

# ***European Commission***



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

**MECOPROP-P**

**Volume 1**

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

**Version History**

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

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# **Level 1**

**MECOPROP-P**

## **1. STATEMENT OF SUBJECT MATTER AND PURPOSE FOR WHICH THIS REPORT HAS BEEN PREPARED AND BACKGROUND INFORMATION ON THE APPLICATION**

### **1.1. CONTEXT IN WHICH THIS DRAFT ASSESSMENT REPORT WAS PREPARED**

#### **1.1.1. Purpose for which the draft assessment report was prepared**

Mecoprop-P was originally included in Annex I of the EU Council Directive 91/414/EEC on 1 June 2004 via Commission Directive 2003/70/EC. The active substance was subsequently approved under Regulation (EC) 1107/2009 via Implementing Regulation (EU) 540/2011. In accordance with Commission Regulation (EU) 844/2012 of 18 September 2012, Nufarm submitted a dossier to support the renewal of the approval of mecoprop-P. This substance was originally assigned to Poland as RMS. The RMS was switched at the July 2014 Standing Committee meeting (SCoPAFF) to the UK. IE remains as the co-RMS.

The UK acting as the Rapporteur Member State (RMS) evaluated all aspects of the renewal dossier via a Renewal Assessment Report (RAR). The RAR was the subject of a peer review by the Co-RMS Ireland.

This RAR provides a discussion of relevant new studies and information submitted and evaluated since the Annex I inclusion of mecoprop-P in 2004, and how these data affect the human health and environmental risk assessments, residue definitions, and MRLs. Some studies submitted for the original EU evaluation for Annex I inclusion have been re-evaluated as necessary, whilst others may have been reconsidered for context and to validate previous conclusions and/or calculations.

A proposal for MRL-setting is not included at this time as further residue trials data are required to support the proposed residue definition. Proposed classification according to Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures can be found at Level 2.10.

#### **1.1.2. Arrangements between rapporteur Member State and co-rapporteur Member State**

The RAR was the subject of a peer review by the Co-RMS Ireland.

#### **1.1.3. EU Regulatory history for use in Plant Protection Products**

For the review of mecoprop-P under Council Directive 91/414/EEC, BASF AG submitted a dossier to the RMS on behalf of the ‘Mecoprop-P Dossier Preparation Working Group’ formed between BASF AG, Rhone-Poulenc Agro and A H Marks and Co Ltd.

Nufarm UK Limited submitted a dossier on behalf of the ‘Nufarm Dossier Preparation working group’ formed by Agrolinz (later Nufarm Pflanzenschutz GmbH & Co. LG) and Nufarm UK Limited.

The ‘Mecoprop-P Dossier Preparation Working Group’ and the ‘Nufarm Dossier Preparation Working Group’ were the only parties to submit dossiers to the Rapporteur Member State which did not contain substantial data gaps, taking into account the supported uses, and were therefore considered the main data submitters.

In April 2008 Nufarm UK Limited acquired A H Marks & Company Limited and all data relating to the EU Review of mecoprop-P.

The dossier for mecoprop-P submitted on behalf of the ‘Mecoprop-P Dossier Preparation Working Group’ formed between BASF AG, Rhone-Poulenc Agro and A H Marks and Co Ltd was first evaluated by Denmark as RMS in 1998 as part of the programme of work set out in Commission Regulation (EEC) No. 3600/92 to review existing active substances referred to in Article 8(2) of Council Directive 91/414/EEC concerning the placing of plant protection products on the market. Mecoprop-P was on the first list for review. EU peer review was initiated under ECCO in 1999 (Round 08 Expert Meetings 089 –

098) and the final Commission Review Report (SANCO/3065/99-Final) was published on 14 April 2003 (EFSA conclusions were not produced at that time).

No confirmatory data were identified in Commission Directive 2003/70/EC.

Mecoprop-P MRLs are currently under Article 12 review. A Reasoned Opinion is not yet available.

#### 1.1.4. Evaluations carried out under other regulatory contexts

There are currently no JMPR evaluations published for mecoprop-P.

### 1.2. APPLICANT INFORMATION

#### 1.2.1. Name and address of applicant(s) for approval of the active substance

Company: Nufarm UK Limited  
Address: Wyke Lane  
Wyke  
Bradford  
West Yorkshire  
BD12 9EJ  
United Kingdom  
Contact: [REDACTED]  
Phone: [REDACTED]  
E-Mail: [REDACTED]  
  
Alternative contact  
Contact: [REDACTED]  
Phone: [REDACTED]  
E-Mail: [REDACTED]

#### 1.2.2. Producer or producers of the active substance

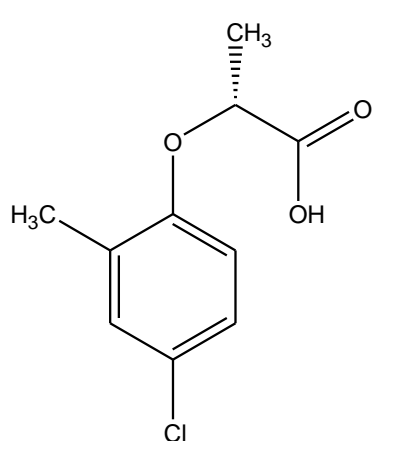
**Producer**  
Company: Nufarm UK Limited  
Address: [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
Contact: [REDACTED]  
Phone: [REDACTED]  
E-Mail: [REDACTED]  
  
Alternative contact  
Contact: [REDACTED]  
Phone: [REDACTED]  
E-Mail: [REDACTED]



**1.2.3. Information relating to the collective provision of dossiers**

Nufarm UK Limited is the sole company in the European Union involved in the manufacture of mecoprop-P holding registration data therefore it is not necessary to present a collective dossier as Nufarm is the only interested party.

**1.3. IDENTITY OF THE ACTIVE SUBSTANCE**

<b>1.3.1. Common name proposed or ISO-accepted and synonyms</b>	Mecoprop-P  Synonyms: Mechlorprop-P, Mécoprop-P MCP-P, CMPP-P
<b>1.3.2. Chemical name (IUPAC and CA nomenclature)</b>	
IUPAC	(R)- 2-(4-chloro-2-methylphenoxy)propanoic acid
CA	(R)(+)-2-(4-chloro-2-methylphenoxy)-propanoic acid
<b>1.3.3. Producer's development code number</b>	G750
<b>1.3.4. CAS, EEC and CIPAC numbers</b>	
CAS	16484-77-8
EEC	240-539-0
CIPAC	475
<b>1.3.5. Molecular and structural formula, molecular mass</b>	
Molecular formula	C <sub>10</sub> H <sub>11</sub> ClO <sub>3</sub>
Structural formula	
Molecular mass	214.65
<b>1.3.6. Method of manufacture (synthesis pathway) of the active substance</b>	Please refer to Volume 4 Annex C.
<b>1.3.7. Specification of purity of the active substance in g/kg</b>	890 g/kg min

<b>1.3.8. Identity and content of additives (such as stabilisers) and impurities</b>	
<b>1.3.8.1. Additives</b>	Please refer to Volume 4 Annex C.
<b>1.3.8.2. Significant impurities</b>	Please refer to Volume 4 Annex C.
<b>1.3.8.3. Relevant impurities</b>	4-chloro-2-methylphenol (PCOC)
<b>1.3.9. Analytical profile of batches</b>	Please refer to Volume 4 Annex C.

**1.4. INFORMATION ON THE PLANT PROTECTION PRODUCT**

<b>1.4.1. Applicant</b>	<p>Nufarm UK Limited          Wyke Lane, Wyke          Bradford          West Yorkshire          BD12 9EJ          United Kingdom          Contact: [REDACTED]          Phone: [REDACTED]          E-Mail: [REDACTED]</p> <p>Alternative contact:          Contact: [REDACTED]          Phone: [REDACTED]          E-Mail: [REDACTED]</p>
<b>1.4.2. Producer of the plant protection product</b>	Nufarm UK Limited
<b>1.4.3. Trade name or proposed trade name and producer's development code number of the plant protection product</b>	<p><u>Product codes:</u>          CA3015, Q121A</p> <p><u>Trade Names:</u>          Clenecorn Super          Compitox Plus          CZ-600          Duplosan KV          Duplosan KV-P          Duplosan MCPP          Duplosan Meko          Duplosan New System          Duplosan 60 SL          Hedonal Optica MCPP-p          Hermoo Mecoprop-P 600          Isomec          Marks Optica MP K          Nufarm Mekoprop          Nufarm Mekoprop-p          Optica          Optica MCPP-p          Optica MP          Optica Mekoprop-p          N-Optica Mekoprop-p          SK-600</p>
<b>1.4.4. Detailed quantitative and qualitative information on the composition of the plant protection product</b>	
<b>1.4.4.1. Composition of the plant protection product</b>	Please refer to Volume 4 Annex C.
<b>1.4.4.2. Information on the active substances</b>	Please refer to Section 1.3 above.

	The active substance is present as the potassium salt (600 g/l). ISO Common name: Mecoprop-P K salt CAS number: 66423-05-0 CIPAC number: 475
<b>1.4.4.3. Information on safeners, synergists and co-formulants</b>	Please refer to Volume 4 Annex C.
<b>1.4.5.</b> Type and code of the plant protection product	Soluble Concentrate [Code: SL]
<b>1.4.6.</b> Function	Herbicide
<b>1.4.7.</b> Field of use envisaged	Spring and winter cereals
<b>1.4.8.</b> Effects on harmful organisms	Mecoprop-p is systemic in plants. It is absorbed primarily by the leaves with some absorption through the roots and translocated acro- and basipetally.

## 1.5. DETAILED USES OF THE PLANT PROTECTION PRODUCT

Please see the GAP table below.

## 1.5.1. Details of representative uses

## List of approved uses (GAP information) – Mecoprop-P K 600

Crop and/ or situation  (a)	Member State or Country	Product name	F, G, or I  (b)	Pests or Group of pests controlled  (c)	Formulation		Application				Application rate per treatment			PHI (days)  (l)	Remarks:  (m)
					Type  (d-f)	Conc. of as (i)	Method kind  (f-h)	Growth stage  (j)	Number min max  (k)	Interval between applications (min)	kg as/hL  min max	water L/ha  min max	kg as/ha  min max		

Cereals															
Winter Cereals Wheat (including durum and spelt), Barley, Rye, Oats, Triticale	Various	Various	F	Broadleaved Weeds	SL	600	tractor mounted boom	In the spring at BBCH 20 - 32	1	N/A		200 – 400	1.2	N/A	Applied from 01/03 (2l/ha)
Spring Cereals Wheat (including durum and spelt), Barley, Rye, Oats, Triticale	Various	Various	F	Broadleaved Weeds	SL	600	tractor mounted boom	In the spring at BBCH 13 - 32	1	N/A		200 – 400	1.2	N/A	Applied from 01/03 (2l/ha)

SL – Soluble concentrate

N/A – Not Applicable

Remarks:

- (a) For crops, the EU and Codex classifications (both) should be used; where relevant, the situation should be described (e.g. fumigation of a structure)
- (b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
- (c) e.g. biting and sucking insects, soil born insects, foliar fungi, weeds
- (d) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
- (e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
- (f) All abbreviations used must be explained
- (g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench

- (h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between plants- type of equipment used must be indicated
- (i) g/kg or g/l
- (j) Growth stage at last treatment (BBCH Monograph, Growth stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4); including where relevant, information on season at the time of application
- (k) Indicate the minimum and maximum number of application possible under practical conditions of use
- (l) PHI - minimum pre-harvest interval
- (m) Remarks may include: Extent of use / economic importance / restrictions

### 1.5.2. Further information on representative uses

The method of application is by conventional field crop sprayer with medium nozzles at a pressure of 2-3 bar (30-45 psi) and water volume of 200 - 400 litres per hectare.

