-), the (S-) enantiomer (mecoprop-M) is herbicidally inactive and is present as an impurity.

B.7. RESIDUE DATA

B.7.1. STORAGE STABILITY OF RESIDUES

Plant Storage Stability

The storage of samples in the supporting residue trials evaluated in Section B.7.3 are summarised in Table 7.1-1.

Table Error! No text of specified style in document.-1 Sample storage in supporting residue trials

Study	Sampling to extraction	Extraction to analysis
Tandy, (2014a) 4 x NEU trials on cereals	174 – 309 days (ca. 10 months)	2 – 12 days
Perny, 2002 4 x SEU trials on cereals	266 – 273 days (ca. 9 months)	
Gallais, 2002 6 x SEU trials on cereals	205 – 310 days (ca. 10 months)	

Storage stability of extracts in cereal were considered in the DAR (1998) and Addendum II (July 2002) in the following plant metabolism and storage studies. A summary of the storage stability is included below for clarity.

Previous evaluation:	In DAR for original approval.
Report:	Cooper J.L.D., Jones M.K. Lowdon P. and Parsons R., 1998
Title	14C-mecoprop-P: Wheat Metabolism Study. Study No. P93/169. BASF# 98/10444
Guidelines:	OECD 1982 and UK principles 1989
GLP:	Yes
Deviations	None

Cereal samples were all extracted within 1½ months. Concerning storage at -20°C the metabolism study in wheat with mecoprop-P reported that the profile of grain extracts did not vary significantly from the initial profile within 3 years, and that of straw extracts not within 1½ year, but no quantitative values were given.

Conclusion

No quantitative values were reported; therefore the storage stability of extracts cannot be reliably determined.

Previous evaluation:	In DAR (Addendum II) for original approval.
Report:	Perny, A., 2002
Title	Storage Stability of Mecoprop-P Residues in Cereals. Final Report No. A0128. HMARKS Study No. AHMR 00141.
Guidelines:	OECD, No. [C(97)186Final]
GLP:	Yes
Deviations	None

The study was conducted in compliance with GLP-OECD, No. [C(97)186Final]. The analytical method used was ATM 592: Analytical Method for the Determination of MCPA, HMCPA and MCPB in cereals and grass (validated in accordance with SANCO/3029/99/rev.4, see section CA B.5.1.2.5). The principle was based on an extraction of the crop with alkaline methanol, followed by a clean up of the crude extract by liquid/liquid partition and, further clean up on a solid phase extraction cartridge.

The eluent from the column was methylated using methanol/sulphuric acid. The methylated sample was extracted with hexane and solutions analysed by GC-ECD.

Control samples of green plants, grain and straw were fortified with ca 0.5 mg/kg and stored at < -18°C for up to 1 year. Procedural recoveries carried out at the different sampling times were 81- 106% of the 0.5 mg/kg fortification level. The results of the study were a recovery of 98-106% in green plants, 81-97% in grain and 84-100% in straw at the sampling times 90, 180, 270 and 365 days. The recoveries at the different sampling times are given in relation to the recovery at zero days.

Conclusion

The study demonstrates that samples of wheat grain, straw and green plant can be stored frozen (< -18°C) for 12 months with an acceptable retention of mecoprop-P residues. This adequately covers the storage periods of samples in the residue trials submitted for the purposes of renewal (Table 7.2.1-1). However, no data is available on the stability of plant metabolites HMCPP and CCPP, which are proposed as being included in the plant residue definition for risk assessment. This will be required as confirmatory information.

A new freezer storage stability study on cereals was conducted over 19 months (Anding, C. 2001). However, this is considered superfluous as the previously evaluated study (Perny, A., 2002) covers the storage stability of the samples in the residue trials. The time period between extraction to analysis reported in the Tandy, 2014 NEU residue trial study does not cause concern, as the extracts were stored at -18°C for a maximum of 12 days.

The new storage study supplied (Anding, C. 2001) is summarised below for completeness.

Report:	CA 6.1/03, Anding, C. (2001)
Title	Stability study of Mecoprop-P in soft winter wheat (grain, straw and green plant) after nineteen months storage in a congelator at a temperature under minus 18°C. Report No. AVE/00-033
Guidelines:	Not stated
GLP:	Yes
Deviations	N/A
Previous evaluation:	Submitted for purposes of renewal.

A storage stability study was conducted to evaluate the stability of residues of Mecoprop-P in soft winter wheat when stored under frozen storage conditions.

Test materials:	Mecoprop-P technical
Description:	Not reported
Lot/Batch #:	PJS288
Purity:	99.9 %
CAS #:	16484-77-8
Stability of test compound:	Stable
Test commodity	Soft winter wheat – grain, straw and green plant

Specimens were fortified with mecoprop-P at 0.20 mg/kg (grain) and 0.50 mg/kg (straw and green plant) and transferred to a freezer set to maintain a specimen temperature of <-18°C. The specimens

Analysis for radioactivity in samples was carried out on the day of collection of those when possible; otherwise samples were stored at -20°C for 2-3 months as the longest period. Since metabolite profiles for the kidney methanol/water extract and enzyme hydrolysis extracts were similar, this indicates that ¹⁴C-mecoprop-P residues were stable over this interval of 2-3 months at -20°C.

Conclusion

No quantitative values were reported; therefore the storage stability of samples cannot be reliably determined.

A new livestock feeding study has been submitted in which the samples were stored frozen and extracts were stored at 4°C. Storage stability of extracts is reported first and the frozen storage stability of samples is reported subsequently.

Report:	CA 6.1/01 [REDACTED] (2013)
Title	Mecoprop-P livestock feeding study: magnitude of residue in milk, muscle, liver, kidney and fat of lactating dairy cattle [REDACTED]
Guidelines:	OECD 505, OPPTS 860.1480, Working document 7031/VI/95 rev. 4, APVMA residue guideline No. 1
GLP:	Yes
Deviations	None
Previous evaluation:	Submitted for purposes of renewal.

Selected specimen extracts were reanalysed after storage at approximately 4°C, in order to assess the storage stability of the analytes in the final extracts. The results for storage stability of extracts over a period of 8 to 23 days generally show acceptable storage stability, with the exception of PCOC in some matrices. The results are displayed in Table 7.1-2.

Table Error! No text of specified style in document.-2 Recoveries before and after storage of extracts in various animal matrices

Matrix	Analyte	Days of extract storage	Fortification level (mg/kg)	Original mean recovery (%)	Stored mean recovery (%)
Whole milk	Mecoprop-P	19	0.01	97.5	113.5
			0.10	110.5	114.5
	HMCPP	19	0.01	85	117
			0.10	101	131.5
	CCPP	19	0.01	101	114
			0.10	100	113
PCOC	23	0.01	92	79.5	
		0.10	97.5	89	
Skimmed milk	Mecoprop-P	15	0.01	100	119
			0.10	109	117
	HMCPP	15	0.01	101	138.5
			0.10	109	144.5
	CCPP	15	0.01	107.5	143

Matrix	Analyte	Days of extract storage	Fortification level (mg/kg)	Original mean recovery (%)	Stored mean recovery (%)
	PCOC	22	0.10	113.5	156
			0.01	97.5	72.5
			0.10	103	94.5
Cream	Mecoprop-P	14	0.01	86.5	81
			0.10	87	81.5
	HMCPP	14	0.01	88.5	108.5
			0.10	78	105.5
	CCPP	14	0.01	90.5	115.5
			0.10	90	107
PCOC	8	0.01	82	89	
		0.10	82	98	
Muscle	Mecoprop-P	14	0.01	96.5	124.5
			0.10	104	131.5
	HMCPP	14	0.01	99	128.5
			0.10	107	145
	CCPP	14	0.01	88.5	111.5
			0.10	109.5	131.5
PCOC	14	0.01	87	66.5	
		0.10	94	56.5	
Liver	Mecoprop-P	10	0.01	93.5	96
			0.10	91	95
	HMCPP	10	0.01	107	98
			0.10	108	98.5
	CCPP	10	0.01	118	102
			0.10	110.5	107.5
PCOC	10	0.01	74	45	
		0.10	85	39	
Kidney	Mecoprop-P	15	0.01	116.5	123.5
			0.10	114.5	131
	HMCPP	15	0.01	119.5	133.5
			0.10	113.5	142
	CCPP	15	0.01	119.5	144
			0.10	115.5	137.5
PCOC	15	0.01	78.5	39	
		0.10	91	44	
Fat	Mecoprop-P	12	0.01	99.5	107.5
			0.10	97.5	112.5
	HMCPP	12	0.01	98.5	134

Matrix	Analyte	Days of extract storage	Fortification level (mg/kg)	Original mean recovery (%)	Stored mean recovery (%)
	CCPP	12	0.10	105.5	142.5
			0.01	110	163
			0.10	114	160.5
	PCOC	15	0.01	67	80.5
			0.10	75.5	83.5

Conclusion

Post-storage recoveries of mecoprop-P, HMCPP and CCPP in cream and liver were generally within the acceptable range of 70 – 110%. The remaining matrices however demonstrated high recovery values (>110%). These are believed to be caused by changes to the specimen matrix during storage. PCOC extracts seemed to degrade in several matrices at the time periods tested with a decrease of >30% compared to the pre-storage recoveries. These results indicate that a shorter storage time for the extracts is required. The extracts of specimens in this study were analysed within 7 days of extraction.

In the livestock feeding study (██████████ 2013), samples of animal matrices were frozen prior to analysis. No storage stability of residues in animal matrices was considered in the DAR, therefore the following report was submitted for the purposes of renewal.

Report:	CA 6.1/02 ██████████ (2014)
Title	Frozen Storage Stability Study for Mecoprop-P, HMCPP, CCPP and PCOC in Bovine Specimens Report No. ██████████
Guidelines:	Not stated
GLP:	Yes
Deviations	N/A
Previous evaluation:	Submitted for purposes of renewal.

The stability of residues of mecoprop-P, 2-(2-hydroxymethyl-4-chlorophenoxy)propionic acid (HMCPP), 2-(2-carboxy-4-chlorophenoxy) propionic acid (CCPP) and 4-chloro-2-methyl phenol (PCOC) in bovine whole milk, skimmed milk, cream, muscle, liver, kidney and fat when stored under frozen storage conditions are reported.

Specimens were fortified with reference items of mecoprop-P, HMCPP, CCPP and PCOC at 0.10 mg/kg (10 x LOQ) and transferred to a freezer set to maintain a specimen temperature of <-18°C. The specimens were maintained under frozen storage conditions typical of those employed for storage of actual residue specimens. Specimens were analysed immediately, 3 months and 9 months after fortification. The samples were extracted using the QuEChERS method before analysis by LC-MS/MS. This method has been deemed fit for purpose (see Volume 3 of the active dossier, section B.5.1.5.5). The recoveries prior to and post storage are displayed in Table 7.1-3.

Table Error! No text of specified style in document.-3 Freezer storage stability recoveries of animal matrices

Matrix	Time-point (months)	Mean uncorrected recovery (%)			
		Mecoprop-P	HMCPP	CCPP	PCOC
Whole milk	0	107	103	103	97
	3	102	117	109	88
	6	103	99	118	87

Matrix	Time-point (months)	Mean uncorrected recovery (%)			
		Mecoprop-P	HMCPP	CCPP	PCOC
Skimmed milk	0	104	107	102	96
	3	110	112	115	89
	6	106	108	98	122
Cream	0	94	103	107	87
	3	84	101	114	69
	6	87	109	118	72
Muscle	0	103	105	99	85
	3	106	105	103	74
	6	106	101	92	<u>53</u>
Liver	0	109	105	110	107
	3	104	105	106	<u>77</u>
	6	125	83	101	<u>65</u>
Kidney	0	107	108	101	89
	3	107	105	104	<u>55</u>
	6	112	98	95	<u>41</u>
Fat	0	99	107	109	71
	3	96	118	121	<u>43</u>
	6	88	121	122	<u>38</u>

Pre and post storage recoveries of mecoprop-P, HMCPP and CCPP residues in all animal matrices were generally within the acceptable range 70 – 110%. No significant degradation (>30% decrease in recovery) of was observed in whole milk, skimmed milk, cream, muscle, liver, kidney or fat after approximately 6 months of frozen storage. No significant degradation of PCOC residues was observed in whole milk, skimmed milk or cream after approximately 6 months of frozen storage. Low post-storage recoveries of PCOC in muscle, liver, kidney and fat after 3 and 6 months of frozen storage indicate that residues of PCOC do degrade on storage (those of concern are underlined in the table above. Recovery in muscle at 3 months was acceptable (not more than a 30% difference in recovery), thus the main concern is PCOC residue in fat, liver and kidney which would appear to be stable for less than 3 months.

Conclusion

Residues of mecoprop-P, HMCPP and CCPP in all animal matrices are considered stable following frozen storage (<-18°C) for 9 months. Residues of PCOC in muscle, liver, kidney and fat do not seem stable over the time periods tested. This is not of concern as levels of PCOC are controlled as part of the manufacture of the technical active substance and as PCOC is not formed as a result of metabolism in animals the levels expected in the animal samples would be very low, well below the level of toxicological relevance.

B.7.2. METABOLISM, DISTRIBUTION AND EXPRESSION OF RESIDUES

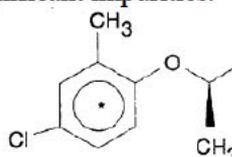
B.7.2.1. Plants

A study on metabolism, distribution and expression of residues in wheat was evaluated in the original DAR. A summary of this study is presented below and it has been assessed in accordance with Regulation 283/2013 using OECD guideline 501. Also presented in the DAR was a metabolism study

conducted with racemic mecoprop on winter wheat (Keller W.; Otto S., 1979). This however is considered supplementary only as was not to GLP and therefore does not comply with Regulation 283/2013. EFSA have included it in their Article 12 Review (2013;11(4):3191) and it should be noted that although extraction recoveries were low (14% grains, 20% straw), the results were comparable to those reported in the Cooper mecoprop-P study discussed below.

Previous evaluation:	In DAR for original approval, but re-evaluated to current guidelines.
Report:	Cooper J.L.D., Jones M.K. Lowdon P. and Parsons R., 1998
Title	¹⁴ C-mecoprop-P: Wheat Metabolism Study. Study No. P93/169. BASF# 98/10444
Guidelines:	OECD 1982 and UK principles 1989
GLP:	Yes
Deviations	None

Test substance: ¹⁴C-mecoprop-P, uniform labelled in the aromatic ring, specific activity of 1105 MBq mmole⁻¹, ≥ 98.5% pure, free of any significant impurities.



* Denotes position of radi

Test site: UK, outdoor in pots.

Test plants: winter wheat variety Riband. Treatment: spraying (5 May) with mecoprop-P potassium salt in aqueous solution at growth stage Z32 (2. node detectable), the latest recommended stage for spraying. The achieved rate was 1.41 Kg as/ha (1.2N rate) as a mixture of the radioactive material (purity 100%) and cold mecoprop-P (purity 99.9%) (ratio of 1:15 labelled: non-labelled). Treatment is in accordance with normal practise for use of mecoprop-P. Some plants were sprayed with 14.1 kg as/ha (11.8N rate). Sampling was immediately after treatment, at growth stage Z45 (booting, PHI 28 days) and at Z90 (ripening/harvest, PHI 103 days). Plants were taken by cutting of stems just above the ground level. Samples were stored at -20° until analysis.

Samples of 1.2N rate were all extracted within 1½ month. Extracts were stored at 4°C and examined within 15 days with some exceptions, but in those cases re-examinations were made of the 1.2N rate samples used or 11.8N rate samples including suitable comparisons to initial chromatograms to ensure original profiles. No loss was seen during extraction procedures, checked at each step by radioassay.

Extraction of 1.2N rate samples: samples taken at day 0 post treatment were extracted with methanol. Samples taken at day 28 post treatment were extracted with methanol and refluxed in hydrochloric acid and sodium hydroxide solutions. Grain samples were extracted with methanol/water and hot acid. Chaff and straw samples were extracted with hot hydrochloric acid, then hot sodium hydroxide and refluxed in sodium hydroxide solution (methanol extraction was included for straw, but not chaff, because poor results were obtained with methanol extraction of grains and straw). Soaking in salt and/or surfactant solutions were included in the procedure for day 28 and day 103 samples. Modified abbreviated procedures for some 11.8N rate samples, carried out 6 months after sampling, comprising salt extraction followed by hot acid and hot base treatments, ensured more than 90% extraction of TRR. The extraction processes and efficiency for each matrix are summarised in Table 7.2-1.

All 1.2N and 11.8N rate sample extracts were examined by HPLC and LSC. Straw and grains of 1.2N rate and straw of 11.8N rate were examined by LC/MS. Chaff and straw samples of 11.8N rate were examined by dialysis to estimate molecular weights of metabolites. Fractions with polar components from the 11.8N rate samples of straw were treated with enzymes and refluxed in acid and base to examine for conjugates present. Grain extracts of the 11.8N rate samples were treated with phe-

nylhydrazine, making osazones, to investigate if sugars were present. The results of the 11.8N rate are not presented in the original study report, therefore they are not considered any further.

Table Error! No text of specified style in document.-4 Extraction process and efficiency for whole plants, straw and grain

Day 0 Plant Sample (%TRR)		Day 28 Plant Sample (%TRR)	
Water wash	27.0	Maceration in MeOH and MeOH/H ₂ O (1:1)	82.6
Maceration in MeOH	47.9	Shake with 2M HCl	2.04
Dry and combust	25.1	MeOH wash	0.72
Total	100	2M HCL reflux	3.78
Grain 1.2N rate (%TRR)		Na ₂ EDTA soak	0.55
NaCl soln.	33.76	Triton-X 100 soak	0.21
Sonication in NaCl soln.	5.40	NaOH shake	2.83
Sonication in MeOH/H ₂ O	2.61	MeOH	0.17
1.0M HCl, 12h	30.11	NaOH reflux	1.46
MeOH	4.28	Total	94.62
1.0M HCl	2.98	Chaff 1.2N rate (%TRR)	
Total	79.84	NaCl soak	29.84
Straw 1.2N rate (%TRR)		0.5M HCl	7.64
NaCl soak	38.19	Macerated in NaOH	16.19
MeOH/H ₂ O/HCl	7.00	NaOH stir	20.73
HCl stir	4.61	NaOH reflux	5.43
Macerated in NaOH	15.79	Total	79.83
NaOH stir	13.72		
HCl reflux	4.91		
NaOH reflux	6.37		
Triton-X 100	1.46		
Na ₂ EDTA	0.04		
Total	92.08		

Storage stability of extracts of the 1.2N rate samples of straw and 11.8N rate samples of grains extracted 1 and 6 months after the final harvest, respectively, were compared with extracts of stored samples, made 1½ and 3 years later. All extraction after the initial were carried out using abbreviated methods, i.e. radioactivity was extracted into the same solvents for both stored and non-stored samples, but stored samples were not subjected to steps which had removed little or no radioactivity from the non-stored samples. All extracts were examined soon after their extraction by radio-HPLC using standard reference substances. Deviations in absolute retention times were detected because of different types of columns or age/use of columns between 1st and 2nd examinations. The profile of grain extracts prepared 1½ and 3 years later did not vary significantly from the initial profile. The 1½ year stored straw samples showed no appreciable change in composition of extractable residues. Storage for 3 years caused changes, but in all cases parent mecoprop-P was the main component. Two major and some polar metabolites were the same, but major metabolites were not necessarily in exactly the same proportion as in initial extracts, i.e. residues in straw were approximately stable over 1½ year. No quantitative values were given, and chromatograms were not transparent.

The results of the study are given in Table 7.2-2 to -5. Diagram of proposed metabolic pathway is displayed in Figure 7.2-1.

Table Error! No text of specified style in document.-5 Total radioactive residues (TRR) as mg/kg mecoprop-P equivalents in plants, sampled at 0, 28 and 103 (harvest) days after treatment.

Plant part	Treatment, kg as/ha	PHI, days	TRR, mg/kg
Whole plant	1.41	0	86.31
Whole plant	1.41	28	11.67
Grains	1.41	103	0.165
Chaff	1.41	103	0.460
Straw, upper part	1.41	103	3.07
Straw, stubble	1.41	103	25.07
Straw, total	1.41	103	10.00
Grains	14.1	103	1.45
Chaff	14.1	103	5.07
Straw, total	14.1	103	130.9

TRR in grains, chaff and upper part of straw was 0.165, 0.460 and 3.07 mg/kg, respectively, whereas total straw residues were 10.00 mg/kg, indicating a relatively minor translocation of active substance to upper parts of plants.

Whole plants

Table Error! No text of specified style in document.-6 Identification of metabolites in plants sampled 28 days after treatment with 1.41 kg as/ha.

Component	mg/kg ¹	% of TRR
U1 (polar metabolite)	0.02	<1
U2 (polar metabolite)	0.78	6.7
4-glucosyl-MPP	3.06	26.2
U3	1.03	8.8
2-glucosylmethyl-mecoprop	0.69	5.9
2-hydroxymethyl-4-chloro-phenoxypropionic acid glucoside	1.33	11.4
2-carboxy-4-chloro-phenoxypropionic acid	1.15	9.9
2-hydroxymethyl-4-chloro-phenoxypropionic acid	1.74	14.9
Mecoprop-P	0.48	4.1
U4	0.20	1.7
U5	0.17	1.5
U6	0.05	<1
U7	0.03	<1

Component	mg/kg ¹	% of TRR
U8	0.02	<1
Unassigned	0.15	1.3
Extractable, not characterised	0.15	1.3
Non-extractable	0.63	5.4
Total radioactive residues recovered	11.67	99

¹As mg/kg mecoprop-P equivalents.

- Readily extractable residues (methanol/water extracts) were 82.9% of TRR (9.67 mg/kg mecoprop-P equivalents).
- Further 11.4% of TRR (1.33 mg/kg mecoprop-P equivalents) was removed by successive extraction using acid and base reflux. Extracts contained some more parent mecoprop-P and some non-identified polar components, i.e. such components were not fully extracted with methanol.
- Non-extractable residues amounted to 5.4% of TRR (0.63 mg/kg mecoprop-P equivalents). This is bigger than the trigger value of 0.05 mg/kg, therefore bioavailability should have been investigated, but as residues were 5.4% of TRR only and ADI not low, no further work was required.
- Readily extractable residues comprised at least 14 metabolites of which individual not identified residues were <1-8.8% of TRR (0.02-1.03 mg/kg mecoprop-P equivalents).
- Six components were identified, namely parent mecoprop (4.1% of TRR, 0.48 mg/kg mecoprop-P equivalents), 2-hydroxymethyl-4-chloro-phenoxypropionic acid (14.9%, 1.74 mg/kg), its glucoside (11.4%, 1.33 mg/kg), 2-carboxy-4-chloro-phenoxypropionic acid (9.9%, 1.15 mg/kg), 4-glucosyl-MPP (26.2%, 3.06 mg/kg) and 2-glucosylmethyl-mecoprop (5.9%, 0.69 mg/kg).

Straw and grain

Table Error! No text of specified style in document.-7 Identification of metabolites in grains and straw sampled 108 days after treatment with 1.41 kg as/ha.

Component	Grains		Straw		
	TRR ¹ mg/kg	% TRR	TRR ² mg/kg	Upper p. ² mg/kg	% of TRR
Metabolites U1a-h, polar	0.070	42.4			
Metabolite U1a, polar			0.85	0.26	8.4
Metabolite U1b, polar			0.56	0.17	5.5
Metabolite U2	0.005	3.0			
Metabolite U2, cluster of peaks, all <5% TRR			1.40	0.43	13.9
Metabolite U3	0.009	5.5	0.77	0.24	7.8
2-hydroxymethyl-4-chloro-phenoxypropionic acid			1.18	0.37	12.0
2-carboxy-4-chloro-phenoxypropionic acid	0.010	6.1	1.42	0.44	14.3
Mecoprop-P	0.004	2.4	2.20	0.68	22.0
Metabolite U4	0.007	4.2	0.41	0.13	4.2
Metabolite U5	0.003	1.8	0.07	0.02	<1
Metabolite U6	0.005	3.0	0.09	0.03	<1

Component	Grains		Straw		
	TRR ¹ mg/kg	% TRR	TRR ² mg/kg	Upper p. ² mg/kg	% of TRR
Metabolite U7	0.005	3.0	0.04	0.01	<1
Metabolite U8	0.003	1.8	0.06	0.02	<1
Unassigned metabolites	0.011	6.7			
Extractable, not characterised components			0.15	0.05	1.6
Non-extractable components	0.033	20.0	0.79	0.24	7.8
Total radioactive residues recovered	0.165	99.9	10.03	3.09	100.1

¹Total radioactive residues (TRR) as mg/kg mecoprop-P equivalents.