Maximum number of applications and their timings: 1 application per crop/year.

Growth stages of crops or plants to be protected: In the spring at BBCH 20 – 32 (for Winter Cereals: Wheat (including durum and spelt), Barley, Rye, Oats, Triticale) and In the spring at BBCH 13 – 32 (for Spring Cereals: Wheat (including durum and spelt), Barley, Rye, Oats, Triticale).

Development stages of the harmful organism concerned: Not applicable.

Duration of protection afforded by each application and duration of protection afforded by the maximum number of applications: The product is applied as a single application per crop/year. The latest timing of application is BBCH 32 for both winter and spring cereals.

Mecoprop-P has been tested in numerous field trials which demonstrated effective herbicidal activity. Mecoprop-P has been registered in many EU countries based on detailed national assessments of efficacy data in compliance with requirements and according to the uniform principles, with which Member State authorities were satisfied. The list of weeds controlled differs slightly from the list included in the EU DAR used to support the first approval of mecoprop-P. It is likely that this reflects the slightly reduced dose rate – but this will need to be checked by Member States at product renewal. There may, for example be effectiveness data at a dose of 1.2 kg/ha mecoprop-P submitted as part of the re-registration process under EU Directive 91/414/EEC which indicate acceptable levels of control of certain weed species at 1.2 kg/ha. In addition this dose may give useful control as part of a co-formulation.

Overall the RMS view is that there is some evidence that this dose would be ‘sufficiently effective.’

### 1.5.3. Details of other uses applied for to support the setting of MRLs for uses beyond the representative uses

There are no other uses applied for beyond the representative use.

### 1.5.4. Overview on authorisations in EU Member States

The active substance mecoprop-P has been registered for many years in the European Union in a range of different liquid (SL) formulations, including numerous mixture products. The Table below gives details of the current EU registrations of the example formulation Mecoprop-P K 600:

Country	Trade name	Approval number
Austria	Duplosan KV	3048
	Optica MP	2609
Belgium	Duplosan KV-P	7615/B
	Hermoo Mecoprop-P 600	8786/B
Czech Republic	CZ-600	4082-4
	Duplosan KV	3855-2
	Optica	4082-3
Estonia	Optica	0016/18.01.06
Finland	Duplosan Meko	1719
France	Optica	9100410
Germany	Duplosan KV	043678-00
	Marks Optica MP K	3950-00
Hungary	Duplosan KV	02.5/3131/2/2008
	Optica	02.5/3743/1/2008
Ireland	Compitox Plus	PCS 02843
	Duplosan KV	PCS 02842
	Duplosan New System CMPP (K salt)	PCS 91667
Italy	Duplosan KV	13335

Country	Trade name	Approval number
Luxembourg	Duplosan KV-P	L01044-090
Netherlands	Duplosan MCPP	9531 N
Slovakia	Optica	11-11-1216
	SK-600	11-11-1215
Slovenia	Duplosan KV	327-02-350/2002/17
UK	Clenecorn Super	MAPP 14628
	Compitox Plus	MAPP 14390
	Duplosan KV	MAPP 13971
	Isomec	MAPP 14385
	Optica	MAPP 14373

## **Level 2**

**MECOPROP-P**

## **2. SUMMARY OF ACTIVE SUBSTANCE HAZARD AND OF PRODUCT RISK ASSESSMENT**

### **2.1. IDENTITY**

Mecoprop-P ((R)-2-(4-chloro-o-tolyloxy)-propionic acid) is a phenoxy herbicide with a molecular mass of 214.65 and CAS No. 16484-77-8. The minimum purity is 890 g/kg. Mecoprop-P is a systemic herbicide for use in cereals at 1.2 kg a.s/ha. Acceptable information has been provided on the identity of mecoprop-P and a new reference specification has been proposed (see Volume 4 Confidential information).

However, there is no batch analysis for the majority of the batches used in the toxicity studies (see Table C.10 in Volume 4). It is not possible to conclude if the impurities in the proposed specification were present in the batches used in the toxicity studies. Therefore the toxicity studies cannot be relied on to determine the toxicity profile of the impurities present in the proposed specification. Further information is required to address the toxicity of the impurities in the specification. Information requirements are listed in Table C.6 in the confidential section.

From an ecotoxicology perspective the proposed specification of mecoprop-P was confirmed as equivalent to the previous specification set at first EU review. As such the original Annex I data set with the technical active substance is suitable to support the specification proposed at renewal. However, no batch specification was provided for the studies conducted with the technical active substance and submitted for the purposes of renewal. Nor could it be confirmed that these ecotoxicology-tested batches were included in the 7-batch analysis used to propose the specification at renewal. As such it cannot be confirmed whether studies conducted with the technical a.s. for the purposes of renewal are suitable to support the proposed specification of mecoprop-P.

### **2.2. PHYSICAL AND CHEMICAL PROPERTIES**

#### **2.2.1. Summary of physical and chemical properties of the active substance**

Mecoprop-P is a white solid (pure grade substance) or a dark cream solid (technical grade active substance). Mecoprop-P has a melting point of 93.5 - 97.5°C, is not flammable and has no oxidising or explosive properties. It has a relative density of 1.31 at 22°C and a vapour pressure of  $1.4 \times 10^{-3}$  Pa at 25°C. It has a solubility of > 250 g/L in water (pH 7) at 20°C and solubilities of > 250 g/L in acetone, dichloromethane, ethyl acetate, methanol, toluene and 7.69 g/L in heptane at 20°C. The n-octanol/water partition coefficient (Log Pow) was determined to be -0.19 at pH7 and 20°C, this indicates the active does not bio-accumulate. A volatility constant (Henry's Law constant) of  $1.7 \times 10^{-4}$  Pa.m<sup>3</sup>mol<sup>-1</sup> was calculated for mecoprop-P.

Spectroscopic data for the relevant impurity, PCOC, has been assessed and is sufficient to allow identification of this impurity. However, no information was provided on the metabolites HMCPP and CCPP (plant metabolites). The following data gap was identified:

- Data point 2.7 has not been fully addressed. The n-octanol/water partition coefficient is required for all components of the residue definition.

#### **2.2.2. Summary of physical and chemical properties of the plant protection product**

Mecoprop-P K 600 is a yellow/brown liquid which is not classified as flammable or oxidising. The physical and chemical properties are all acceptable for an SL formulation.

The product is deemed stable in the HDPE commercial packaging following accelerated, ambient 2 year and low temperature storage.

### **2.3. DATA ON APPLICATION AND EFFICACY**

For active substance renewal the applicant has satisfactorily addressed all the Efficacy related points outlined in Appendix 2 of SANCO/2012/11251 (see applicant summary of efficacy information provided in MCA



section 3 final 17 July 2014). The representative uses supported at renewal are at a maximum dose which is less than that currently authorized in cereals in most Member States i.e. 1.2 kg a.s/ha compared to the 1.5-2.4 kg a.s/ha currently authorized (ref: Document D2 final 17 July 2014). This has not been addressed by the applicant. Nonetheless, there may, for example be effectiveness data at a dose of 1.2 kg/ha mecoprop-P submitted as part of the re-registration process under EU Directive 91/414 which indicate acceptable levels of control of certain weed species at 1.2 kg/ha. In addition this dose may give useful control as part of a co-formulation. It is therefore considered that the supported GAP is representative.

### **2.3.1. Summary of effectiveness**

Mecoprop-P has been tested in numerous field trials which demonstrated effective herbicidal activity. Mecoprop-P has been registered in many EU countries based on detailed national assessments of efficacy data in compliance with requirements and according to the uniform principles, with which Member State authorities were satisfied. The list of weeds controlled differs slightly from the list included in the EU DAR used to support the first approval of mecoprop-P. It is likely that this reflects the slightly reduced dose rate – but this will need to be checked by Member States at product renewal. There may, for example be effectiveness data at a dose of 1.2 kg/ha mecoprop-P submitted as part of the re-registration process under EU Directive 91/414 which indicate acceptable levels of control of certain weed species at 1.2 kg/ha. In addition this dose may give useful control as part of a co-formulation.

Overall the RMS view is that there is some evidence that this dose would be ‘sufficiently effective.’

### **2.3.2. Summary of information on the development of resistance**

The risk of future development of weed resistance to mecoprop-P is considered to be low because of the mode of action of the herbicide and its use pattern. The risk can be minimised by adopting a resistance management strategy based on good agricultural practice. This would include the rotation of crops, the use of mixtures and rotation of herbicides with differing modes of action, cultural control and ensuring weeds are treated with the correct application rate, at the optimum timing and under suitable conditions for maximum activity. The guidelines published by the Herbicide Resistance Action Committee (HRAC) should be followed.

### **2.3.3. Summary of adverse effects on treated crops**

Mecoprop-P has been used as an herbicide for a significant period of time and incidences of phytotoxicity are very rare when the product is used as per the label instructions.

### **2.3.4. Summary of observations on other undesirable or unintended side-effects**

Mecoprop-P degrades rapidly (geometric mean soil  $DT_{50}$  = 5.24 days) and is used early in the growing season for cereal crops (latest time of application BBCH 32). This ensures there will be no phytotoxic effects on succeeding crops.

## **2.4. FURTHER INFORMATION**

### **2.4.1. Summary of methods and precautions concerning handling, storage, transport or fire**

Acceptable information has been provided to address these points. Refer to Volume 3 CA and CP, Section B.4.

### **2.4.2. Summary of procedures for destruction or decontamination**

Acceptable information has been provided to address these points. Refer to Volume 3 CA and CP, Section B.4.

### **2.4.3. Summary of emergency measures in case of an accident**

Acceptable information has been provided to address these points. Refer to Volume 3 CA and CP, Section B.4.

## **2.5. METHODS OF ANALYSIS**

### **2.5.1. Methods used for the generation of pre-authorisation data**

Methods of analysis have been submitted to determine the active substance, optical ratio and impurities in the technical material. These are generally HPLC-UV methods and they have been fully validated in accordance with SANCO/3030/99 rev. 4.

An HPLC-UV method of analysis for determining mecoprop-P in the representative product Mecoprop-P K 600 has been assessed and is considered validated in accordance with SANCO/3030/99 rev. 4. A CIPAC method for determination of the relevant impurity, 4-chloro-2-methylphenol, in Mecoprop-P K 600 has also been provided.

Satisfactory methods of analysis for wheat (grain, straw and foliage) and animal matrices have been provided using QUeChERS HPLC-MS/MS methods. The methods for wheat used in the SEU trials are not strictly validated in accordance with SANCO/3029/99/rev.4, but are considered fit for purpose. Methods for wheat in NEU and for animal matrices are validated in accordance with SANCO/3029/99/rev.4. Methods of analysis for other areas of the risk assessment (toxicology and ecotoxicology) have also been assessed in accordance with SANCO/3029/99 rev. 4. The validation evaluation has been conducted in section B.5 of the CA and CP RARs, but applicability of these methods is addressed in the respective sections for the studies which these methods support.

### **2.5.2. Methods for post control and monitoring purposes**

Enforcement methods of analysis for detection of total mecoprop-P, present as acid, ethylhexyl ester or glycine conjugate in cereals (grain, straw and foliage), animal matrices, olives and orange have been provided using a QUeChERS LC-MS/MS method. This covers high acid content (orange), high oil content (olives), dry/high starch content (cereal grain/straw) and high water content (wheat foliage) crops with an LOQ of 0.01 mg/kg in all matrices. These methods were validated in accordance with the requirements of SANCO 825/00 rev. 8.1.

Methods have also been validated for mecoprop-P and corresponding 2-ethyl hexyl ester in soil, water and air in accordance with the requirements of SANCO 825/00 rev. 8.1. The LOQs are 0.01 mg/kg (soil), 0.05 µg/tube (air) and 0.01 µg/L (water).

No method for determining mecoprop-P in body fluids and tissues is required, as mecoprop-P is not classified as toxic or highly toxic.

## 2.6. EFFECTS ON HUMAN AND ANIMAL HEALTH

Since the 91/414/EC review, a number of new toxicology studies have been conducted and are submitted in support of this renewal. Some studies were generated in support of other regulatory requirements or became available to the notifier because of mergers and acquisitions and are submitted here for completeness. Others are submitted to support the new guidelines to be followed and reflect the new data requirements under Regulation (EC) No.1107/2009 (as set out in Regulation (EC) No. 283/2013). New studies submitted to support this renewal are listed in the table below:

### New studies submitted for the current renewal of approval of Mecoprop-P

Data point in volume 3	Study type	Reference
B.6.1.1.2	Absorption, distribution, metabolism and excretion by oral route - interspecies comparison	Timchalk C (2004)
B.6.2.1.2	Acute oral toxicity in the mouse – dietary administration	Lowe, C. (2009)
B.6.2.1.1	Phototoxicity	Heppenheimer, A. (2014)
B.6.5.1.1	Carcinogenicity study in the rat	Milburn, G.M. (2008)
B.6.5.1.2	Carcinogenicity study in the rat: enzyme activity assay	Elcombe, B.M. (2007)
B.6.6.1.2	Preliminary one-generation reproductive toxicity study in the rat	Clode, S.A. (2003)
B.6.7.1	Neurotoxicity studies in rodents	Mellert, W. et al. (1995)
B.6.8.1	Toxicity studies on metabolites and relevant impurities Acute oral toxicity of HMCPP	Ruff, M. (1980)
B.6.9.1	Medical surveillance on manufacturing plant personnel and monitoring studies	White, S. (2014)

**Mecoprop-P** is a systemic herbicide which belongs to the group of auxin-type herbicides. Its mode of action is to mimic auxin, a natural plant growth hormone, but unlike endogenous auxin mecoprop-P is metabolically stable. It is toxic to plants in high concentrations.

There are two isomers of mecoprop, but only the P isomer has herbicidal activity. Most of the studies in this submission have been conducted on mecoprop-P. However, studies on the racemate (mixture of both isomers) are also included where there is limited information on the P isomer. Overall, the studies on the racemate are considered also to be applicable to mecoprop-P, as the toxicity and target organs are very similar.

### 2.6.1. Summary of absorption, distribution and excretion in mammals

The toxicokinetic properties of mecoprop-P have been investigated in the rat in acceptable GLP studies.

#### Absorption and excretion

Mecoprop-P is rapidly and extensively absorbed, reaching peak blood levels at 2 hours at the low dose (5 mg/kg bw) or 4 hours at the high dose (100 mg/kg bw). Based on urinary excretion, absorption is between 90 to 100% in males at the low and high dose, including after repeated dosing. In females absorption was slightly lower, being between 80 and 95% depending on dose or repeated exposure.

Following oral administration mecoprop-P is rapidly excreted, predominantly via the urine. The elimination half-life was under 8 hours with both the low and high dose.

Biliary excretion was not investigated, but studies on the mecoprop racemate included in the 1998 DAR indicated extensive biliary excretion and evidence of significant enterohepatic recirculation which may be presumed to also occur in mecoprop-P.

Metabolism

Mecoprop-P is largely excreted as parent material. The only metabolite of any significance was hydroxymethyl-mecoprop-P (HMCPP), which has an OH group attached to a methyl group, and accounted for approximately one third of the urinary excretion in males but considerably less in females. Carboxy-mecoprop-P (CCPP) was identified as a minor metabolite in females (up to 0.07% in urine).

Tissue distribution

The thyroid, kidney, blood and plasma were the main organs with the highest exposure to mecoprop-P. The decline of the levels in fat and skin during the elimination phase is remarkably slower than for other tissues.

Comparison of rat metabolism with animal, plant and environmental metabolism

Evidence from the open literature suggests that rat and mouse studies are more relevant to humans than the studies in the dog. The dog appears to have reduced capacity for renal clearance of mecoprop which may make it more sensitive to toxic effects at equivalent doses in rats and humans. Therefore the dog is not the most relevant species for determining the effects of mecoprop in humans. Mecoprop-P is a phenoxy herbicide and this finding is believed to apply to all phenoxy herbicides (eg. 2,4-D). Despite this evidence of reduced renal capacity in dogs, in repeat dose studies rodents were more sensitive to mecoprop-P than the dog.

When radiolabelled mecoprop-P was administered to goats, 96% and 93% of the radioactivity in urine at the low and high dose respectively was identified as the parent compound. A similar profile was observed in faeces. Further identification of minor metabolites was considered unnecessary as it is apparent that mecoprop-P is excreted largely unmetabolised.

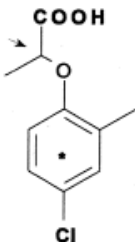


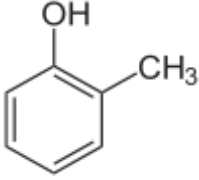
Plant metabolism

The metabolites 2-hydroxymethyl-4-chloro-phenoxypropionic acid (HMCPP) and 2-carboxy-4-chloro-phenoxypropionic acid (CCPP) have been detected in grain and straw. The absolute levels of the metabolites in grain are low but they occur at significant levels in straw (12% and 14% of the administered dose for HMCPP and CCPP respectively). Carboxy-mecoprop-P (CCPP) is a minor urinary metabolite in female rats. Owing to the low levels of this metabolite, the toxicity studies on mecoprop-P are not sufficient to determine the toxicity of carboxy-mecoprop-P. As HMCPP is a major rat metabolite in male rats, the toxicity of HMCPP has been adequately investigated in studies conducted on mecoprop-P.

Environmental metabolism

The environmental metabolite *o*-cresol (also known as 2-methylphenol) was observed only in aqueous photolysis studies (mecoprop-P in pH buffered solutions exposed to artificial sunlight) and was reported at a maximum of 30.4% of the parent dose at pH 7. It is only likely to occur in surface waters. The structure of *o*-cresol is shown below. This metabolite was not detected in rats so its toxicity to mammals has not been investigated.

**Diagram showing structure of mecoprop-P, and its identified metabolites**

Mecoprop-P	Hydroxymethyl-mecoprop-P (HMCPP)	Carboxy-mecoprop-P (CCPP)	2-methylphenol ( <i>o</i> -cresol)
			
Parent compound	Main metabolite in rats	Minor metabolite in female rats	Environmental metabolite

Mecoprop-P	Hydroxymethyl-mecoprop-P (HMCP)	Carboxy-mecoprop-P (CCPP)	2-methylphenol ( <i>o</i> -cresol)
Levels in rat urine: approximately 66 % of the excreted dose in males and 83 % in females.	Levels in rat urine: up to 32.6 % of the excreted dose in males, considerably less in females. Detected in straw at 12% administered dose. Trace levels in grain.	Levels in rat urine: up to 0.07% of excreted dose in females (not detected in males). Detected in straw at 14% administered dose. Trace levels in grain.	Levels: up to 30.4% of parent dose at pH7 in surface waters. Not found in rats.

### 2.6.2. Summary of acute toxicity

Most of the acute toxicity studies were submitted for the previous review in the 1998 DAR. The studies considered to be most relevant and reliable for classification purposes, and any new studies submitted, are shown in the table below. New studies are highlighted in **bold**.

#### Summary of acute toxicity studies conducted on Mecoprop-P

Study	Species	Test Substance: Racemate or D-Isomer	LD <sub>50</sub> (mg/kg bw)	Reference
Acute oral	Rat	D-Isomer (Mecoprop-P)	431 (for both m and f)	Dange (1994a)
Acute dietary	Rat	<b>D-Isomer (Mecoprop-P)</b>	<b>3393</b>	<b>Lowe (2009)</b>
Acute dermal	Rat	D-Isomer (Mecoprop-P)	>2000	Dange (1994b)
Acute inhalation	Rat	D-Isomer (Mecoprop-P)	> 2.13mg/L	Coombs & Clarke 1977
Skin irritation	Rabbit	D-Isomer (Mecoprop-P)	Non-irritant	Dange (1994c)
Eye Irritation	Rabbit	D-Isomer (Mecoprop-P)	Category 1 eye irritant	Smith KD (1990b)
Skin sensitisation (M&K)	Guinea pig	D-Isomer (Mecoprop-P)	Not a skin sensitiser	Rossbacher (1995)
Phototoxicity	<i>In vitro</i> BALB/c 3T3 cell line	<b>D-Isomer (Mecoprop-P)</b>	<b>Not phototoxic</b>	<b>Heppenheimer, A. (2014)</b>

#### Summary and classification for acute toxicity under (EC) 1272/2008

Three acute oral toxicity studies have been conducted on mecoprop-P. The LD<sub>50</sub> ranged from 431 to 1050 mg/kg bw. The study by Dange (1994a) with LD<sub>50</sub> of 431 mg/kg bw is considered the most reliable as a basis for classification. In conclusion, mecoprop-P should be classified Category 4 for acute oral toxicity with the hazard statement H302 - Harmful if swallowed. This is in agreement with the current harmonised classification for mecoprop-P.

There are three suitable acute dermal studies which indicate that mecoprop-P is of low toxicity via the dermal route so does not require classification for dermal toxicity. The most reliable study is considered to be the one by Dange (1994b) with a LD<sub>50</sub> > 2000 mg/kg bw.

Three acute inhalation studies conducted on mecoprop-P report LC<sub>50</sub> values of >0.87 mg/L, >2.13 mg/L, and >5.6 mg/L. In all three studies a dust aerosol was generated but in all the studies there were some technical difficulties in achieving particles in the respirable range. There was no evidence that mecoprop-P is toxic by the inhalation route. The most reliable study is the one by Coombs and Clarke (1977) with LC<sub>50</sub> of >2.13 mg/L. It is concluded that mecoprop-P does not require classification with respect to acute inhalation toxicity.

Three skin irritation studies have been conducted on mecoprop-P. In all three studies mecoprop-P was not classified as a skin irritant. The most reliable study is considered to be the one by Dange (1994c). Mecoprop-P does not require classification as a skin irritant.

There are two eye irritation studies conducted on mecoprop-P. In both studies mecoprop-P was severely irritating to the eyes. In conclusion mecoprop-P should be classified Category 1 for eye irritancy/corrosion with the hazard statement H318 - causes serious eye damage. This is in agreement with the current harmonised classification for mecoprop-P.

Three skin sensitisation studies have been conducted on mecoprop-P, a Buehler test and two guinea pig maximisation tests. Mecoprop-P was not found to be a skin sensitiser in any of the studies. The most reliable study was the one by Rossbacher (1995) submitted in the 2002 DAR addendum. In conclusion mecoprop-P does not require classification with regards to skin sensitisation.