²Total radioactive residues (TRR) in straw or upper p. (part) of straw.

Grains

- Extractability was 79.8% of TRR (0.132 mg/kg mecoprop-P equivalents).
- Parent mecoprop-P constituted 2.4% of TRR (0.004 mg/kg mecoprop-P equivalents)
- Metabolite 2-carboxy-4-chloro-phenoxypropionic acid constituted 6% of TRR (0.01 mg/kg mecoprop equivalents), whereas 2-hydroxymethyl-4-chloro-phenoxypropionic acid not was detected.
- Three metabolites (U2,6,7) represented 3% of TRR, each 0.005 mg/kg, and four (U8,5,4,3) represented <6% of TRR, each <0.01 mg/kg mecoprop-P equivalents.
- A cluster of peaks comprised 42% of TRR, each peak representing 2-8% of TRR (0.004-0.14 mg/kg mecoprop-P equivalents by analogy with x10 treatment. These metabolites were almost certainly natural products (probably sugars) into which radioactivity had been incorporated. Although not proved, this was deduced from uptake to some degree in neighbouring control plants of radioactive labelled carbon dioxide which is the ultimate breakdown product of phenoxy herbicides in soil, see table B.6-6. In addition incorporated material in treated plants may include fragments of the labelled ring and conjugated compounds.
- Non-extractable residues amounted 20.0% of TRR (0.033 mg/kg mecoprop-P equivalents).

Table Error! No text of specified style in document.-8 Total radioactive residues in samples of grains, chaff and straw from 1.41 kg as/ha treated plants and in neighbouring untreated plants.

Plant part	TRR, mg/kg as mecoprop-P equivalents		
	Treated plants		
		Inside controls ¹	Outside controls ²
Grains	0.165	0.015	0.009
Chaff	0.460	0.021	0.020
Straw	10.00	0.19	0.060

The previous DAR evaluation concluded that the study was satisfactory. The main metabolic pathway was hydroxylation of the aromatic ring placed 2-methyl group. Another minor pathway was hydroxylation of the aromatic ring. Parent mecoprop-P and primary metabolites from the main pathway were, as % of TRR:

Table Error! No text of specified style in document.-9 Parent and main metabolites determined as %TRR in wheat

	Parent (mecoprop-P)	HMCPP ⁽¹⁾	CCPP ⁽²⁾
Whole plants	4.1%	14.9%	9.9%

Grain	2.4%	not detected	6.1%
Straw	22.0%	12%	14.3%

⁽¹⁾ 2-hydroxymethyl-4-chloro-phenoxypropionic acid

⁽²⁾ 2-carboxy-4-chloro-phenoxypropionic acid

As specified in Regulation 283/2013, the plant metabolism study was evaluated in accordance with OECD guideline 501. The rate at which the metabolism study was conducted was more critical compared to the proposed GAP (1.2N rate) and the growth stage identical (BBCH32). Acceptable sample stability and extraction efficiency were reported.

Whole plant

The positively identified metabolites (Table 7.2.3) represented 72.4% TRR, which is close to the acceptable 75% as stated in the guidance. There were a large number of unidentified metabolites in plants sampled at 28 days after treatment with 1.2N rate (Table 7.2.1-3), labelled U1 – U8. Four of these (U1, 6, 7 & 8) are not of concern as represent < 10% TRR and are at a concentration ≤ 0.05 mg/kg. U4, U3 and U5 individually represent < 10%TRR, but are individually > 0.05 mg/kg, therefore should be identified according to OECD 501. However as much of the TRR has been positively identified (72.4%) and the method used in identification attempts was comprehensive (LC/MS), it can be considered that significant effort has been made to identify the components. Additionally, the whole plant sampled at this early stage (PHI 28 days *c.f.* 103 days at harvest) is not intended for the food chain therefore no further consideration of the metabolite identification is required.

Grain

In grain sampled at 108 days after treatment with 1.2N rate (table 7.2.1-3) there was 20% TRR non-extractable components. According to the OECD guideline 501 *“If radioactivity is present in the unextracted fraction down to trigger values of 0.05 mg/kg or 10% TRR, whichever is greater, release should be attempted for further identification.”*

As 10% TRR equates to 0.0165 mg/kg, the concentration must be < 0.05 mg/kg (which at 0.033 mg/kg it is) to not require further identification. The largest contribution at 42.4% TRR was assigned to metabolites U1a-h (polar). A case was submitted and accepted in the previous DAR evaluation that these were natural products (probably sugars) into which radioactivity had been incorporated. This was supported by data that demonstrated uptake in nearby control plants from radiolabelled CO₂, which is the ultimate breakdown product of phenoxy herbicides in soil. The metabolite 2-carboxy-4-chloro-phenoxypropionic acid was present at levels much greater than parent mecoprop-P (*ca.* 3:1 ratio respectively) therefore consideration of the toxicity of 2-carboxy-4-chloro-phenoxypropionic acid is necessary. The toxicological studies submitted by the applicant were insufficient to conclude that the metabolite CCPP was significantly less toxic than parent. It can therefore be concluded that the metabolites are of similar toxicity to parent, based on a consideration of their similar chemical structures and thus should be included in the residue definition.

Straw

The distribution of metabolites in straw (total) was of a comparable profile to that observed in just the upper part of the straw, though the latter had concentrations of radioactivity *ca.* 1/3rd of the total straw. The greater %TRR observed in straw compared to the whole plant can be attributed to the drying out of the commodity thus concentration of radioactivity. Three metabolites (2-hydroxymethyl-4-chloro-phenoxypropionic acid, 2-carboxy-4-chloro-phenoxypropionic acid and mecoprop-P) were positively identified and represented 48% of the total radioactivity. According to the OECD guideline 501, this total TRR identification is insufficient and warrants further characterisation of unidentified components, to include the selection of unidentified metabolites (U1a, 1b, 3 & 4) that were present at concentrations > 0.05 mg/kg, but < 10%TRR. The method used for metabolite characterisation was LC/MS, which is a comprehensive and sophisticated technique. It can therefore be concluded that an appropriate effort was made to identify these metabolites, which mitigates the requirement for identification as they all individually fall below 10%TRR. Metabolite U2 (cluster of peaks) represented 14%TRR and was present at a concentration of 0.43 mg/kg. However, each peak in this

cluster was reported to be individually < 5% TRR (equivalent to a max. concentration of 0.14 mg/kg) and in accordance with OECD guideline 501 identification is decided on a case-by-case basis. As the characterisation technique employed was LC/MS, which is a comprehensive technique, it is considered that sufficient efforts were made to identify the peaks in the U2 cluster.

It should be noted that the EFSA Article 12 Reasoned Opinion (2013;11(4):3191) states:

'Further data on metabolism in plants are needed as the studies are not fully reliable ... a high level of TRR remains unidentified in straw and levels of parent in straw were greater than in green plants. Consequently, further clarifications on the identity of the radioactive residue are still required.'

The RMS consider that although only 48% of total TRR was positively identified, each of the individual unidentified components were determined to be < 10% TRR and at low concentrations (max. 0.85 mg/kg, 8.4% TRR). Furthermore, as the method used for characterisation, LC/MS, was comprehensive further attempts for characterisation were considered unnecessary. Additionally, the higher levels in straw are attributed to the drying process and are unlikely to affect the overall metabolic pathway. The RMS considers the metabolism study acceptable.

EFSA is also of the opinion that the identified metabolites, 2-hydroxymethyl-4-chloro-phenoxypropionic acid and 2-carboxy-4-chloro-phenoxypropionic acid, should be included in the residue definition for risk assessment, as *'measurable residues of parent compound were determined in all commodities, significant residues of metabolites are therefore expected as well.'*

The RMS are in agreement with this decision and due to the significant quantities of HMCPP and CCPP observed in straw and the absence of acceptable toxicological data indicating that they are considered significantly less toxic than parent, these metabolites should be included in the risk assessment residue definition.

Conclusion

The plant metabolism study conducted on wheat, previously evaluated and considered acceptable in the original DAR is considered acceptable when evaluated under Regulation 283/2013 using the recommended guideline OECD 501.

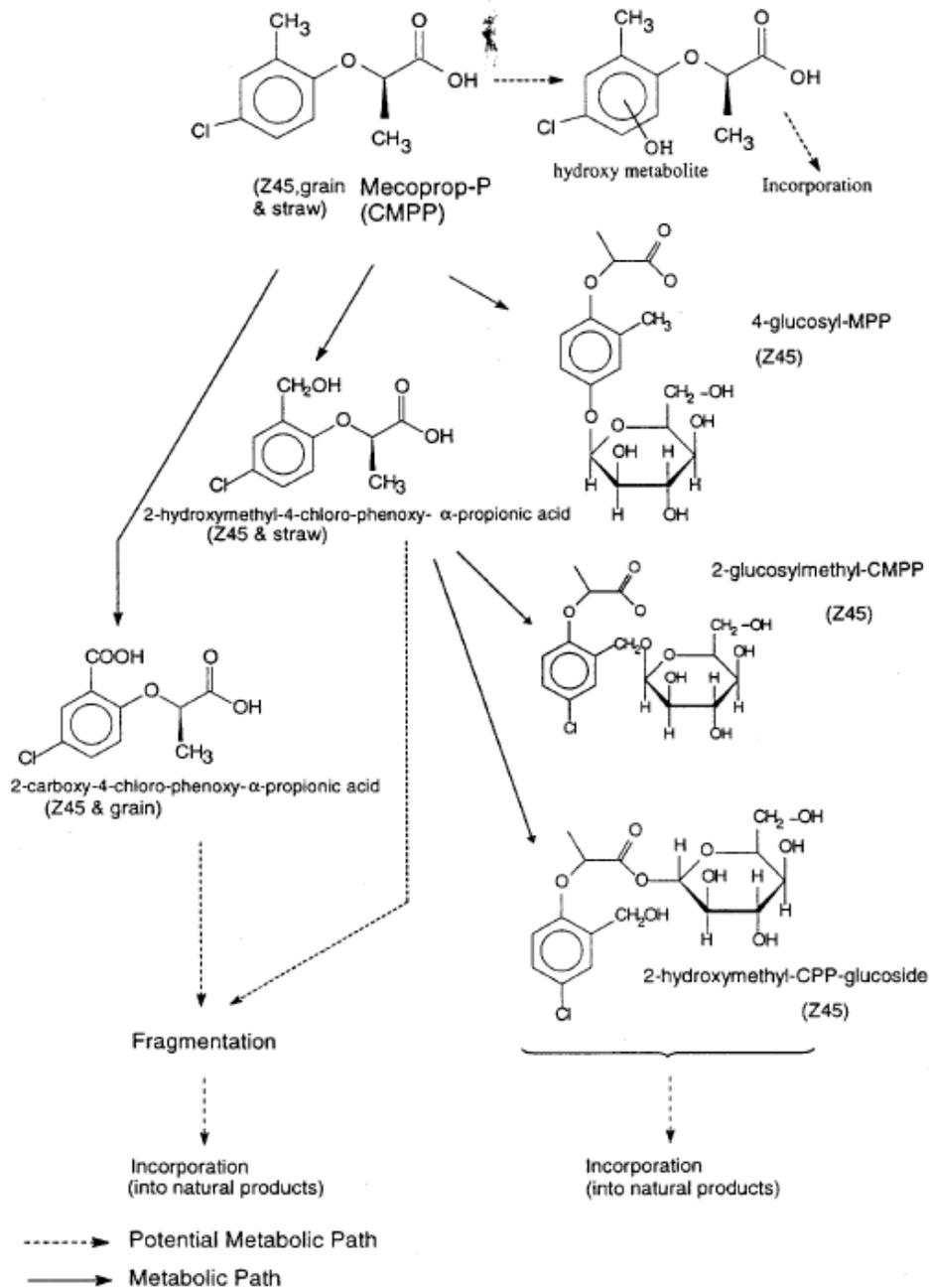
The absolute levels of the metabolites 2-hydroxymethyl-4-chloro-phenoxypropionic acid and 2-carboxy-4-chloro-phenoxypropionic acid in grain are low, but they occur at more significant levels in straw, which raises concerns regarding metabolism in animals. The RMS are in agreement with EFSA [Reasoned Opinion 2013;11(4):3191] that these metabolites should be included in the **residue definition for risk assessment:**

Mecoprop-P, 2-carboxy-4-chloro-phenoxypropionic acid (CCPP) and 2-hydroxymethyl-4-chloro-phenoxypropionic acid (HMCPP), expressed as mecoprop-P.