A new acute dietary mouse study has been submitted for this renewal. In the study, mice were given diet containing 20,000 ppm mecoprop-P (3,393 mg/kg bw) over the duration of 1 day, rather than receiving a single gavage dose. Under the conditions of the study there were no mortalities. The median lethal dietary dose (LDD<sub>50</sub>) to female mice of mecoprop-P after a single dietary dose is >3,393 mg/kg bw. The study reflects a more typical exposure for wild mammals feeding on food contaminated with mecoprop-P, and therefore this endpoint should be used in the mammals' risk assessment (refer to CP Section 10).

Mecoprop-P triggers the need for a phototoxicity study. There were no indications of phototoxicity in a new guideline-compliant study.

#### Consideration of STOT SE classification

Specific target organ toxicity – single exposure (STOT SE) is defined as specific, non lethal target organ toxicity arising from a single exposure. STOT SE classification is relevant to effects caused after a single exposure that are not covered more appropriately by another hazard class. Mecoprop-P already has a harmonised classification for acute oral toxicity H302 because of lethal effects via oral exposure. Clinical signs observed prior to death were generalised indicators of toxicity and distress, and did not indicate any particular type of target organ toxicity (such as neurotoxicity or narcotic effects) nor was any target organ toxicity identified during the pathology examination. It is concluded that mecoprop-P does not require STOT SE classification.

### **2.6.3. Summary of short-term toxicity**

#### Rat, oral

Two oral studies (repeated dose studies with a duration of 7 weeks and 3 months, respectively) were conducted both with mecoprop-P (purity: 99-100%) and with racemic mecoprop (purity of 93%) and comparison was made between the toxicity of the two substances.

In the 7 weeks study (Kirsch et al. 1985) rats were fed a diet containing 0, 50 and 400 ppm mecoprop-P. At 400 ppm the following was observed: increased kidney weight (females), increased blood level of urea (females) and creatinine (females), reduced blood level of cholesterol (males and females). Thus the NOAEL in this study was 50 ppm (equal to 4.4(m)-4.8(f) mg/kg bw/day). In two groups of rats receiving racemic mecoprop at the same dose levels identical effects were observed and no distinction between the toxicity of mecoprop-P and racemic mecoprop could be made.

In the three months study (Reinert 1979) rats were fed 0, 200, 400, 800, 1600, and 3200 ppm mecoprop-P in the diet. Further groups received a diet containing 0, 200, 800, and 3200 ppm racemic mecoprop. At 1600 ppm mecoprop-P (females) and 3200 ppm mecoprop-P (both males and females) reduced body weight was observed. At the highest dose levels for both substances decreases in white blood cell counts, haemoglobin concentration, and red blood cell count were observed during the study. At 400 ppm mecoprop-P and at 800 ppm mecoprop racemate and above increases in urea, alkaline phosphatase and alanine aminotransferase were determined in the blood samples. Increased kidney weight was most prominently found in males, at 200 (equal to 16 mg/kg bw/day), 400 and 800 ppm mecoprop-P and at 200 and 800 ppm mecoprop. Increased liver weights (in females) and relative liver weights (in males) were observed at 1600 and 3200 ppm mecoprop-P and at 3200 ppm mecoprop. Also in this study no distinction in the toxic effects could be made between racemic mecoprop and mecoprop-P. The increase of the kidney weight in the 200 ppm groups of male rats is slight (less than 10%) and as there are no histopathological findings in the kidneys the effect is not considered adverse. However in females relative kidney weight was 12% higher than controls in the 200 ppm mecoprop and mecoprop-P dose groups, and

was also increased at all doses above this. There were no other adverse findings at this dose in females so it is questionable whether this finding is adverse. The RMS has taken a precautionary approach and considers this finding to be adverse so the LOAEL is considered to be 200 ppm (ADME studies indicate the kidney is highly exposed to the test substance, the kidney is a target organ at higher doses in this study, and findings in the kidney are confirmed in other studies). There was no evidence of any immunotoxicity, neurotoxicity, or hormonal system changes.

Further, a 3 month study (Kirsch et al. 1985) in which rats were dosed with a diet containing 0, 50, 150 and 450 ppm racemic mecoprop (purity of 92.7%) was submitted with the dossier. Increases in the organ weight of the kidney and the relative kidney weight were found at both 150 and 450 ppm. Increase in creatinine value was found in females at 450 ppm. Thus a NOAEL of 150 ppm (equal to 11.4 (m) and 13.4 (f) mg/kg bw/day) was found in this study, as the effect in 150 ppm is not considered adverse. The RMS considers this study is of limited relevance as it was conducted on racemic mecoprop and there are adequate studies available on mecoprop-P.

A scientific publication (Moeller et al. 1989) was submitted considering short term studies with oral (gavage) dosing of racemic mecoprop (potassium salt with a purity of 97%) to rats. Both in a 14 day study (dose levels 0, 100, 320, and 800 mg/kg bw/ day) and in a 90 day study (dose levels: 0, 0.8, 8, 80 and 320 mg/kg bw/day) reduced organ weight of the thymus was seen. At microscopy degenerative processes in the cortex of the organ was observed at and above 320 mg/kg bw/day. In the 90 day study the LOAEL with respect to organ weight of the thymus was a dose level of 8 mg/kg bw/day for males (NOAEL: 0.8 mg/kg bw/day) and 320 mg/kg bw/day for females (NOAEL: 80 mg/kg bw/day). Reduced organ weight of the spleen was found at 800 mg/kg bw/day in the 14 day study. At microscopic examination of the spleen, reduction of the white pulp tissue and enlargement of the haematopoietic tissue was observed. Morphometry of the tissue confirmed these findings also at the 320 mg/kg bw/day dose level. Further dose-dependent changes in differential leucocyte counts were reported (decrease in lymphocytes and increase in neutrophilic granulocytes). The findings in the thymus and spleen were not seen in other studies at much higher dose level therefore the relationship to treatment with mecoprop-P is doubtful. The RMS considers this study is of limited relevance as it was conducted on racemic mecoprop and there are adequate studies available on mecoprop-P.

#### Mouse, oral

In a three months' study with mice (Mellert et al. 1993) concerning oral administration of 0, 100, 1000, and 2500 ppm mecoprop-P (purity: 96.5%) in the diet, haematological effects were found at the dose level of 2500 ppm. Clinicochemical findings included increased urea and decreased triglyceride values at all dose levels except in males at 100 ppm. At the top dose increased liver weight (males and females) and decreased kidney weight (males) were observed. The NOAEL in this study was 100 ppm for males (equal to 20 mg/kg bw/day) but could not be established for females owing to the increased level of urea in blood. There was no evidence of any immunotoxicity, neurotoxicity, or hormonal system changes in mice.

#### Dog, oral

In a three months' study (Reuzel & Hendriksen 1979) beagle dogs were gavaged with either 0, 4, 16 or 64 mg/kg bw/day mecoprop racemate (purity: 93.3%). There were increased relative liver and kidney weights and effects on some of the haematological and biochemical parameters in the highest dose group, as e.g. decreased haemoglobin, packed cell volume and red blood cell count and increased urea. At 16 mg/kg bw/day packed cell volume and red blood cell count were only significantly decreased after 6 weeks. Therefore it is concluded that the NOEL is 4 mg/kg bw/day while the NOAEL is 16 mg/kg bw/day.

In a one year dog study on mecoprop-P (Bachmann et al. 1997) the NOAEL was 5 mg/kg bw/day based on decreased body weight and body weight gain and minor effects on blood cells (decreased haemoglobin and haematocrit) and decreased phosphate and calcium in the highest dose group 19 mg/kg bw/day.

There was no evidence of any immunotoxicity, neurotoxicity, or hormonal system changes in either of the studies in the dog.

Evidence from the literature (see Volume 3 Section B.6.1.1.2) shows that plasma half-life and renal clearance of mecoprop are prolonged in the dog compared with rats and humans; therefore the dog is not the most relevant species for risk characterisation for humans.

Rabbit, dermal

In a twenty-one day study with dermal exposure to rabbits at dose levels of 0, 10, 100, and 1000 mg/kg bw/day (Allan et al. 1993) signs of dermal irritation were recorded with increasing severity at increasing dose levels. The spleen weight was reduced at all dose levels in females (at the two highest dose levels to a significant degree), however, this finding is thought to be due to rather high organ weights in control females. In females, the blood level of urea was significantly decreased at all dose levels and the level of cholesterol was decreased at the two highest dose levels, although they were within the range of normal values. The NOAEL is 1000 mg/kg bw/day.

Overall appraisal

The RMS considers that the studies submitted have sufficiently investigated the repeat dose toxicity of mecoprop-P, including neurotoxic, immunotoxic or endocrine system effects. Toxicokinetic data (blood concentration) and micronuclei were not measured as these were old studies that were conducted before (EU) 283/2013 applied. It is considered that in the interests of minimising vertebrate testing it is not necessary to meet these data requirements.

The studies provide convincing evidence to conclude that there was no difference in toxicity between mecoprop (racemic form, purity 93-97%) and mecoprop-P (D-form, purity > 99%). The most common findings from the studies were haematological effects in the dog and effects on liver and kidney in rats, mice and dogs. One study with the racemate reported reduced organ weight of the thymus and the spleen, and toxicity towards these organs was verified by histopathological findings. However such findings were not seen in other studies at much higher doses.

Consideration of specific target organ toxicity repeat exposure (STOT RE) classification

STOT RE is defined as specific target organ toxicity following repeated exposure. The classification is relevant to effects caused by repeated exposure that are not covered more appropriately by another hazard class. Classification is appropriate where substances cause significant or severe toxic effects in animals. Significant effects are defined as changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant and impair function, both reversible and irreversible.

The kidneys are the most sensitive target organs in the repeat dose studies on rats, mice and dogs. The LOAEL for kidney effects in the 90 day studies are between 10 and 100 mg/kg bw/day which is within the guidance value for STOT RE Category 2 classification. The findings at these doses are characterised in particular by a significant increase in relative kidney weight, and increased blood urea nitrogen. Although increased blood urea nitrogen might indicate kidney damage, in the absence of any effects on other biochemical parameters indicative of kidney damage and in the absence of any histopathological findings up to the highest doses tested (> 400 mg/kg bw/day in rats, > 700 mg/kg bw/day in mice), it is concluded that these effects in the kidney observed below the guidance values for classification with STOT-RE are minor and do not warrant classification.

In the carcinogenicity study in rats there was a slight increase in histopathological findings in the kidneys but only at doses higher than the guidance cut-off values for STOT RE classification, and there was no increase in chronic nephropathy. In the carcinogenicity studies in mice there was an increase in chronic nephropathy but only at doses higher than the guidance cut-off value for STOT RE classification.

It is concluded that though the kidney is a target organ, the findings are not of sufficient magnitude to be considered to be significant or severe in the context of the classification criteria at doses relevant to STOT RE classification.

In the 90 day and 1 year dog studies the LOAELs were 16 and 19mg/kg bw/day respectively which are within the guidance value for STOT RE classification. The findings at the LOAEL were primarily confined to minor haematological changes indicative of anaemia. In the 90 day study there was reduced packed cell volume (8% reduction) and reduced red blood cells (9% reduction). In the 1 year dog study there was a reduction in haemoglobin (5% reduction) and a reduced haematocrit (6% reduction), but both findings were only seen in males. These changes are small in magnitude, and there was no increase in severity in the 1 year study compared with the 90 day study. In addition, the dog is not a relevant species for human risk characterisation because of differences in kinetics (slower renal clearance). Overall, these haematological findings in dogs at dose levels below the guidance value for STOT-RE are considered to be minor and not relevant to humans.



Overall, based on the evidence from repeat dose toxicity studies in rats, mice and dogs, it is concluded that classification for STOT RE is not required.

#### Summary of short term studies with mecoprop-P and mecoprop

(no new studies have been submitted since the previous review; studies considered superfluous are highlighted in grey)

Study	Dosing	Effects at LOAEL	LOAEL/ NOAEL	Reference
Rat; 7 weeks; oral; 10m+10f/ group	0, 50, 400 ppm mecoprop in diet Equivalent to 0, 4.4/4.8, 35.1/37.5 mg/kg bw/day in m/f  0, 50, 400 ppm mecoprop-P in diet Equivalent to 0, 4.4/4.8, 35.2/38.0 mg/kg bw/day in m/f	Mecoprop: In males 7% ↑ abs. and rel. kidney weight, ↑ blood urea nitrogen, ↓ cholesterol. In females ↓ calcium, ↓ cholesterol.  Mecoprop-P: In males 8% ↑ abs. kidney weight, 10% ↑ rel. kidney weight, ↓ cholesterol. In females 8% ↑ abs. kidney weight, 10% ↑ rel. kidney weight, ↓ cholesterol. ↑ blood urea nitrogen, ↑ creatinine.	Mecoprop: LOAEL 400 ppm NOAEL 50 ppm (4.4/4.8 mg/kg bw/day in m/f)  Mecoprop-P: LOAEL 400 ppm NOAEL 50 ppm (4.4/4.8 mg/kg bw/day in m/f)	Kirsch <i>et al.</i> (1986)
Rat; 3 months; oral; 15m+15f/group	0, 200, 800, 3200 ppm mecoprop in diet Equivalent to 0, 16.5/18.2, 67.9/75.9, 390.8/398.7 mg/kg bw/day in m/f  0, 200, 400, 800, 1600, 3200 ppm mecoprop-P in diet Equivalent to 0, 15.6/18.4, 31.9/37.8, 67.6/75.8, 146.4/170.1, 403.2/403.5 mg/kg bw/day in m/f	Mecoprop: 12% ↑ kidney weight in females.  Mecoprop-P: In females 12% ↑ rel. kidney weight.	Mecoprop: LOAEL 200 ppm (18.2 mg/kg bw/day in f) NOAEL < 18.2 mg/kg bw/day in females  Mecoprop-P: LOAEL 200 ppm (18.4 mg/kg bw/day in f) NOAEL < 18.4 mg/kg bw/day in females	Reinert (1979)
Rat; 3 months; oral; 15m+15f/group	0, 800 and 3200 ppm racemic Mecoprop (93% purity) in diet Equivalent to 0, 81.7/121.1, 452.5/537.1 mg/kg bw/day in m/f  0, 800, 1600, and 3200 ppm Mecoprop-P (D-isomer, 99.9% purity) in diet Equivalent to 84.1/117.8, 178.1/239.9, 429.5/539.0 mg/kg bw/day in m/f	Only ocular effects were examined; this study is a supplementary study to the Reinert (1979) study.	Mecoprop and mecoprop-P : NOAEL > 3200 ppm in diet (equal to 430-539 mg/kg bw/day) for ocular effects	Rondot et al (1979)
Rat; 3 months; oral; 15m+15f/ group	0, 50, 150, 450 ppm mecoprop in diet Equivalent to 0, 3.8/4.4, 11.4/13.4, 34.0/39.3 mg/kg bw/day in m/f	In males 13% ↑ kidney weight, 14% ↑ rel. kidney weight. In females 9% ↑ rel. kidney weight.	Mecoprop: LOAEL 150 ppm NOAEL 50 ppm (3.8/4.4 mg/kg bw/day in m/f)	Kirsch et al (1985) <sup>1</sup>
Rat; 3 months; oral; 20m+20f/ group	0, 0.8, 8, 80, 320 mg/kg bw/day mecoprop potassium salt solution, gavage	↓ thymus weight	Mecoprop: LOAEL: 8 mg/kg bw/day NOAEL: 0.8 mg/kg bw/day	Moeller et al (1989) <sup>1</sup>

Study	Dosing	Effects at LOAEL	LOAEL/ NOAEL	Reference
Mouse; 3 months; oral; 10m+10f/ group	0, 100, 1000, 2500 ppm mecoprop-P in diet  Equivalent to 20/30, 220/330, 740/930 mg/kg bw/day in m/f	In females at 100 ppm: ↑ blood urea nitrogen, ↓ triglycerides.	Mecoprop-P: LOAEL females: 100 ppm (30 mg/kg bw/day in f)  NOAEL < 30 mg/kg bw/day in females	Mellert <i>et al.</i> (1993)
Dog; 3 months; oral; 4m+4f/ group	0, 4, 16, 64 mg/kg bw/day mecoprop in diet	Haematological changes: ↓ PCV, ↓RBC, (both sexes analysed together).	Mecoprop: LOAEL: 16 mg/kg bw/day  NOAEL: 4 mg/kg bw/day	Reuzel PGJ & Hendriksen CFM (1979)
Dog; 12 months; diet; 5m+5f/ group	0, 2, 5, 19 mg/kg bw/day Mecoprop-P in diet	Males: Slightly reduced body weight, and haematological changes: ↓Hb, ↓HCT  Females : Slight clinical chemistry changes : ↓ phosphate, ↓calcium	Mecoprop-P : LOAEL : 19 mg/kg bw/day  NOAEL : 5 mg/kg bw/day	Bachmann <i>et al.</i> (1997)
Rabbit; 3 month; dermal; 5m+5f/ group	0, 10, 100, 1000 mg/kg bw/d mecoprop-P dermal	Local effects: Dermal irritation at all dose groups.  Systemic effects: no adverse findings at any dose group.	Mecoprop-P: NOAEL (systemic effects): 1000 mg/kg /day  LOAEL (local effects): 10 mg/kg bw/day	Allan <i>et al.</i> (1993)

<sup>1</sup> Study on mecoprop included in DAR for first review (1998) and included here for completeness but not relevant for mecoprop-P as adequate studies are available on mecoprop-P  
m/f = males/females

## 2.6.4. Summary of genotoxicity

The following table presents those genotoxicity studies submitted with the dossier from the notifier that are considered acceptable with respect to purpose and quality. No new studies have been submitted since the previous review. Mecoprop-P triggers the need for a photomutagenicity study; however, a study has not been submitted. There was no OECD test guideline available at the time of submission for photogenotoxicity and no photogenotoxicity assays are currently recommended by regulatory agencies in the EU. Therefore it is not clear how this data requirement should be met. The phototoxicity test (see Section B.6.2.7) shows that mecoprop-P is not photoreactive.

Tests highlighted in grey were included in the 1998 DAR but are not considered further in this renewal as they were conducted on the racemic mix and there are adequate studies available on the P isomer.

### Summary of genotoxicity testing of mecoprop and mecoprop-P

Test system	Dose range, mecoprop-P	Response -S9 / +S9	Reference
<b>Bacterial assays</b>			
<i>Salmonella typhimurium</i> strain TA98, TA100, TA1535, TA1537, TA1538	20-5000 mg/plate	negative/ negative	Gelbke & Engelhardt (1984)
<i>Salmonella typhimurium</i> strain TA98, TA100, TA1535, TA1537	50-5000 mg/plate	negative/ negative	Jones & Christopher (1993)
<i>Salmonella typhimurium</i> strain TA98, TA100, TA1535, TA1537	10-1000 mg/plate	negative/ negative	May (1990)
<i>Salmonella typhimurium</i> strain TA97, TA98, TA100, TA102	0.001-1000 mg/plate (racemic mecoprop)	negative/ negative	Mersch-Sundermann et al. (1988)

Test system	Dose range, mecoprop-P	Response -S9 / +S9	Reference
<i>Salmonella typhimurium</i> strain TA98, TA100, TA1535, TA1537	20-5000 mg/plate (racemic mecoprop)	negative/ negative	Zeller & Engelhardt (1983)
<i>Escherichia coli</i> strain PQ37	0.1-100 000 mg/ml (racemic mecoprop)	negative/ negative	Mersch-Sundermann et al. (1989)
<b>Mammalian cell <i>in vitro</i> assays</b>			
Chinese hamster ovary cells/ HGPRT locus	23-1040 µg/ml	negative/ negative	Adams et al. (1993)
Chinese hamster V79 cells/ HGPRT locus	6-4500 µg/ml	negative/ negative	Lloyd (1990)
Human lymphocytes cytogenetic test	100-2000 µg/ml	positive*/ negative	Heidemann & Knoell (1994)
Human lymphocytes cytogenetic test	100-3200 µg/ml	negative/ positive*	Edwards (1990)
<b>Mammalian <i>in vivo</i> assays</b>			
Chinese hamster, bone-marrow cytogenetic test	60-2600 mg/kg bw	negative	Gelbke & Engelhardt (1985a)
Chinese hamster, bone-marrow cytogenetic test	60-3800 mg/kg bw (racemic technical mecoprop)	positive at 3800 mg/kg bw*	Gelbke & Engelhardt (1985b)
Chinese hamster, bone marrow sister chromatid exchange	60-3800 mg/kg bw (racemic technical mecoprop)	positive dose related*	Gelbke & Engelhardt (1985c)
Mouse, micronucleus test	20-500 mg/kg bw	negative	Edwards (1991)

\* only positive results at cytotoxic/ toxic levels.

In bacterial assays and in mammalian cell *in vitro* assays no mutagenic potential was found for mecoprop-P. Conflicting results were obtained in two *in vitro* assays with human lymphocytes at cytotoxic levels. One test showed positive clastogenic response with S9 mix and the other test showed positive effect without S9 mix, however, only at clearly cytotoxic levels. *In vivo* no genotoxic potential was found at any time in a bone-marrow cytogenetic test in which mecoprop-P was administered above the limit dose, and in a micronucleus test with mecoprop-P in which systemic toxicity was observed, indicating that exposure to the bone marrow would have occurred.

Further, as the valid, reliable *in vivo* tests with mecoprop-P are negative there is no clear evidence for genotoxicity *in vivo* and thus the test results do not meet the criteria under (EC) 1272/2008 for classification as a mutagen.

In the review report for the previous review it was concluded that taking a weight-of-evidence approach there was no genotoxic concern for mecoprop-P.

The RMS for current renewal agrees with the conclusion of the previous evaluation for Annex I inclusion. Mecoprop-P had equivocal evidence of clastogenicity in mammalian cells *in vitro* at doses where cytotoxicity was evident, but two *in vivo* studies for clastogenicity were clearly negative. Most of the studies submitted were conducted to older versions of the OECD test guidelines, but overall this is not considered to invalidate the test results. It is concluded that from the evidence provided, mecoprop-P does not require classification for mutagenicity under (EC) 1272/2008.

### 2.6.5. Summary of long-term toxicity and carcinogenicity

A new 2 year carcinogenicity study in the rat conducted on mecoprop-P was submitted for this renewal. All other studies have been previously evaluated.