Using the metabolism study tentative conversion factors have been calculated for cereal grain (4) and cereal straw (2.2) for use in the risk assessment. These agree with those proposed by EFSA in the Reasoned Opinion (2013;11(4):3191), but are not calculated from residue trials data so should not be regarded as formal conversion factors, but as a method for estimating the worst case for use in the risk assessment.

As only the single isomer of mecoprop-P is being supported, and the monitoring methods of analysis (see Volume 3, section of the active dossier) monitor of the single mecoprop-P isomer and the metabolites are considered to be of similar toxicity to parent, the **residue definition for monitoring/enforcement is proposed as: mecoprop-P.**

Figure Error! No text of specified style in document.-1 Proposed metabolic pathway for mecoprop-P in wheat



B.7.2.2. Poultry

A poultry metabolism study is not required since the dietary intake is calculated to be below 0.004 mg/kg bw/day in NEU and it is considered that in a scenario appropriate to the proposed SEU GAP that intakes will be < 0.004 mg/kg bw/day hence no poultry metabolism study is considered to be required (see Volume 1, section 2.7.5).

B.7.2.3. Lactating ruminants

A study on metabolism in lactating goat was evaluated in the original DAR (Addendum II, July 2002). A summary is presented below and it has been assessed in accordance with Regulation 283/2013 using OECD guideline 503. Also in the original DAR published papers and metabolism studies on related active substances were summarised, but it was concluded that these were not of relevance to the evaluation and are not therefore considered in the RAR any further.

Previous evaluation:	In DAR (Addendum II, July 2002) for original approval.
Report:	████████████████████ 2001
Title	The distribution and metabolism of ¹⁴ C-mecoprop-P in the lactating goat. ████████████████████ (Study No. 169174).
Guidelines:	OPPTS 860.1300 and FAO guidelines as recommended by EU commission directive 96/68/EC Annex I, section 6.2 (21 Oct 1996).
GLP:	Yes
Deviations	None

Two lactating goats received twice daily an oral administration of ¹⁴C-(U-phenyl)-mecoprop-P in gelatine capsules over a period of 7 consecutive days. Radiochemical purity of the substance was 98.5%, and the specific activity 4.945 MBq.mg⁻¹. Daily nominal doses were 5 and 50 mg/kg feed (actual 4.9 and 46.0 mg/kg feed) for goats No. 1 and No. 2, respectively. Weight of goats was 80.5 kg (No. 1) and for 82.5 kg (No. 2) prior to first dose. Animals were fed ½ kg protein concentrate at each time of milking in the morning (0830 h) and afternoon (1630 h). Hay was given ad libitum. Daily feed consumption was 2.11 and 2.28 kg for goat No. 1 and No. 2, respectively. This corresponds to intakes of 0.13 mg/kg bw/day (goat 1) and 1.27 mg/kg bw/day (goat 2). In relation to the estimated dietary intakes (see Volume 1, section 2.7.5.) the dosing of goat 1 at 0.13 mg/kg bw/day is the most appropriate dosing level and corresponds to a dose rate of 14N with respect to dairy cattle and 5.8N with respect to beef cattle in SEU (worst case intakes).

Urine and faeces were collected daily at intervals of 24 hours following administration of the first dose until sacrifice. The cages were rinsed with water at each collection time and the rinses retained. Milk samples were collected from animals in the morning prior to administration of the first dose and then twice daily throughout the study period, the final immediately before sacrifice. Approximately 23 hours after administration of the final dose, the goats were sacrificed and samples of milk and tissues taken.

Analysis for radioactivity in samples was carried out on the day of collection when possible; otherwise samples were stored at -20°C for 2-3 months as the longest period. This time period is adequately covered by the storage stability studies discussed in Section B.7.1. Additionally, since metabolite profiles for the kidney methanol/water extract and enzyme hydrolysis extracts were similar, this indicates that ¹⁴C-mecoprop-P residues were stable over this interval of 2-3 months at -20°C. Total radioactivity was determined in all samples by LSC either directly (urine, cage wash, plasma, milk) or after combustion of samples (blood, liver, kidney, faeces, muscle, fat). Tentative identification was carried out by radio-HPLC using co-chromatography (YMC ODS-AQ 250 x 4.6 mm, 5µm column), with UV detection at 254 nm in all matrices. Moreover, residues of mecoprop-P in urine, faeces and kidney were confirmed by ESI-LC-MS (transitions monitored m/z 213→141; 215→143).

The extraction processes and efficiency for each matrix are summarised in Table 7.2-7.

Table Error! No text of specified style in document.-10 Extraction process and efficiency for animal matrices (PES = post extracted solid)

Urine	
Centrifuged only	Quantitative recovery (97 – 99.8%)
Faeces	
MeOH wash	97%
Milk	
MeCN precipitation, diethylether and hexane partitioning	89.8%
2 nd MeCN wash and aq. extract	30.8%
Liver and Kidney	
MeOH/water extraction and partition against hexane	58% (liver) 47.7 (kidney)
Concentrated MeOH/water extract	54.7% (liver) 44.3% (kidney)
Protease enzyme extraction of PES	5.7% (liver) 3.5% (kidney)
Pepsin enzyme extraction of PES	20.1% (liver) 20.2% (kidney)
Caustic MeOH extraction at 58°C	2.7% (liver) 2.4% (kidney)
Caustic MeOH extraction at 70°C	13.5% (liver) 13.0% (kidney)

Distribution, excretion and recovery of the administered doses are given in Table 7.2-8.

Table Error! No text of specified style in document.-11 Cumulative total radioactivity in urine, faeces, cage wash and milk and TRR in tissues in mg/kg expressed as mecoprop-P equivalents or in % of total administered dose.

Matrix	Dose level of 5 mg/kg feed		Dose level 50 mg/kg feed	
	mg/kg	% of adm. dose	mg/kg	% of adm. dose
Urine	NA ¹	80.96	NA	64.53
Faeces	NA	10.97	NA	24.86
Cage wash	NA	5.31	NA	6.52
Milk	NA	0.02	NA	0.02
Omental fat	0.001 ²	NA	0.003 ²	NA
Renal fat	0.001 ²	NA	0.003	NA
Kidney	0.007	<0.01	0.097	<0.01
Liver	0.001 ²	<0.01	0.031	<0.01
Muscle hind	<0.001	NA	0.001 ²	NA
Muscle fore	<0.001	NA	0.001 ²	NA
Whole blood	0.005	NA	0.029	NA
Plasma	0.004	NA	0.035	NA
Total radioactivity	NA	97.3	NA	95.9

1. NA = not applicable.
2. Residues calculated from data less than 30 dpm above background.

The overall recovery of the administered radioactivity 7 days after start of dosing was 97.3% and 95.9% for the 5 and 50 mg/kg feed level, respectively. The major route of excretion was via urine where radioactivity was 81.0% and 64.5% of administered doses 7 days after start of dosing in tests at the 5 and 50 mg/kg feed level, respectively. The corresponding excretions via faeces were 11.0 and 24.9%, respectively and via milk 0.02% for both doses. Residues in tissues were very low, the highest in kidney and liver with 0.097 and 0.031 mg/kg mecoprop-P equivalents, respectively at the feed level of 50 mg/kg. At the 5 mg/kg feed level <0.01mg/kg, corresponding to <0.01% of administered dose, was observed in liver and kidney. Residues in fat and muscles were <0.01 mg/kg mecoprop-P equivalents at the 5 and 50 mg/kg feed level.

The distribution of radioactivity in goat 1 (5 mg/kg feed) is displayed in Table 7.2-9. The study does contain the results for goat 2 at 50 mg/kg feed, but as this is not the most appropriate dosing level to support the cereal use of mecoprop-P then these results have not been presented, but are described in the following paragraphs.

Table Error! No text of specified style in document.-12 Quantitative distribution of radioactivity in goat 1 (low dose) excreta following administration of ¹⁴C-mecoprop-P.

Sample	Component	Retention Time (min)	Individual components as:	
			% TRR	% Dose
Urine (48 h)	Unknown	18	0.3	0.04
	Unknown	19	1.5	0.16
	Unknown	21	1.3	0.14
	Mecoprop-P	27	96.9	10.33
Urine (168 h)	Unknown	18	1.1	0.15
	Unknown	19	1.5	0.20
	Unknown	21	1.5	0.21
	Mecoprop-P	27	95.9	13.14
Faeces (48 h)	Unknown	20	1.8	0.04
	Mecoprop-P	27	93.3	2.19
Faeces (168 h)	Mecoprop-P	27	87.3	1.14

% TRR = % Total radioactive residue

Parent mecoprop-P amounted in urine to 95.9 and 92.7% of TRR 7 days after start of administration at the 5 and 50 mg/kg feed level, respectively. Three minor unidentified metabolites represented up to 1.6% of TRR, including both doses. In accordance with OECD guidelines 503, as these unknowns are < 10%TRR and < 0.01 mg/kg then no characterisation is required providing they are not toxic. Parent mecoprop-P in a methanol extract of faeces amounted to 87.3 and 91.1% of TRR 7 days after start of dosing at the 5 and 50 mg/kg feed level, respectively. At the low dose, one minor metabolite represented up to 1.8% of TRR. At the higher dose, two unknowns up to a maximum of 2.2%TRR (0.06% dose) were also observed. . In accordance with OECD guidelines 503, as these unknowns are < 10%TRR and < 0.01 mg/kg then no characterisation is required providing they are not toxic.

A milk extract in acetonitrile from a sample at the 50 mg/kg feed level taken 6-7 days after start of administration and containing 29.6% of TRR (0.004 mg/kg mecoprop-P equivalents) showed evidence for the presence of mecoprop-P in an amount of <LOQ. Residues in milk reached plateau 2 days after start of dosing. A kidney extract in methanol/water from a sample at the 50 mg/kg feed level contained 44.3% of TRR, 31.1% of TRR were parent mecoprop-P (0.03 mg/kg mecoprop-P equivalents) and 2 unknowns amounted to 10.5 and 2.7% of TRR. Liberated parent mecoprop-P using pepsin hydrolysis amounted to 16.6% of TRR. A liver extract in methanol/water from a sample at the 50 mg/kg feed level contained 54.7% of TRR. The radioactive residue consisted of a polar unknown of 0.017 mg/kg, expressed as mecoprop-P equivalents. Non-extractable residues in kidneys from the 50 mg/kg feed level post extraction with methanol and methanol/water amounted to 0.051 mg/kg (52.3% of TRR); for liver the same residues were 0.013 mg/kg (42.0% of TRR). Following consecutive administration for 7 days, there was no evidence for any accumulation of radioactivity in milk and edible tissues.

In conclusion, mecoprop-P was rapidly excreted, most of it as parent compound. Excretion was mainly via urine, less in faeces and minimal in milk; residues in tissues were very small. Non-extractable residues were also very small. There was no evidence for accumulation of residues in milk and fatty

tissues. The study is assessed as acceptable referring to the EU-guidelines concerning residues, 1607/VI/97 rev. 2, Appendix F.

Conclusion

The lactating goat metabolism study is acceptable according to the OECD guideline 503. The study was conducted at a 14 N and 5.8N rate with respect to dairy and beef cattle in SEU. The majority of radioactivity was rapidly excreted in urine and faeces (combined *ca.* 90% at both doses) and after 7 days of dosing the positively identified component of the radioactivity in urine was parent mecoprop-P, which represented 96% (lower dose) and 93% (higher dose) of the total radioactivity. A similar profile was observed in faeces: 83% TRR (lower dose) and 91% TRR (higher dose). These values exceed the limit of 75% proposed as acceptable in the guideline OECD 503. Further identification of metabolites is therefore not considered necessary. Additionally, the unidentified metabolites were individually < 3% TRR in urine and faeces. Radioactive residues in milk and tissues were minimal.

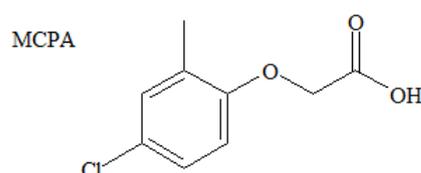
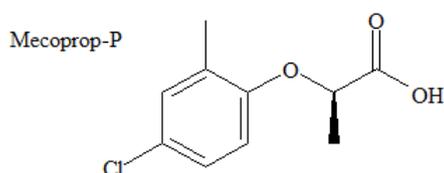
In conclusion, the residue definition in animal products should be: **Mecoprop-P both for enforcement and risk analysis.**

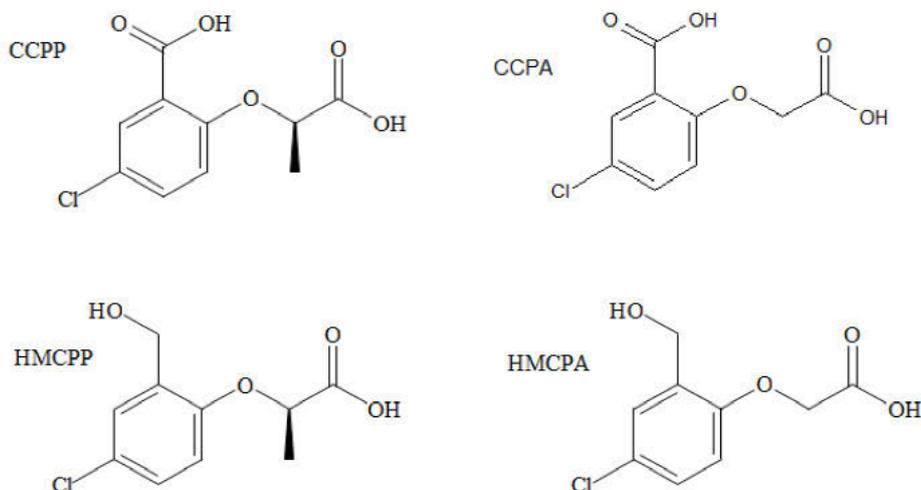
It should be noted that in their Article 12 Reasoned Opinion, EFSA concluded that this study was under-dosed, but this is in comparison to the dietary intake expected from grassland uses and is not applicable to the cereal use proposed in the GAP. In relation to the estimated dietary intakes (see Volume 1, section 2.7.5.) the dosing of goat 1 at 0.13 mg/kg bw/day is the most appropriate dosing level and corresponds to a dose rate of 14N and 5.8N with respect to dairy cattle and beef cattle. It can be concluded that the metabolism study is appropriately dosed.

The metabolism study only doses with parent mecoprop-P, but as the metabolites HMCPP and CCPP are to be included in the plant residue definition and are significant residue components in straw, in accordance with the guidance, a consideration of the effect of dosing with these metabolites is necessary. However, the applicant has submitted a case claiming these metabolites are rapidly absorbed and excreted in livestock and therefore would not give rise to any significantly different animal metabolites that would be of toxicological concern. Thus additional vertebrate studies to investigate the metabolism of HMCPP and CCPP in ruminants are not required. This case is based on consideration of a similar active substance, MCPA, and its known metabolism in livestock. The case is presented below.

Case: Are HMCCP and CCPP metabolism studies required?

Comparison can be made to the metabolism of the related active ingredient, MCPA, along with its known metabolites CCPA and HMCPA, which have similar chemical structures to mecoprop-P, CCPP and HMCPP respectively:





In the renewal MCPA dossier metabolism studies on rat ([REDACTED] 1978) and cows (literature publication: M.A. Loos, *Herbicides: chemistry, degradation and mode of action*) were referenced and demonstrated that the metabolic pathway of MCPA was comparable to that of mecoprop-P. Rats dosed with MCPA were found to excrete approximately 90% of the dose via urine with a further 95% excreted in faeces. The major residue component in rat urine was unchanged parent (51 – 80%) with a further 6 – 16% identified as HMCPA (the MCPA analogue metabolite for HMCPP). A metabolism study on goat [REDACTED] 1995) concluded that MCPA is rapidly excreted with 99.5% of the administered dose being excreted within 23 hr of the last dose. Milk and tissues collected in this study accounted for less than 0.1% of the dose. The small amount of MCPA that is not excreted is metabolised to the glycine conjugate of MCPA, which was only detected in milk.

Both MCPA and mecoprop-P are rapidly excreted in urine and faeces and residues are low in edible tissues. Due to the similar structures of mecoprop-P and MCPA and the comparative patterns of absorption, metabolism and elimination demonstrated in the rat and ruminant, it can reasonably be concluded that the behaviour of the respective metabolites would also be comparable.

No study was conducted dosing with the mecoprop-P metabolite CCPP, but an additional goat metabolism study [REDACTED] 2004) conducted with CCPA (the MCPA analogue metabolite for CCPP) that has not been previously evaluated as part of the MCPA dossier has been referenced to support the fact that feeding with CCPP is not necessary. This study has been briefly evaluated below to assess whether it can be used as supporting information.

Report:	[REDACTED] (2004)
Title	The distribution and metabolism of [¹⁴ C]-CCPA in the lactating goat Report No. 23562 Study No. 204941
Guidelines:	OPPTS 860.1300, Directive 91/414/EEC Annex II
GLP:	Yes
Deviations	None
Previous evaluation:	None. Will be fully evaluated at renewal of MCPA. This is a brief evaluation to determine if it is fit for purpose to act as supporting information.

A goat was dosed daily for three consecutive days with 10 mg/kg diet consumed (equivalent to 0.28 mg/kg bw/day). Urine, faeces and cage washings were collected at 24 hr intervals and milk samples

were collected twice daily. 24 hours after final dose the goat was sacrificed and muscle and tissue samples taken. Radioactivity was determined by LSC analysis and the recovery of the total radioactivity is displayed below:

Recovery of Total Radioactivity (%)	
Sample	001F
Urine	66.56
Faeces	26.28
Cage Wash	5.16
Milk	0.02
Fat	0.00
Kidneys	0.02
Liver	0.01
Muscle	0.00
Blood Cell Fraction	0.00
Plasma	0.00
Total	98.06

Excretion via urine was the major route of elimination, accounting for 66.56% of administered dose. Excretion in faeces accounted for 26.28% and in milk 0.02%. Radioactivity in tissues was also very low. HPLC analysis of the urine samples demonstrated the major residue (97% TRR) was unchanged parent and 3 minor components ranged from 0.41 – 1.25% TRR. In faeces the major residue was again parent (86% TRR) and a minor component represented 1.19% TRR. Due to the large amount of identified TRR (>75%), these minor metabolites do not require characterisation. This study indicates that CCPA is well absorbed and rapidly excreted, with no evidence of accumulation of radioactivity in milk or edible tissues.

Conclusion

Using the metabolic behaviour of CCPA to represent that of CCPP, sufficient evidence is provided to conclude that the metabolite CCPP would be rapidly excreted, unchanged in a similar manner to parent mecoprop-P. Residues of CCPP in matrices for human consumption (milk and edible tissues) would therefore be very low and not of concern.

The mecoprop-P dairy cow feeding study evaluated in section B.7.4.2. dosed with mecoprop-P only, but demonstrated that no residues of HMCCP (or CCPP) were observed in any matrix destined for human consumption. Furthermore intakes of HMCPP are lower than those of CCPP and the similarity in structure suggests HMCCP metabolite will behave in a similar manner to CCPP and significant residues will not arise in ruminant tissue.

Thus further vertebrate studies assessing the metabolism of HMCPP and CCPP in livestock are not required.

B.7.2.4. Pigs

Metabolism in rats and goats is observed to be similar – parent mecoprop-P being the main constituent of the radioactivity, therefore no further metabolism study in swine is required. Additionally, the dietary intake is calculated to be below 0.004 mg/kg bw/day in NEU and the SEU dietary burden calculation was only exceeded by an insignificant amount considering the significantly worst case inputs used (see Volume 1, section 2.7.5).

B.7.2.5. Fish

A fish metabolism study is not required since no guidance has been released.

B.7.3. MAGNITUDE OF RESIDUE TRIALS IN PLANTS

The residue trials evaluated in the DAR are not considered appropriate under Regulation 283/2013. As stated in the DAR, raw data and GLP/GEP for the trials was not included with the dossier. Missing raw data meant lack of information, for example about storage temperature, stability studies as well as detailed analytical validation (later received), chromatograms and data for time elapse between sampling and analyses. Additionally, no trials conducted in Southern Europe were evaluated in the DAR and 8 trials on cereals in SEU were requested by EFSA in their Reasoned Opinion for mecoprop-P (2013).

In order to address these inadequacies in the original dossier, new residue trials have been submitted in order to support the proposed GAP and only these will be relied upon. The residue trials submitted are summarised in Table 7.3-1.

Table Error! No text of specified style in document.-13 Summary of residue trials GAP compliant

No. of trials	Analyte	Location	Commodity	Study reference (report no.)
3	MCPPP-P	SEU	2 x winter wheat, 1 x winter barley	Old, J & Duncan, P., 2001, (19513/397315)
5	MCPPP-P	SEU	2 x winter barley, 3 x winter wheat,	Warman, J P., 2002a (20472/680333)
4	MCPPP-P	NEU	2 x winter wheat, 2 x spring barley	Tandy, R., 2014a (S13-00323)

A total of 8 trials are supplied to support use of mecoprop-P in SEU and 4 in NEU. Cereals are major crops therefore a minimum of 8 trials are required in each region. Insufficient data has been provided to support the NEU use, as positive residues are observed in straw (animal feed commodity) a reduced data set is not considered appropriate in this case. Crop variety was demonstrated as the trials were conducted on wheat and barley (7 wheat, 3 winter barley and 2 spring barley). According to SANCO 7525/VI/95-rev.9 extrapolation between wheat and barley and to winter and spring oats, rye and triticale is acceptable for an active used early in the growing season.

Details of the trials conforming to the proposed GAP are given in Tables 7.3-2 and 7.3-3 below. Data which do not reflect the GAP ($\pm 25\%$) have not been included. Results from the trials conforming to the GAP, reported in sufficient detail and acceptable analytical information are underlined. Basic criteria for acceptability are given below:

Trials details

Crop/variety

Location/position/year

Formulation type

Application/dilution rate

Maximum number of treatments

Growth stage of crop at treatment

PHI

Residue level (treated – control plot samples contained residues below the limit of quantification [0.01 mg/kg and 0.05 mg/kg])

Geo-climatic information

Analytical aspects

Method specified and submitted (see CA Volume 3, Section B.5.1.2.5 of mecoprop-P RAR)

Storage of samples prior to analysis (cereal samples were stored for less than 12 months)

Limit of quantification at acceptable level (0.01 and 0.05 mg/kg)

Acceptable recovery (usually 70-110%)

Note: In Tables 7.3-2 & 3 (below) the magnitude of residues of mecoprop-P (MCP-P) *only* were reported. This is not in line with the proposed residue definition for risk assessment: mecoprop-P, 2-carboxy-4-chloro-phenoxypropionic acid (CCPP) and 2-hydroxymethyl-4-chloro-phenoxypropionic acid (HMCPP), expressed as mecoprop-P. (See Section 7.3.1 for discussion of conversion factors).