#### Summary of long-term and carcinogenicity studies (new study submitted for current evaluation highlighted in bold)

Study	Test Substance	Dosing	Effects at LOAEL	NOAEL	Reference
Rat; 2 years dietary 50m/f, per dose Included 1 year chronic cohort 10m/f per dose	Mecoprop racemate	0, 20, 100, and 400 ppm Equivalent to 0, 1.1/1.4, 5.5/6.9, 22.2/27.9 mg/kg bw/day in m/f	<u>Non-neoplastic:</u> In males at 2 years 7% ↑abs. kidney weight. In males at 1 year 16% ↑abs. kidney weight. No adverse findings in females  <u>Neoplastic:</u> No tumours identified	<u>Non-neoplastic:</u> Males: 20 ppm (1.1 mg/kg bw/day) Females: >27.9 mg/kg bw/day  <u>Neoplastic:</u> > 22.2/27.9 mg/kg bw/day in m/f	Kuhborth et al. (1988) <sup>1</sup>
Rat; 2 years; dietary 52m/f per dose	D-Isomer (Mecoprop-P)	0, 100, 600, 1200 ppm Equivalent to 0, 5.3/6.6, 32.0/39.9, 64.6/81.7 mg/kg bw/day in m/f	<u>Non-neoplastic:</u> Males at 1200 ppm: ↓ bw gain, 21% ↑ rel. kidney weight, ↑ histopathological kidney findings. Peroxisome proliferation in liver.  Females: at 100 ppm: 51% ↑ rel. kidney weight  <u>Neoplastic:</u> No neoplastic findings	<u>Non-neoplastic</u> Males: 600 ppm (32 mg/kg bw/day)  Females: below 100 ppm (<6.6 mg/kg bw/day)  <u>Neoplastic:</u> > 64.6/81.7 mg/kg bw/day	Milburn (2008)
Mouse; 18 months; dietary 50m/f per dose	D-Isomer (Mecoprop-P)	0, 25, 250, (2500) <sup>2</sup> ppm in the diet Equivalent to 0, 4/4, 40/46, 592/732 mg/kg bw/day in m/f	<u>Non-neoplastic findings:</u> At 2500 ppm all animals sacrificed at one year due to severe body weight loss. Males: At 250 ppm: no adverse findings Females: at 25 ppm: 20% ↑ rel. kidney weight ↑ chronic nephropathy.  <u>Neoplastic:</u> At 250 ppm: Males: not carcinogenic Females: ↑ hepatocellular carcinoma (4 animals versus 3 in controls)	<u>Non-neoplastic:</u> Males: > 250 ppm (40 mg/kg bw/day) Females: 25 ppm (4 mg/kg bw/day)  <u>Neoplastic:</u> 25 ppm (4 mg/kg bw/day)	Mellert (1996)



Study	Test Substance	Dosing	Effects at LOAEL	NOAEL	Reference
Mouse; 18 months; dietary 50 m/f per dose	D-Isomer (Mecoprop-P)	0, 700 (males), 800 (females) ppm Mecoprop-P in the diet Equivalent to 112/188 mg/kg bw/day in m/f	<u>Non-neoplastic:</u> Males: 13% ↓ bw gain, 12% ↑ rel. liver weight, ↑ chronic nephropathy. Females: 19% ↓ bw gain, 14% ↑ rel. liver weight, ↑ chronic nephropathy, 26% ↑ rel. kidney weight  <u>Neoplastic:</u> Males: not carcinogenic Females: ↑ hepatocellular carcinomas at 800 ppm (5 animals versus 0 in controls)	<u>Non-neoplastic:</u> Males: < 700 ppm (112 mg/kg bw/day) Females: < 800 ppm (188 mg/kg bw/day)  <u>Neoplastic:</u> Males: > 700 ppm (112 mg/kg bw/day) Females: < 800 ppm (188 mg/kg bw/day)	Mellert <i>et al.</i> (1999)
Dog; 12 months; dietary; 5m/f per dose	Mecoprop racemate	0, 2, 5, 19 mg/kg bw/day Mecoprop-P in diet	Males: Slightly reduced body weight, and haematological changes: ↓Hb, ↓HCT Females: Slight clinical chemistry changes: ↓ phosphate, ↓calcium	Mecoprop-P : LOAEL : 19 mg/kg bw/day  NOAEL : 5 mg/kg bw/day	Bachmann <i>et al.</i> (1997)

<sup>1</sup> Study on mecoprop racemate included in DAR for first review (1998) and included here for completeness but not relevant as sufficient studies are available on mecoprop-P

<sup>2</sup>: This dose group was terminated after 12 months and not investigated further  
m/f = males/females

#### Rat, chronic and carcinogenicity studies

One combined chronic toxicity/carcinogenicity study with mecoprop racemate (Kuhborth 1988) conducted with rats was originally included in the 1998 dossier from the notifiers. Rats were during 24 months fed with diet containing 0, 20, 100, and 400 ppm racemic mecoprop equivalent to 0, 1.1/1.4, 5.5/6.9, 22.2/27.9 mg/kg bw/day in males/females (purity of 92.7%). No histopathological and neoplastic changes were found. Increased kidney weight was found in male rats at 100 and 400 ppm and significantly increased level of blood urea nitrogen was found in males at 400 ppm. The NOAEL is considered to be 20 ppm (corresponding to 1.1 mg/kg bw/day for males based on 7% increase in absolute kidney weight after 2 years administration and a 17% increase in relative kidney weight after 1 year in the 100 ppm dose group.

Since the original 1998 DAR a new rat carcinogenicity study (Milburn 2008) has been conducted on mecoprop-P. Rats were fed mecoprop-P in the diet at a dose of 0, 100, 600, 1200 ppm equivalent to 0, 5.3/6.6, 32.0/39.9, 64.6/81.7 mg/kg bw/day. Reduced body weight gain and food consumption were evident in both sexes at the top dose, but also in females at 600 ppm. Both sexes had a marked increase in relative kidney weight and slight changes in kidney histopathology at 1200 ppm. In females the liver was also a target organ as evidenced by increased relative liver weight, hepatocyte hypertrophy and other histopathological changes at 1200 ppm. Further investigations revealed significantly increased hepatic cyanide-insensitive palmitoyl CoA oxidation in both sexes at 1200 ppm and in females at 600 ppm, which is a typical marker of peroxisome proliferation. There were no adverse findings in males at 600 ppm or 100 ppm, whereas in females a 51% increase in relative kidney weight was seen at 100 ppm and due to the magnitude of the effect is considered to be an adverse finding although it was not accompanied by any other indicators of toxicity.

There was no increase in malignant tumours. The only finding of note was an increase in subcutaneous lipoma (benign) at 1200 ppm in males (4/52 at 1200 ppm versus 0/52 in controls) which exceeded the historical control incidence (2/52, although it is recognised that only two relevant historical control studies were available). Adipose tissue was found to be highly exposed to the test substance in the metabolism studies. However, these tumours are probably incidental since lipoma only occurred in a single sex, and only marginally exceeded the historical control

incidence. Only animals with gross masses under the skin were examined histopathologically for lipomas. This tumour type is relatively common and is not thought to progress to malignancy. The NOAEL for neoplastic findings in males is therefore > 64.6 mg/kg bw/day. There were no neoplastic findings in females therefore the neoplastic NOAEL in females is > 81.7 mg/kg bw/day.

#### Mouse carcinogenicity study

Mice were fed for 18 months with diets containing 0, 25, 250 or 2500 ppm with mecoprop-P (purity of 92.7%) equivalent to 0, 4/4, 40/46, 592/732 mg/kg bw/day in males/females (Mellert 1996). However, the highest dose group was killed after 12 months because of severe reduction in bodyweight gain that indicated the maximum tolerated dose was exceeded and not investigated further. A NOAEL for systemic effects was found to be 25 ppm (corresponding to 4 mg/kg bw/day) for the females and 250 ppm (corresponding to 40 mg/kg bw/day) for the males. At 250 ppm increased kidney weight was seen in females and they had chronic nephropathy. In males there were decreased absolute and relative adrenal weights in both the 25 and 250 ppm dose groups. This effect was not clearly dose-related and there were no other effects on the adrenals. Therefore this effect is not considered substance related. There was a slight increase in hepatocellular carcinoma (5/50 versus 3/50 in controls) in females at 250 ppm (46 mg/kg bw/day). This slightly exceeds the maximum historical control incidence (of 1/50 (2%) ) from seven concurrent studies. As tumour incidence in the concurrent controls was also higher than the historical controls, however, the historical control data do not provide meaningful information. The very slight increase in tumours is not clearly treatment-related so is not considered evidence of a carcinogenic effect.

A supplementary study in mice (Mellert 1999) was conducted because the maximum tolerated dose was exceeded in the former study. Mice were fed for 18 months with diets containing 0, 700 ppm (males) or 800 ppm (females) corresponding to 0, 112/188 mg/kg bw/day in males/females. Both sexes had decreased bodyweight gain (13%/19% in males/females). The target organs were the liver and kidney. Findings in the liver were increased relative liver weight (12/14% in males/females) but the only histopathological finding in the liver was increased incidence of basophilic foci of cellular alteration (in 11/50 males versus 4/50 in controls, and in 4/50 females versus 0/50 in controls); this incidence was within the historical control range, however, so is of limited toxicological relevance. In the kidney there was an increase in relative kidney weight in females (26%) and increased chronic nephropathy in both sexes (30% increase in males, 5-fold increase in females). There was an increased incidence of hepatocellular carcinomas (4/50 versus 0/50 in concurrent controls) in females that slightly exceeded the maximum relevant historical control incidence of 3/50 (6%) from six studies, although only by one animal. This marginal increase is not considered to be sufficient evidence of a carcinogenic effect, especially when taking into account that the historical control data are from a limited number of historical studies.

The overall NOAEL for neoplastic findings in female mice is 188 mg/kg bw/day based on a slight increase in hepatocellular carcinoma. There were no treatment-related neoplastic findings in males so the NOAEL in males is > 112 mg/kg bw/day.

#### One year dog study

In a one year dog study (Bachmann et al. 1997) summarised in Section B.6.3.3.1, the NOAEL was 5 mg/kg bw/day based on decreased body weight and body weight gain and minor effects on blood cells (decreased haemoglobin and haematocrit) and decreased phosphate and calcium in the highest dose group 19 mg/kg bw/day.

#### Classification and labelling for carcinogenicity

In the previous review it was concluded that increased liver tumour incidence occurred in female mice at the highest dose tested, but that overall there was no carcinogenic potential relevant to humans.

In the new 2 year rat study on mecoprop-P the only finding was an increased incidence of benign lipoma in male rats; however, these are not considered to be evidence of carcinogenic potential as they only marginally exceeded the historical control level, were sex-specific and and this tumour type is not thought to progress to malignancy. It is concluded that mecoprop-P shows no carcinogenic potential in the rat.

In mice hepatocellular carcinoma in females exceeded the concurrent control incidence and marginally exceeded historical control levels in both studies; however, in the first study the concurrent control incidence was also in excess of the maximum historical control incidence. It is noted that the historical control data provided by the applicant for both studies were limited only to a few historical studies, which limits the value of these data. The increase was very slight, sex-specific, only marginally above the (rather limited) historical control data and without a dose-response relationship in the first study. It is therefore concluded that the studies did not provide evidence of a

treatment-related response. Furthermore, the strain of mouse used in these two studies was B6C3F/CrlBR, which is reported to have a high spontaneous incidence of liver tumours (as reported in Guidance on the Application of the CLP Criteria version 4.1, June 2015 section 3.6.2.3.2). Therefore the significance of this slight increase in tumours in females only is considered to be of limited relevance for human risk assessment.

Overall the RMS considers that there was no evidence of a treatment-related increase in tumour incidences of relevance to humans, and thus classification for carcinogenicity is not warranted.

### 2.6.6. Summary of reproductive toxicity

The table below presents the overall results (NOAELs) from the studies for an evaluation of the reproduction and developmental toxicity of mecoprop-P.

#### Overview of NOAELs for reproduction and developmental toxicity studies submitted with the mecoprop-P dossier.

New study submitted for the current evaluation highlighted in **bold**.

Studies shaded grey were included in the 1998 DAR but are not considered in the current renewal as they are supplementary to requirements as sufficient data is available on mecoprop-P.

Study	Test Substance	Dosing	Effects at LOAEL	NOAEL in mg/kg bw/day	Reference
Rat (Han Wistar) ; One-generation dietary (10 week dose ranger) Parental animals : 12m/12f per dose group Pups: 10 per litter	Mecoprop-P	0, 500, 800, 1200 ppm Equivalent to 0, 34.5/38.2, 53.7/60.6, 82.9/88.8 mg/kg bw/day in m/f Dose during lactation: 0, 300, 530, 790 ppm Equivalent to 0, 48.1, 85.8, 130.2 mg/kg bw/day	Parental: 20%/26% ↓ bw gain in m/f during premating, 50% ↓ bw gain in f on days 0-7 during gestation  Offspring: No adverse effects  Fertility: 21% ↓ implantation sites	Parental: 800 ppm (530 ppm during lactation) equivalent to 53.7/60.6 mg/kg bw/day in m/f (85.8 mg/kg bw/day in f during lactation)  Offspring: > 1200 ppm (82.9/88.8 mg/kg bw/day in m/f)  Fertility : 800 ppm equivalent to 53.7/60.6 mg/kg bw/day in m/f	Clode (2003)
Rat (Wistar); Two-generation dietary Parental animals: 25m/f per dose group Pups: 8 per litter	Mecoprop	0, 20, 100, 500 ppm  Equivalent to 0, 1.8/1.6, 9.3/8.0, 47.3/40.0 mg/kg bw/day in m/f (0, 2.5, 13.2, 67.3 mg/kg bw/day in lactating females)	Parental: ↑ relative kidney weight 12%/9% in m/f  Offspring: ↑ pup mortality days 0 – 4, up to 11% ↓ pup body weight gain.  Fertility: no affects	Parental: 100 ppm (9.3/8.0 mg/kg bw/day in m/f)  Offspring: 100 ppm (9.3/8.0 mg/kg bw/day in m/f)  Fertility: >500 ppm (> 47.3/40.0 mg/kg bw/day in m/f)	Hellwig (1992)
Rat (CD); Developmental Gavage, 19 to 25 per dose group	Mecoprop	0, 20, 50, 125 mg/kg bw/day	Maternal: ↓ bodyweight gain  Developmental: ↓ bodyweight, ↓ crown/rump length, ↑ delayed ossification	Maternal: 50 mg/kg bw/day  Developmental: 50 mg/kg bw/day	Irvine (1980a)

Study	Test Substance	Dosing	Effects at LOAEL	NOAEL in mg/kg bw/day	Reference
Rat (Wistar); Developmental Gavage, 25 per dose group	Mecoprop-P	0, 20, 50, 100 mg/kg bw/day	Maternal: 22% ↓ food consumption, 18% ↓ bodyweight gain  Developmental: 2% ↓ foetal weight, four fold ↑ rudimentary cervical ribs, ↑ sternbrae not ossified	Maternal: 50mg/kg bw/day  Developmental: 50mg/kg bw/day	Hellwig (1993a)
Rabbit (Himalayan); Developmental Gavage, 15 per dose group	Mecoprop-P	0, 5, 20, 50 mg/kg bw/day	Maternal: no adverse findings  Developmental: no affects	Maternal: >50 mg/kg bw/day  Developmental: >50 mg/kg bw/day	Hellwig (1993b)
Mouse (NMRJ); Developmental Gavage 22 to 59 per dose group	Mecoprop and Mecoprop-P	0, 200, 300, 400, 500 mg/kg bw/day mecoprop-P 0, 100, 200, 300, 400, 500, 700 mg/kg bw/day mecoprop racemate	Maternal: maternal effects not specified but only seen in mecoprop at 700 mg/kg bw/day  Developmental: ↓ foetal weight (both subst.)	Maternal: 500 mg/kg bw/day*  Developmental: 200 mg/kg bw/day * * both substances	Roll (1983)
Rabbit (Dutch belted); Developmental Gavage 15 per dose group	Mecoprop	0, 12, 30, 75 mg/kg bw/day	Maternal: No adverse findings  Developmental: No adverse findings	Maternal: 75 mg/kg bw/day  Developmental: 75 mg/kg bw/day	Irvine (1990b)

The studies submitted are considered adequate to investigate the reproductive and developmental toxicity of mecoprop-P. The only new study submitted for this renewal was a range-finding one generation reproductive study in the rat conducted on mecoprop-P, which supplements the information provided by the two-generation study. The original evaluation in the 1998 DAR is considered relevant for the current renewal of mecoprop-P, but taking into account the new study.

In the two-generation reproductive study using mecoprop racemate there was no effect on fertility up to the highest dose tested. The main findings in the pups were increased pup mortality on days 0 to 4 post partum and a reduction in pup body weight gain at the top dose of 500 ppm (47.3/40.0 mg/kg bw/day in males/females). Delayed pinna unfolding in the F1a and F2 generational and delayed auditory canal opening in the F2 generation are probably secondary to body weight effects. In the parental generation the only treatment-related effect was an increase in relative kidney weight at 500 ppm. There were no effects on fertility. The significance of the increased pup mortality which occurred in the absence of clear maternal toxicity is not clear. It is possible that the finding is due to systemic toxicity in young pups rather than reproductive toxicity (mecoprop-P is acutely toxic in adults with an acute oral toxicity of 431 mg/kg bw day, and pups are likely to be more susceptible as their food consumption relative to bodyweight is higher than in adults). The new one-generation study did not replicate the increase in pup mortality even at much higher doses.

In the new one-generation study using mecoprop-P the doses were increased to 500, 800 and 1200 ppm to ensure that a MTD was achieved in adults, but was reduced to 300, 530 and 790 ppm during lactation in an attempt to mitigate adverse effects on body weight and mortality in pups post partum seen in the two generation study. In this new study there was a significant reduction in bodyweight gain in parental animals at the top dose of 1200 ppm (82.9/88.8 mg/kg bw/day), demonstrating sufficient parental toxicity had been achieved. There were no adverse effects on pup body weight or survival. The only reproductive finding was a statistically significant reduction in implantation sites and consequently mean pups born in all dosed groups, although the RMS concludes that some uncertainty surrounds the biological significance of the finding in the low- and mid-dose groups. This finding was accompanied by maternal toxicity in the form of reduced body weight gain in the high-



dose group and is therefore possibly secondary to maternal toxicity. The two-generation study did not investigate all reproductive endpoints required in current OECD test guidelines; however, it is considered sufficient for the determination of effects on sexual maturation and fertility as parental males of both generations were exposed to the test substance for at least one sperm cycle prior to mating to determine effects on spermatogenesis, and for the second generation section of the study the parental animals were exposed from prior to conception through to full sexual maturity and mating, which includes oocyte development in females in the womb, and sexual development and maturity of male and female reproductive organs. The reproductive studies can be supplemented with the short term toxicity studies where histological examination and weights of reproductive organs were investigated, but no adverse effects were detected.

The developmental effects of mecoprop-P were investigated in the rat, rabbit and mouse. In rabbits administered doses of 0, 5, 20 and 50 mg/kg bw/day mecoprop-P the only finding was a statistically significant increase in late resorptions at 50 mg/kg bw/day, in the absence of any signs of maternal toxicity. The increase in late resorptions was not considered to be biologically relevant as total number of resorptions remained similar to the controls; therefore this finding is considered to be incidental. In rats administered 0, 20, 50 and 100 mg/kg bw mecoprop-P the only developmental finding was a slight retardation in foetus weight accompanied by unossified sternebrae and increased incidence of rudimentary cervical ribs at 100 mg/kg bw/day. At the same dose parental toxicity was evident in a statistically significant retardation of body weight gain (18%) and reduced food consumption (22%). Therefore the developmental effects in the rat are considered to be secondary to maternal toxicity. In mice administered 0, 200, 300, 400 and 500 mg/kg bw mecoprop-P or 0, 100, 200, 300, 400, 500, 700 mg/kg bw/day mecoprop racemate the most sensitive endpoint was a reduction in foetal weight at 300 mg/kg bw/day (seen in both the racemate and P isomer). Maternal effects were only evident at a higher dose of 700 mg/kg bw/day. However, a reduction in foetal weight on its own is not considered sufficient for classification. The developmental studies were all conducted to previous OECD test guidelines with the main difference compared with the current guideline being that the test substance was only administered during organogenesis. This protocol is considered sufficient to determine any developmental effects.

There was no evidence of any neurotoxic or immunotoxic effects or effects related to changes in the hormonal system.

The overall reproductive/fertility NOAEL was 53.7/60.6 mg/kg bw/day (in males/females) based on a 21% decrease in implantation sites in the one generation study on mecoprop-P (at a dose of 82.9/88.8 mg/kg bw/day in m/f). These findings occurred in the presence of significant parental toxicity (reduction in parental bodyweight gain).

In the two generation study on mecoprop the NOAEL for offspring toxicity was 9.3/8.0 mg/kg bw/day (in males/females) based on reduced pup body weight gain (accompanied by increased pup mortality and delayed pinna opening and auditory canal opening) at 47.3/40.0 mg/kg bw/day (in males/females). This finding was accompanied by increased kidney weight in the parental animals.

The overall NOAEL for developmental effects is 50 mg/kg bw/day based on delayed ossification, reduced pup weight and reduced crown/rump length in the developmental rat study at 100 mg/kg bw/day.

In the previous review it was concluded that there was no evidence of reproductive or developmental toxicity in the absence of maternal toxicity. Since then, new data has become available that provides further information on the reproductive toxicity of mecoprop-P to supplement the existing data.

#### Classification and labelling for reproductive toxicity

Mecoprop-P does not currently have any classification for reproductive toxicity.

#### **Hazard categories for reproactive toxicity according to EC 1272/2008**

Category	Criteria
1A	Category 1A are known human reproductive toxicants largely based on evidence from humans.
1B	Category 1B are presumed human reproductive toxicants largely based on animal studies where there is clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other

toxic effects.

- 2 Category 2 are suspected human reproductive toxicants where there is some evidence from humans or animal studies, of an adverse effect on sexual function and fertility, or on development and where the evidence is not sufficiently convincing to place the substance in Category 1. Such evidence shall have occurred in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

Classification for reproductive effects: According to the CLP criteria, adverse effects on sexual function and fertility that may warrant classification include any effect of substances that has the potential to interfere with sexual function and fertility. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

The only effect on fertility was a reduction in implantation sites (and consequently the mean number of pups born) in the one-generation study that occurred in all the treatment groups but was only considered by the RMS to be of biological significance in the high-dose group, in which maternal toxicity was also reported.

Classification for developmental effects: According to the CLP criteria adverse effects on development of the offspring that may warrant classification include in its widest sense any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency. Adverse effects on or via lactation are included under reproductive toxicity.

In the two generation study increased pup mortality on days 0 to 4 post partum as well as a reduction in pup body weight gain and signs of delayed development were seen in the absence of any significant maternal toxicity (maternal toxicity was limited to increased relative kidney weight). However, increased pup mortality was not replicated in the one generation range-finding study, in which higher doses were administered.

Minor developmental effects in the rat developmental study (unossified sternebrae, and increased rudimentary ribs) are considered secondary to severe maternal toxicity so do not warrant classification. A reduction in foetal weight in the mouse developmental study is also not sufficient to warrant classification. Additionally an increase in late resorptions in the rabbit developmental study can be dismissed as incidental as the overall number of resorptions was not affected by treatment.