Table Error! No text of specified style in document.-14 Results of residue trials in the Southern EU on winter cereals with mecoprop-P

Trial No./ Location/ Year	Commodity/ Variety	Date of 1.Sowing or planting 2.Flowering 3. Harvest	Application rate per treatment			Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analysed	Residues (mg/kg) MCP-p	PHI (days)	Remarks
			g a.s./ ha	Water (l/ha)	g a.s./hl						
Proposed GAP	Winter and spring cereals: Wheat (including durum and spelt), barley, rye, oats and triticale.		1200	200 - 400		1	BBCH 20 – 32 (winter) BBCH 13 – 32 (spring)				
IRI 19513 (field); R A0119 (analytical) 397315/1 Charantonnay, Southern France (2000)	Winter wheat (variety Isengrain)	1) 22/10/99 2) N/A 3) 19/07/00	1500 (actual 1524) (2.5 L/ha)	250 (act 254)	600	14/04/00	33	Green plant Green plant Green plant Green plant Grain Straw	64 0.79 0.40 0.14 <u><0.05</u> <u>0.06</u>	0 7 14 28 96 96	Method: GC-MSD LOQ = 0.05 mg/kg
IRI 19513 (field); R A0119 (analytical) 397315/2 Janneyrais, Southern France (2000)	Winter barley (variety Pertine)	1) 05/10/99 2) N/A 3) 21/06/00	1500 (actual 1554) (2.5 L/ha)	250 (act 259)	600	14/04/00	33	Green plant Green plant Green plant Grain Straw	42 0.68 0.38 0.14 <u><0.05</u> <u>0.20</u>	0 7 14 28 68 68	Method: GC-MSD LOQ = 0.05 mg/kg
IRI 19513 (field); R A0119 (analytical) 397315/3 Olius, Lleida, Spain (2000)	Winter wheat (variety Tremier)	1) 11/11/99 2) N/A 3) 07/07/00	1500 (actual 1500) (2.5 L/ha)	250 (act 250)	600	04/04/00	32	Green plant Green plant Green plant Green plant Grain Straw	64 2.8 1.7 0.18 <u><0.05</u> <u>0.10</u>	0 7 14 28 94 94	Method: GC-MSD LOQ = 0.05 mg/kg

Trial No./ Location/ Year	Commodity/ Variety	Date of 1.Sowing or planting 2.Flowering 3. Harvest	Application rate per treatment			Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analysed	Residues (mg/kg) MCP-P	PHI (days)	Remarks
			g a.s./ ha	Water (l/ha)	g a.s./hl						
IRI 20472 (field); R A01135 (analytical) 680333/1 St Trivier, Southern France (2001)	Winter barley (variety Ladoga)	1) 29/09/00 2) N/A 3) 25/06/01	1200 (actual 1207) 2.0 L/ha	250 (act 254)	480	30/03/01	32	Green plant Green plant Green plant Green plant Grain Straw	14 0.81 0.61 0.44 <u><0.05</u> <u><0.05</u>	0 7 13 28 87 87	Method: GC-MSD LOQ = 0.05 mg/kg
IRI 20472 (field); R A01135 (analytical) 680333/3 St Trivier, Southern France (2001)	Winter wheat (variety Cezanne)	1) 20/10/00 2) N/A 3) 11/07/01	1200 (actual 1175) 2.0 L/ha	250 (act 247)	480	30/03/01	32	Green plant Green plant Green plant Green plant Grain Straw	15 3.0 1.5 0.73 <u><0.05</u> <u>0.07</u>	0 7 13 28 103 103	Method: GC-MSD LOQ = 0.05 mg/kg
IRI 20472 (field); R A01135 (analytical) 680333/4 Charantonnay, Southern France (2001)	Winter wheat (variety Cezanne)	1) 25/10/00 2) N/A 3) 10/07/01	1200 (actual 1144) 2.0 L/ha	250 (act 241)	480	03/04/01	32	Green plant Green plant Green plant Green plant Grain Straw	42 1.5 0.64 0.23 <u><0.05</u> <u><0.05</u>	0 7 14 27 98 98	Method: GC-MSD LOQ = 0.05 mg/kg
IRI 20472 (field); R A01135 (analytical) 680333/5 Almacelles Lleida, Spain (2001)	Winter barley (variety Graphic)	1) 24/11/00 2) N/A 3) 06/06/01	1200 (actual 1208) 2.0 L/ha	250 (act 254)	480	19/03/01	32-33	Green plant Green plant Green plant Green plant Grain Straw	30 6.5 6.0 0.32 <u><0.05</u> <u>0.32</u>	0 7 14 29 79 79	Method: GC-MSD LOQ = 0.05 mg/kg
IRI 20472 (field); R A01135 (analytical) 680333/6 Menarguens Lleida, Spain (2001)	Winter wheat (variety Sarina)	1) 05/12/00 2) N/A 3) 20/06/01	1200 (actual 1196) 2.0 L/ha	250 (act 252)	480	26/03/01	32-33	Green plant Green plant Green plant Green plant Grain Straw	42 6.1 3.3 0.89 <u><0.05</u> <u>0.28</u>	0 7 14 28 86 86	Method: GC-MSD LOQ = 0.05 mg/kg

Table Error! No text of specified style in document.-15 Results of residue trials in the Northern EU on winter and spring cereals with mecoprop-P

Trial No./ Location/ Year	Commodity/ Variety	Date of 1.Sowing or planting 2.Flowering 3. Harvest	Application rate per treatment			Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analysed	Residues (mg/kg) MCP-p	PHI (days)	Remarks
			g a.s./ ha	Water (l/ha)	g a.s./hl						
S13-00323 S13-00323-01 Melbourne, Derbyshire, DE73 1BW, UK (2013)	Winter wheat (variety Oakley)	1) 18/10/12 2) N/A 3) 18/08/13	1215	203	599	20/05/13	32	Green plant Green plant Green plant Green plant Green plant Green plant Green plant Grain Straw	41.77 23.73 11.54 7.92 4.29 0.62 0.59 <u>< 0.01</u> <u>0.29</u>	0 1 3 5 7 14 29 92 92	Method: LC-MS/MS LOQ = 0.01 mg/kg
S13-00323 S13-00323-02 Mansfield Woodhouse, Nottinghamshire, NG19 9EG, UK (2013)	Winter wheat (variety Gallant)	1) 15/09/12 2) N/A 3) 09/08/13	1245	208	599	13/05/13	32	Green plant Green plant Green plant Green plant Green plant Green plant Grain Straw	61.93 12.41 2.34 1.68 1.45 0.54 0.11 <u>< 0.01</u> <u>0.11</u>	0 1 3 5 7 15 31 88 88	Method: LC-MS/MS LOQ = 0.01 mg/kg
S13-00323 S13-00323-03 21739, Dollern, Niedersachsen, Germany (2013)	Spring barley (variety Marthe)	1) 16/04/13 2) 20- 24/06/13 3) 05/08/13	1200	200	600	03/06/13	32	Green plant Green plant Green plant Green plant Green plant Green plant Grain Straw	47.90 32.52 22.76 14.44 8.10 3.55 0.83 <u>< 0.01</u> <u>0.27</u>	0 1 3 5 7 14 30 63 63	Method: LC-MS/MS LOQ = 0.01 mg/kg

Trial No./ Location/ Year	Commodity/ Variety	Date of 1.Sowing or planting 2.Flowering 3. Harvest	Application rate per treatment			Dates of treatment or no. of treatments and last date	Growth stage at last treatment or date	Portion analysed	Residues (mg/kg) MCP-P	PHI (days)	Remarks
			g a.s./ ha	Water (l/ha)	g a.s./hl						
S13-00323 S13-00323-04 71665, Vaihingen an der Enz, Baden- Wurttemberg, Germany (2013)	Spring barley (variety Grace)	1) 10/04/13 2) Early June 3) 02/08/13	1268	211	601	20/05/13	32	Green plant Green plant Green plant Green plant Green plant Green plant Green plant Grain Straw	28.00 1.77 1.31 0.69 0.37 0.25 0.08 <u>< 0.01</u> <u>< 0.01</u>	0 1 3 5 7 13 25 69 69	Method: LC-MS/MS LOQ = 0.01 mg/kg

Report:	CA 6.3.1/01, Old, J & Duncan, P (2001) + Doig, A (2011)
Title	Residue decline of Mecoprop-P potassium salt in cereals in Southern Europe, Report and amendment 1 Report No. 19513/ 397315 (AHM R 00 115F)
Guidelines:	Directive 91/414/EEC
GLP:	Yes
Deviations	None
Previous evaluation:	Submitted for purposes of renewal.

Report:	CA 6.3.1/02, Perny, A (2002a)
Title	Residue decline of Mecoprop-P potassium salt in cereals in Southern Europe Report No. R A011939 (AHM R 00 115A) [Analytical phase for Report No. 19513/ 397315]
Guidelines:	Not stated
GLP:	Yes
Deviations	None
Previous evaluation:	Submitted for purposes of renewal.

Four trials were conducted in 2000 at two locations in Southern France and two locations in Spain. One trial was accidentally harvested before grain and straw samples could be taken therefore this was disregarded. Mecoprop-P was applied *via* sprayer as formulated product Optica (Mecoprop-P K 600 g a.s/L) to winter cereals (2 wheat and 1 barley) at the growth stage BBCH 32 – 33. This growth stage is considered applicable to that proposed in the GAP (max. BBCH 32) as at this early timing the difference in crop development between BBCH 32 and 33 is not of concern. The actual application rate in each of the trials was reported to be: 1500, 1524 and 1554 g a.s./ha. These are more critical than that proposed in the GAP, but are still considered applicable, as they only just fall outside the +25% extrapolation considered acceptable. Additionally, the more critical rate and later growth stage represents a worse case.

Samples of whole plants were collected immediately and at 7, 14 and 28 days after last application and the results clearly show significant decline of residues. Grain and straw were collected at harvest. All samples were stored frozen (< -18°C) prior to analysis for a maximum of 273 days, this time period is adequately covered by the storage stability studies discussed in Section B.7.1. Analysis was conducted under a separate contract and study (Perny, 2002a).

Residues of mecoprop-P were determined according to GC-MS method ATM 592. This analytical method has been deemed fit for purpose (see Volume 3 of Active dossier, section B.5.1.2.5). The LOQ was 0.05 mg/kg for all matrices.

In grain no detectable residues above the LOQ were observed and in straw the residues ranged from 0.06 to 0.22 mg/kg. No residues above the LOQ were detected in any of the control samples. The individual trials are summarised in Table 7.3-2.

Report:	CA 6.3.1/03, Wardman, J P (2002a)
Title	Optica residue decline of Mecoprop-P in cereals in Southern Europe Report No. 20472/ 680333 (AHM R 01 115F)
Guidelines:	91/414/EEC
GLP:	Yes
Deviations	None
Previous evaluation:	Submitted for purposes of renewal.

Report:	CA 6.3.1/04, Gallais, C (2002a)
Title	Residue decline of Mecoprop-P potassium salt in cereals in Southern Europe Report No. R A1135 (AHM R 01 115A) [Analytical phase for Report No. 20472/ 680333]
Guidelines:	91/414/EEC
GLP:	Yes
Deviations	None
Previous evaluation:	Submitted for purposes of renewal.

Six trials were conducted in 2001 at four locations in Southern France and two locations in Spain. One trial was accidentally harvested before grain and straw samples could be taken therefore this was disregarded. Mecoprop-P was applied *via* sprayer as formulated product Optica (Mecoprop-P K 600 g a.s/L) to winter cereals (3 wheat, 2 barley) at the growth stage BBCH 32 – 33. This growth stage is considered applicable to that proposed in the GAP (max. BBCH 32) as at this early timing the difference in crop development between BBCH 32 and 33 is not of concern. The application of mecoprop-P was at the GAP rate (1200 g a.s./ha) and the actual rates reported were well within $\pm 25\%$.

Samples of whole plants were collected immediately and at 7, 14 and 28 days (± 1 day) after application and the results clearly show significant decline of residues. Grain and straw were collected at harvest (79 – 103 days after application). All samples were stored frozen ($< -18^{\circ}\text{C}$) prior to analysis for a maximum of 310 days, this time period is adequately covered by the storage stability studies discussed in Section B.7.1. Analysis was conducted under a separate contract and study (Gallais, 2002a).

Residues of mecoprop-P were determined according to GC-MS method ATM 592. This analytical method has been deemed fit for purpose (see Volume 3 of Active dossier, section B.5.1.2.5). The LOQ was 0.05 mg/kg for all matrices.

In grain no detectable residues above the LOQ were observed and in straw the residues ranged from <0.05 to 0.32 mg/kg. No residues above the LOQ were detected in any of the control samples. The individual trials are summarised in Table 7.3-2.

Report:	CA 6.3.1/05, Tandy, R (2014a)
Title	Determination of residues of Mecoprop-P after a single application of Mecoprop-P K 600 in cereals at 4 sites in Northern Europe 2013. Report No. S13-00323
Guidelines:	EU 1999: 1607/VI/97 SANCO/3029/99 rev. 4 Guideline 7029/VI/95 (rev. 5) to Directive 91/414/EEC and Regulations (EU) 544/2011 and 545/2011 implementing Regulation (EC) 1107/2009
GLP:	Yes
Deviations	None
Previous evaluation:	Submitted for purposes of renewal.

Four residue trials were conducted in 2013 at two locations in the UK and two locations in Germany. Mecoprop-P was applied once *via* sprayer as Mecoprop-P K 600 at a rate of 1200 g a.s./ha in 200 L/ha water to winter wheat and spring barley at growth stage BBCH 32. These conditions are identical to the proposed GAP. Samples of whole plant were taken 0, 1, 3, 5, 7, 13-14, 25-31 days after application and grain and straw were collected at harvest (63 – 92 days after last application). Samples were stored frozen (< -18°C) prior to analysis for up to a maximum of 309 days, this time period is adequately covered by the storage stability studies discussed in Section B.7.1.

Residues of mecoprop-P were determined according to an LC-MS/MS method CAM-0004/001 (also the enforcement method). This analytical method was validated prior to and during analysis by spiking control samples (see Section B.5.1.2.5). All procedural recoveries were within the acceptable range 70 – 110%. The LOQ was 0.01 mg/kg for all matrices.

In grain no detectable residues above the LOQ were observed and in straw the residues ranged from <0.01 to 0.29 mg/kg. No residues above the LOQ were detected in any of the control samples. The individual trials are summarised in Table 7.3-3.

B.7.3.1. Summary of residue trials

Eight trials in SEU and four trials in NEU on cereal (wheat and barley) were submitted. As the application of mecoprop-P is early on in the growing season in accordance with SANCO 7525/VI/95 rev.9 the trials on barley and wheat can be combined. In the four NEU trials residues in cereal grain were below the LOQ (0.01 mg/kg), therefore in accordance with SANCO 7525/VI/95 rev.9, a reduced data set is acceptable. The NEU and SEU trials were combined when considering cereal straw, as the data appeared to belong to a similar population (Mann-Witney U-Test). The Mann-Whitney U-Test is reported in the FAO Manual 197, 2009 to be an accepted statistical tool to compare two data sets and to assess whether they can be combined. In the case of the NEU and SEU trials the critical value is 4 and $U_1 > 4$ therefore the populations are considered similar and the straw data can be combined (Table 7.3-4).

Table Error! No text of specified style in document.-16 Mann-Whitney U-Test for cereal straw

Straw residue (mg/kg)	Ranks NEU	Ranks SEU
0.01	1	
0.05		2.5
0.05		2.5
0.06		4
0.07		5
0.1		6
0.11	7	

Straw residue (mg/kg)	Ranks NEU	Ranks SEU
0.2		8
0.27	9	
0.28		10
0.29	11	
0.32		12
Σ Rank	28	50
U values	14	18
Critical value ($n_1 = 4, n_2 = 8$)	4	
$U_{\min} > 4?$	Yes. Populations similar	

The residue trials have been evaluated and deemed acceptable to support the proposed GAP. A summary of the residue endpoints derived from the residue trials is presented in Table 7.3-5.

The trials only looked for residues of mecoprop-P. This is not in line with the revised residue definition, which also contains metabolites HMCPP and CAPP. As the trials did not look for these metabolites, the following tentative conversion factors have been used: cereal grain (4) and cereal straw (2.2). These conversion factors are derived from the metabolism study and were proposed in the EFSA Reasoned Opinion (2013; 11(4):3191), although it was stated that further confirmation of these values was required. In the absence of residue trial data these are currently deemed sufficient to represent the contribution of the additional metabolites for risk assessment. However, it is considered appropriate that further confirmatory residue trials data shall be requested to confirm levels of these metabolites in the harvested crop.

Table Error! No text of specified style in document.-17 Residue endpoints

Crop	Region/ Indoor (a)	Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs	Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs	Recommendations /comments (OECD calculations)	MRL proposals (mg/kg)	HR ¹ (mg/kg) (c)	STMR ¹ (mg/kg) (d)
		Monitoring RD	Risk assessment RD ¹				
Cereal grain	NEU Outdoor	4 x < 0.01*	4 x 0.04	Combines trials on wheat (5) and barley (3), as application is early on in growing season therefore extrapolation acceptable. NEU and SEU trials are also combined for straw as data were confirmed to arise from the same population, according to the Mann-Whitney U test.	0.01*	0.04	0.04
Cereal grain	SEU Outdoor	8 x < 0.05*	8 x 0.2		0.05*	0.2	0.2
Cereal straw	NEU + SEU Outdoor	< 0.01*, 2 x < 0.05*, 0.06, 0.07, 0.10, 0.11, 0.20, 0.27, 0.28, 0.29, 0.32	0.022, 2 x 0.11, 0.132, 0.154, 0.22, 0.242, 0.44, 0.594, 0.616, 0.638, 0.704		N/A	0.704	0.231

¹ These values include the tentative conversion factors; grain (4), straw (2.2).

The proposed MRLs are within the current EU MRL for cereals of 0.05* mg/kg. Risk assessments using these endpoints have been conducted in Volume 1, section 2.7.5. (animal dietary burden) and section 2.7.9. (consumer risk assessments).

No trials in accordance with the proposed residue risk assessment definition have been conducted. The levels of metabolites HMCPP and CCPP should be addressed and the following has been identified as a data gap:

- Trials complying with the GAP of mecoprop-P on wheat and/or barley: 1 x 1.2 kg as/ha, in accordance with the residue definition for risk assessment: Mecoprop-P, 2-carboxy-4-chloro-phenoxypropionic acid (CCPP) and 2-hydroxymethyl-4-chloro-phenoxypropionic acid (HMCPP), expressed as mecoprop-P.

B.7.4. FEEDING STUDIES

B.7.4.1. Poultry

A poultry feeding study is not considered required since the worst case SEU dietary burden calculation was only exceeded by an insignificant amount considering the significantly worst case inputs used (see Volume 1, section 2.7.5).

B.7.4.2. Ruminants

A feeding study on cattle was not submitted as part of the 91/414/EC Review. The SEU dietary burden calculation (Volume 1, section 2.7.5) is worst case and indicates the dietary intake for beef and dairy cattle is 0.013 and 0.010 mg/kg bw/day, respectively. This is above the trigger of 0.004 mg/kg bw/day therefore feeding studies are required and the following report was submitted for the purposes of renewal.

Report:	CA 6.4.2/01, [REDACTED] 013)
Title	Mecoprop-P livestock feeding study: magnitude of residue in milk, muscle, liver, kidney and fat of lactating dairy cattle Report No. [REDACTED]
Guidelines:	OECD 505, OPPTS 860.1480, Working document 7031/VI/95 rev. 4, APVMA residue guideline No. 1
GLP:	Yes
Deviations	None
Previous evaluation:	Submitted for purposes of renewal.

In a dairy cattle feeding study, mecoprop-P dissolved in acetone was administered to groups of Friesian/Holstein cattle *via* the diet for 28 or 29 consecutive days. The daily compound feed ration was administered as a split feed on two occasions each day (morning and afternoon feeding). The dosages were calculated on the basis of the maximum 7-day residue in pasture grass. As this grassland use is not being supported during the renewal, the feeding study is significantly over-dosed with respect to the estimated dietary intake of cattle based on cereals (Table 7.4-1).

Table Error! No text of specified style in document.-18 Doses used in feeding study, including comparable X rate to estimated intakes of beef cattle based on cereals in SEU. The dietary burden calculations are displayed below.

mg/kg DM	mg/kg bw/day*	Rate compared to cereal dietary burden intakes for beef cattle in SEU as a worst-case scenario
194	7	538
582	21	1600
1940	71	5460

*based on a body weight of 550 kg

Intakes calculated using HR input (maximum dietary burden) in SEU

Animals	Median burden (mg/kg bw)	Maximum burden (mg/kg bw)	Above 0.004 mg /kg bw	Maximum burden (mg/kg DM)	Highest contributing commodities	
Dairy cattle	0.006	0.010	Yes	0.40	Barley	straw
Beef cattle	0.006	0.013	Yes	0.33	Barley	straw
Ram/Ewe	0.008	0.019	Yes	0.57	Barley	straw
Lamb	0.010	0.024	Yes	0.57	Barley	straw
Pig (breeding)	0.004	0.004	Yes	0.18	Barley	grain
Pig (finishing)	0.005	0.005	Yes	0.18	Barley	grain
Poultry broiler	0.011	0.011	Yes	0.16	Barley	grain
Poultry layer	0.016	0.019	Yes	0.28	Wheat	straw
Turkey	0.010	0.010	Yes	0.14	Rye	grain

Intakes calculated using HR input (maximum dietary burden) in NEU

Animals	Median burden (mg/kg bw)	Maximum burden (mg/kg bw)	Above 0.004 mg /kg bw	Maximum burden (mg/kg DM)	Highest contributing commodities	
Dairy cattle	0.003	0.006	Yes	0.27	Barley	straw
Beef cattle	0.004	0.010	Yes	0.26	Barley	straw
Ram/Ewe	0.006	0.016	Yes	0.49	Barley	straw
Lamb	0.007	0.021	Yes	0.49	Barley	straw
Pig (breeding)	0.001	0.001	No	0.04	Barley	grain
Pig (finishing)	0.001	0.001	No	0.04	Barley	grain
Poultry broiler	0.002	0.002	No	0.03	Barley	grain
Poultry layer	0.005	0.008	Yes	0.12	Wheat	straw
Turkey	0.002	0.002	No	0.03	Rye	grain

A control group (2 cows) received diet and acetone only.

Three of the cows in the 1940 mg/kg treatment group were used to generate depuration data. At the end of the dosing period, they were transferred to the control diet to measure the decline in residues following withdrawal of the test item from the diet. Animals were sacrificed between 15 and 21 hours of final dosing, except for the three cows used to generate depuration data, which were sacrificed 3, 5 and 10 days after administration of the final dose.

Residues of mecoprop-P and the potential metabolites 2-(2-hydroxymethyl-4-chlorophenoxy) propionic acid (HMCP), 2-(2-carboxy-4-chlorophenoxy)propionic acid (CCPP) and 4-chloro-2-methyl phenol (PCOC) in milk and tissues were measured using an analytical method based on LC-MS/MS. This method is designed to measure residues of mecoprop-P including its esters and conjugates. The limit of quantitation (LOQ) for each of the analytes in milk, skimmed milk, cream, muscle, liver, kidney and fat is 0.01 mg/kg (see Volume 3 of Active dossier, section B.5.1.2.5 for method validation). Samples were stored for a maximum of 235 days (8 months) at -20°C and extracts were stored at 4°C for a maximum of 7 days, these time periods are adequately covered by the storage stability studies discussed in Section B.7.1.

Residues of mecoprop-P were found in all matrices from cows in all groups. The results of the feeding studies are displayed in Table 7.4-2. Residues in whole milk reached a plateau after 5 days of dosing and remained stable throughout the dosing period. The residues in the 1940 mg/kg dosing group declined to less than the LOQ (0.01 mg/kg) after 2 days of withdrawal of mecoprop-P from the diet. Residues of mecoprop-P did not partition selectively into skimmed milk or cream. Residues of mecoprop-P in muscle, liver, kidney and fat in the 1940 mg/kg dosing group showed a decline after withdrawal of mecoprop-P from the diet. No residues of HMCPP or CCPP were found in any of the specimens in any treatment group.

Although not specifically required by the guidance, residues of PCOC were monitored for in the feeding study. Residues of PCOC were found in cream (but not skimmed milk), liver and fat specimens from cows in the 1940 mg/kg dosing group only and in kidney specimens from cows in all the dosing groups. Residues of PCOC in the highest dosing group declined to less than the LOQ in liver after 3 days of withdrawal of mecoprop-P from the diet and in kidney and fat after 5 days of withdrawal of mecoprop-P from the diet. Residues of PCOC up to a maximum of 0.076 mg/kg in the 1940 mg/kg dosed study were observed. These levels are not of a concern, as the feeding studies are significantly overdosed and the level of the relevant impurity (max. of 5 g/kg) is controlled by the specification of the technical grade active substance. As PCOC is not formed as a result of metabolism in animals the levels in the animal samples would be very low, well below the level of toxicological relevance. No further consideration is required.

Regression analysis for mecoprop-P in whole milk, skimmed milk and cream demonstrated a linear relationship between the dose level and the resulting residue concentration. Therefore the expected residues at a 1X rate can be concluded to be < LOQ (0.01 mg/kg). A non-linear relationship between the dose level and residue concentration was found for mecoprop-P in all other matrices. It is therefore infeasible to estimate residue levels of mecoprop-P in muscle, liver, kidney and fat for the 1X rate and to propose MRLs. However, considering the goat metabolism study (B.7.2.3), which was conducted at a much more appropriate rate of 0.13 mg/kg bw/day (10N compared to beef cattle in SEU), residues of mecoprop-P in these matrices were always found well below 0.01 mg/kg. It can therefore be reliably concluded that mecoprop-P residues will be < 0.01 mg/kg in muscle, liver, kidney and fat.

Table 7.4-3 summarises the endpoints for use in the consumer risk assessments, considering the mean and highest residues. The residue definition for animal commodities is ‘mecoprop-P’ both for enforcement and risk analysis.

Conclusion

The livestock feeding study conducted on dairy cows is significantly overdosed (538X rate) compared with the estimated dietary burden calculated for beef cattle based on the intakes of cereal grain and straw. This feeding study was only dosed with parent mecoprop-P, but a case is made in section B.7.2.3. addressing this point and it can reasonably be concluded that residues of HMCPP and CCPP will not be expected in ruminant tissues.

Results of the feeding study demonstrated that no residues of HMCPP and CCPP were observed in any of the matrices. A linear relationship was demonstrated between the dosing level and residue of mecoprop-P in milk and cream, therefore it can be concluded that expected residues at the 1X rate would be < LOQ (0.01 mg/kg) and an MRL can be proposed. However, a non-linear relationship between the dose level and observed residue in muscle, liver, kidney and fat means it is impossible to conclude that at the 1X rate residues of mecoprop-P in these matrices will be < LOQ. However, consideration of the ruminant metabolism study allows for the reasonable conclusion that levels of mecoprop-P in muscle, liver, kidney and fat will be <0.01 mg/kg. These levels will be used in the consumer risk assessments to represent a worst-case.

Table Error! No text of specified style in document.-19 Milk, cream, fat and tissue residues of mecoprop-P, HMCPP, CCPP and PCOC found in dairy cows dosed with mecoprop-P for 28 - 29 days

Sample	Day	Mean residues (highest residue) determined (mg/kg)											
		194 mg/kg (538X) in diet				582 mg/kg (1600X) in diet				1940 mg/kg (5460X) in diet			
		mecoprop-P	HMCPP	CCPP	PCOC	mecoprop-P	HMCPP	CCPP	PCOC	mecoprop-P	HMCPP	CCPP	PCOC
Milk	-1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
	1	0.012 (0.014)	<0.01	<0.01	<0.01	0.047	<0.01	<0.01	<0.01	0.116	<0.01	<0.01	<0.01
	3	0.015 (0.018)	<0.01	<0.01	<0.01	0.046	<0.01	<0.01	<0.01	0.154	<0.01	<0.01	<0.01
	5	0.014 (0.016)	<0.01	<0.01	<0.01	0.034	<0.01	<0.01	<0.01	0.109	<0.01	<0.01	<0.01
	7	0.014 (0.016)	<0.01	<0.01	<0.01	0.036	<0.01	<0.01	<0.01	0.120	<0.01	<0.01	<0.01
	10	0.016 (0.019)	<0.01	<0.01	<0.01	0.034	<0.01	<0.01	<0.01	0.108	<0.01	<0.01	<0.01
	14	0.013 (0.013)	<0.01	<0.01	<0.01	0.029	<0.01	<0.01	<0.01	0.099	<0.01	<0.01	<0.01
	18	0.017 (0.023)	<0.01	<0.01	<0.01	0.038	<0.01	<0.01	<0.01	0.110	<0.01	<0.01	<0.01
	20	0.014 (0.016)	<0.01	<0.01	<0.01	0.044	<0.01	<0.01	<0.01	0.108	<0.01	<0.01	<0.01
	22	0.015 (0.016)	<0.01	<0.01	<0.01	0.037	<0.01	<0.01	<0.01	0.109	<0.01	<0.01	<0.01
	24	0.013 (0.016)	<0.01	<0.01	<0.01	0.047	<0.01	<0.01	<0.01	0.100	<0.01	<0.01	<0.01
28	0.015 (0.017)	<0.01	<0.01	<0.01	-	-	-	-	0.152	<0.01	<0.01	<0.01	
29	-	-	-	-	0.049	<0.01	<0.01	<0.01	-	-	-	-	
Skimmed milk		0.013 (0.014)	<0.01	<0.01	<0.01	0.036	<0.01	<0.01	<0.01	0.111	<0.01	<0.01	<0.01
Cream		0.015 (0.019)	<0.01	<0.01	<0.01	0.040	<0.01	<0.01	<0.01	0.133	<0.01	<0.01	0.024
Muscle	28 - 29	0.084 (0.143)	<0.01	<0.01	<0.01	0.142 (0.245)	<0.01	<0.01	<0.01	0.182 (0.379)	<0.01	<0.01	<0.01
Liver	28 - 29	0.196 (0.314)	<0.01	<0.01	<0.01	0.404 (0.661)	<0.01	<0.01	<0.01	0.773 (1.074)	<0.01	<0.01	0.016
Kidney	28 - 29	0.999 (1.622)	<0.01	<0.01	0.016 (0.018)	2.201 (3.385)	<0.01	<0.01	0.029 (0.034)	6.226 (9.505)	<0.01	<0.01	0.059 (0.076)
Fat	28 - 29	0.192 (0.276)	<0.01	<0.01	<0.01	0.255 (0.276)	<0.01	<0.01	<0.01	0.451 (0.909)	<0.01	<0.01	0.012

Table Error! No text of specified style in document.-20 Animal inputs for consumer risk assessments: original values and scaled values

Commodity	Chronic risk (mean residue, mg/kg)	Acute risk (highest residue, mg/kg)		Proposed MRL (mg/kg)
		Input	Input	
muscle	-	<0.01 ¹	<0.01 ¹	0.01 (default)
liver	-	<0.01 ¹	<0.01 ¹	0.01 (default)
kidney	-	<0.01 ¹	<0.01 ¹	0.01 (default)
fat	-	<0.01 ¹	<0.01 ¹	0.01 (default)
milk and cream	0.015	<0.01 ²	0.023	0.01(default)

¹These values are estimated from the metabolism study.

²These inputs have been scaled to take into account that the feeding study was conducted at 538X rate compared to the calculated intakes from the dietary burden conducted in Volume 1, section 2.7.5 based on cereal consumption only.

B.7.4.3. Pigs

A swine feeding study is not required since the dietary intake is calculated to be below 0.004 mg/kg bw/day for NEU and the SEU dietary burden calculation demonstrated the trigger was only exceeded by an insignificant amount considering the significantly worst case inputs used (see Volume 1, section 2.7.5).

B.7.4.4. Fish

A fish study is not required since no official guidance has been released.

B.7.5. EFFECTS OF PROCESSING**B.7.5.1. Nature of the residue**

In accordance with the data requirements 283/2013, if residues ≥ 0.01 mg/kg are observed then information on the nature of residues during processing is required. Some of the submitted residue trials (SEU) only support an LOQ of 0.05 mg/kg and considering that mecoprop-P is highly water soluble, the nature of residues in cereal grain (the part of the crop to be processed) should be addressed.

A case was submitted by the applicant citing that the plant metabolism study, conducted at 1.2 N, confirms that mecoprop-P is not expected above 0.01 mg/kg in grain (0.004 mg/kg at 1.2N). Additionally, in the DAR (Denmark, 1998) a high temperature hydrolysis study was provided (Annex IIA point 2.9.1). Whilst this study did not mimic the representative hydrolysis conditions for baking and brewing required by OECD 507 (pH 5, 100°C for 60 min), it does demonstrate that mecoprop-P was stable under pH 5, 7 and 9 conditions at 70°C for 8 days.

Considering the likely residues of mecoprop-P in cereal grain, it can be concluded that residues are likely to be <0.01 mg/kg and no further information on the nature of mecoprop-P residues during processing is required.

B.7.5.2. Distribution of the residue in peel and pulp

Not applicable, cereals do not have peel.

B.7.5.3. Magnitude of residues in processed commodities

Processing or household studies are not needed as residues in the parts of the plant to be processed (grains) are lower than the trigger value of 0.1 mg/kg. No residues at or above the LOQ (0.05 mg/kg in SEU, 0.01 mg/kg in NEU) were found in cereal grains.

B.7.6. RESIDUES IN SUCCEEDING OR ROTATIONAL CROPS**B.7.6.1. Metabolism in rotational crops**

Metabolism studies in rotational crops are not required, since mecoprop-P is not persistent in soil (DT_{50} 10.12 days). Additionally, there are no soil metabolites.

B.7.6.2. Magnitude of residues in rotational crops

Not required. See B.7.6.1

B.7.7. OTHER STUDIES**B.7.7.1. Effect on the residue level in pollen and bee products**

A bee study is not required since no official guidance has been released.

B.7.8. REFERENCES RELIED ON

Regarding the literature search undertaken by the applicant (report dated 15/07/2015). It is considered that the search is acceptable in terms of databases searched and the search criteria applied. The search did not reveal any references of relevance to this section.

The references relied on list has been updated to include the newly submitted data relied on as well as those original submitted tests and studies (in *italics*) that are still considered relevant to support the application for renewal.

Data Point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
CA 6.1	<i>Perny, A.</i>	2002	<i>Storage Stability of Mecoprop-P Residues in Cereals Final Report No. A0128, 2002 AHMARKS Study No. AHMR 00141 ANADIAG, 67500 Haguenau France GLP: Y Published: N</i>	<i>N</i>	<i>Y but expired</i>	<i>N/A</i>	<i>BAS</i>	<i>In DAR, Addendum II (July 2002)</i>
CA 6.1/01 & 6.4.2/01	██████████	2013	Mecoprop-P livestock feeding study: magnitude of residue in milk, muscle, liver, kidney and fat of lactating dairy cattle Report No. ██████████ ██████████ GLP: Y Published: N	Y	Y	Cattle intakes triggered so feeding study required.	Nufarm	Submitted for the purposes of renewal
CA 6.1/02	██████████	2014	Frozen Storage Stability Study for Mecoprop-P, HMCPP, CCPP and ██████████	Y	Y	Supporting data for feeding study	Nufarm	Submitted for the purposes of renewal

Data Point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
			PCOC in Bovine Specimens ██████████ GLP: Y Published: N			██████████		
CA 6.1 & CA 6.2.1	Cooper J.L.D., Jones M.K. Lowdon P. and Parsons R	1998	14C-mecoprop-P: Wheat Metabolism Study. Study No. P93/169. BASF# 98/10444 GLP: Y Published: N	N	Y but expired	N/A	BAS	In DAR (1998)
CA 6.1 & CA 6.2.3	██████████	2001	The Distribution and Metabolism 14C-Mecoprop-P in the Lactating Goat. ██████████ p. ██████████ MCCP-P (1988) Task Force, c/o BASF, Limburgerhof, Germany. BASF DocID 2001/1017222 GLP: Y Published: N	Y	Y but expired	N/A	BAS	In DAR (Addendum II, July 2002)
CA 6.3.1/02	Perny, A.	2002a	Residue decline of Mecoprop-P potassium salt in cereals in Southern Europe R A011939 (AHM R 00 115A) Analytical phase for report 19513/397315 Anadiag GLP: Y Published: N	N	N	N/A	Nufarm	Submitted for the purposes of renewal
CA 6.3.1/01	Old, J & Duncan, P + Doig, A (amendment)	2001 (2011 amendment)	Residue decline of Mecoprop-P potassium salt in cereals in Southern Europe, Report and amendment 1 Report No. 19513/397315 (AHM R 00 115F)	N	Y (for amendment)	New data submitted	Nufarm	Submitted for the purposes of renewal

Data Point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous evaluation
			GLP: Y Published: N					
CA 6.3.1/03	Wardman, J P	2002a	Optica residue decline of Mecoprop-P in cereals in Southern Europe Report No. 20472/680333 (AHM R 01 115F) GLP: Y Published: N	N	N	N/A	Nufarm	Submitted for the purposes of renewal
CA 6.3.1/04	Gallais, C.	2002a	Residue decline of Mecoprop-P potassium salt in cereals in Southern Europe R A1135 Analytical phase for report 20472/680333 Anadiag GLP: Y Published: N	N	N	N/A	Nufarm	Submitted for the purposes of renewal
CA 6.3.1/05	Tandy, R	2014a	Determination of residues of Mecoprop-P after a single application of Mecoprop-P K 600 in cereals at 4 sites in Northern Europe 2013 Report No. S13-00323 GLP: Y Published: N	N	Y	New trials in NEU replace old non-GLP trials.	Nufarm	Submitted for the purposes of renewal