Overall, the RMS concludes that further consideration of this endpoint is warranted to reconcile the different findings in the two-generation and one-generation studies.

### 2.6.7. Summary of neurotoxicity

Mecoprop-P does not have a structure that is associated with neurotoxicity. There are no indications of neurotoxicity in any of the existing toxicology studies. Mecoprop-P has no structural alerts for neurotoxicity (Derek Nexus 2.0) and there are no indications from the toxicity studies evaluated that mecoprop-P causes neurotoxicity. In addition the tissue distribution data from the metabolism studies (Section B.6.1.1.1) indicate that the brain is not highly exposed to mecoprop-P. It is concluded that the need for neurotoxicity studies is not triggered. A new acute neurotoxicity study has been submitted and evaluated. This is considered to be a supplementary study.

In an acute oral neurotoxicity study, mecoprop-P did not cause permanent damage to the nervous system of rats up to a maximum dose of 700 mg/kg bw. The NOAEL for this study was < 175 mg/kg bw based on acute systemic toxicity.

### 2.6.8. Summary of further toxicological studies on the active substance

The data requirement Regulation (EU) 283/2013 states that immunotoxicity studies are only required if immunotoxic effects have been observed in other studies on the active substance. There is no evidence of immunotoxicity in the studies conducted on mecoprop-P therefore the need for further specific immunotoxicity studies is not triggered. Two immunotoxicity studies were submitted in the 1998 DAR and are included here. They are considered to be supplementary studies. It was concluded that the studies on immunotoxicity indicate indirect effects related to a stress-induced release of steroid hormones from adrenals. This is likely to be a secondary effect related to general toxicity.

In a liver enzyme study from the open literature review in the previous 1998 DAR it was concluded that the activity of liver enzymes was increased by mecoprop in mice after acute exposure. Thus it was shown that mecoprop has the potential to alter the liver function.

### 2.6.9. Summary of toxicological data on impurities and metabolites

No studies on the metabolites of mecoprop-P were submitted in the 1998 DAR. A new study conducted on the metabolite hydroxymethyl-mecoprop-P (HMCP) has been submitted. This is a rat metabolite (present at levels in urine of up to 32.6%). The LD<sub>50</sub> was concluded to be > 2150 mg/kg bw.

### 2.6.10. Summary of medical data and information

#### Medical surveillance on manufacturing plant personnel and monitoring studies:

A new report is provided which contains the procedures for monitoring the manufacturing plant personnel from 2008 to present day (White, 2014). Nufarm UK performs annual medical checks by the company occupational nurse and compares the results from these medicals against previous medicals to assess for areas of concern. A general practitioner is also available to attend the workforce on a weekly basis. By observing adverse effects through studying those exposed to elevated concentrations of material on a frequent basis Nufarm has no indication of any adverse effects within the workforce.

There have been no medical incidences in the workforce at [REDACTED] (current manufacturing site) or [REDACTED] (previous alternative manufacturing site).

In the 1998 DAR a paper (Becher et al., 1992) was submitted on factory monitoring, but no useful information was available at the time of submission. The manufacturing facility in this paper is no longer involved with the production of mecoprop-P.

#### Clinical cases and poisoning incidents:

No new information has been submitted since the 1998 DAR.

In the 1998 DAR, two published papers (Meulenbelt *et al.*, 1988 and Prescott *et al.*, 1979) were submitted. The papers described the clinical findings from human poisoning with racemic mecoprop. The clinical findings from acute human poisoning at plasma levels of about 300-750 mg/l were reported to be muscle cramps, muscle cell damage, metabolic acidosis, respiratory failure, arterial hypoxemia, renal failure, and coma. Supportive treatment and induction of increased renal clearance by alkaline diuresis is recommended in cases of poisoning.

Effects of poisoning may include coma, muscle cramps, pyrexia, hyperventilation, respiratory failure, arterial hypoxemia, myotonia, skeletal muscle damage and electrocardiographic changes consistent with cardiomyopathy.

In the literature review for this renewal a few papers on clinical cases and poisoning have been dismissed by the applicant as irrelevant, but the RMS considers that further data on poisoning is useful because mecoprop-P is acutely toxic.

#### Epidemiology studies:

No new epidemiological data has been provided since the previous renewal review. In the 1998 DAR, three published papers (Maroni & Fait, 1993; Wiklund *et al.*, 1987 and Bond & Rossbacher, 1993) were submitted.

From available epidemiological studies no clear association between cancer development and exposure to phenoxy herbicides (including mecoprop) could be established.

In the 2003 review report for mecoprop-P it was concluded that the available epidemiological data were inadequate for determining an association between exposure and cancer in humans.

In the literature review for this renewal the applicant has dismissed a number of epidemiology studies that may show a lack of association between exposure to mecoprop and cancer. The RMS considers that any studies that show a lack of association between mecoprop and cancer are relevant and should not have been excluded. Another epidemiology study reports a significant association of mecoprop exposure with multiple myeloma. In particular the RMS questions the case for excluding the following papers as irrelevant:

1. International Journal of Cancer (2013) Vol. 133(8), pp. 1846-1858 (effects of pesticide exposure and risk of multiple myeloma).
2. Journal of Occupational and Environmental Medicine (2011) Vol. 53(11), pp. 1279-1286 (pesticide associations with soft-tissue sarcoma).
3. International Journal of Cancer (2012) Vol. 131(11), pp. 2650-2659 (pesticide use on asthma and lymphoma).
4. American Journal of Epidemiology (2011) Vol. 173 Suppl. 11, P S255 (herbicide exposure and childhood leukaemia).

In conclusion, the applicant should provide further information on the findings from these studies and give further consideration of their relevance. Overall, however, the RMS considers that none of the toxicology papers that have been dismissed are likely to add significant information to the toxicology dossier that would lead to a change in the overall conclusions.

#### First Aid measures

<b>Inhalation:</b>	Remove casualty from exposure ensuring one's own safety whilst doing so. If conscious, ensure the casualty sits or lies down. If unconscious, check for breathing and apply artificial respiration if necessary. If unconscious and breathing is OK, place in the recovery position. Consult a doctor.
<b>Skin contact:</b>	Remove all contaminated clothes and footwear immediately unless stuck to skin. Drench the affected skin with running water for 10 minutes or longer if substance is still on skin. Consult a doctor.
<b>Eye contact:</b>	Bathe the eye with running water for 15 minutes. Consult a doctor.
<b>Ingestion:</b>	Wash out mouth with water. Do not induce vomiting. If conscious, give half a litre of water to drink immediately. If unconscious, check for breathing and apply artificial respiration if necessary. If unconscious and breathing is OK, place in the recovery position. Consult a doctor.
<b>Antidote:</b>	No antidote is available.
<b>Medical treatment:</b>	Alkaline diuresis may be used to treat acute poisoning in the presence of coma or other poor prognostic indicators, such as acidemia, or if total chlorophenoxy concentrations are 0.5 g/l or more. Alkaline diuresis increases renal clearance.

#### **2.6.11. Toxicological end point for assessment of risk following long-term dietary exposure – ADI**

##### *ADI:*

In the rat carcinogenicity study on mecoprop-P the lowest dose was 100 ppm, but a significant increase in relative kidney weight was evident in females at this dose indicating the NOAEL is below 6.6 mg/kg bw/day. In mice carcinogenicity studies on mecoprop-P the minimum dose was 25 ppm which is lower than the lowest dose in rats. This dose was identified as the NOAEL and equivalent to 4 mg/kg bw/day based on increased relative

kidney weight and chronic nephropathy at 46 mg/kg bw/day. In dogs a one year study on mecoprop-P revealed a NOAEL of 5 mg/kg bw/day.

The ADI in the 1998 review was 0.01 mg/kg bw/day based on the 2 year rat study conducted on racemic mecoprop where a critical NOAEL of 1.1 mg/kg bw/day was identified. This is the lowest NOAEL identified in the chronic and carcinogenicity studies. The toxicity of mecoprop racemate and mecoprop-P have been demonstrated to be similar. Therefore the findings in this study are considered also relevant to mecoprop-P. As this is the study with the lowest NOAEL it remains the critical NOAEL and it is still appropriate to use this study to set the ADI.

**In conclusion the proposed ADI for mecoprop-P is 0.01 mg/kg bw/day based on the 2 year rat study conducted on racemic mecoprop with a safety factor of 100 applied.**

#### **2.6.12. Toxicological end point for assessment of risk following acute dietary exposure - ARfD (acute reference dose)**

##### Acute reference dose (ARfD)

The Acute Reference Dose of a chemical is an estimate of the amount of a substance in food and/or drinking water, normally expressed on a body weight basis, that can be ingested in a period of 24 hours or less without appreciable health risk to consumers. Studies potentially relevant to setting the ARfD are discussed below.

In a 24 hour acute dietary study in the mouse (Lowe 2009) consumption of mecoprop-P in the diet at a dose of 3393 mg/kg bw/day for a period of 24 hours produced no mortalities, and the only adverse effect was a 50% reduction in food consumption.

In a developmental study in the rat (Hellwig J & Hildebrand B 1993) there was a reduction in food consumption accompanied by reduced body weight gain at a dose of 100 mg/kg bw/day. The test substance was administered by gavage from days 6 to 15 of gestation. Bodyweight was measured every 2 to 3 days. In the first 48 hours of dosing (by gavage) there was a statistically significant reduction in food consumption that was 9% and 22% lower than the controls in the 50 and 100 mg/kg bw/day groups respectively. In the 100 mg/kg bw/day dose group mean maternal weight was 4% lower than controls 48 hours after dosing, and there was a loss of body weight of 0.2 grams compared with a 7.8 g increase in body weight in the control group in the 48 hours after first dose administration (see table below).

It is considered that the findings in the developmental rat study are acute effects that are appropriate to set the acute reference dose with a NOAEL of 50 mg/kg bw/day. With the application of a safety factor of 100 the acute reference dose is proposed as **0.5 mg/kg bw/day**.

**Findings considered relevant to setting an acute reference dose for mecoprop-P. Body weight and food consumption findings in the rat developmental toxicity study (Hellwig J & Hildebrand B 1993) in the first 48 hours after dose administration**

Dose (mg/kg bw/day)	0	20	50	100
Food consumption days 6 to 8 of gestation (days 0 to 2 of dosing) g/animal/day	25.5	24.2	23.3*	19.9**
Mean maternal body weight day 8 of gestation (day 2 of dosing) g	262.0	258.1	259.6	250.4*
Mean maternal body weight change days 6 to 8 of gestation (days 0 to 2 of dosing)	7.8	5.5	6.0	-0.2**

Statistically different from control \* =  $P < 0.05$ , \*\* =  $P > 0.01$

### 2.6.13. Toxicological end point for assessment of occupational, bystander and residents' risks – AOEL

#### AOEL from previous renewal:

In the ECCO93 discussion for the 1998 DAR the proposed AOEL of the rapporteur MS was not agreed and a new proposal was made: 0.04 mg/kg bw/d based on 90-d dog and rat study (SF 100). One expert proposed a lower SF of 50 with respect to the assumed lower intraspecies variability for workers.

The 2003 List of Endpoints (from the Review Report 2003) states that the most sensitive target organs in the short term toxicity studies are the kidney (increased weight and clinical chemistry changes) and the liver (increased weight and enzyme induction) with the 90 day dog study having the lowest relevant NOAEL.

The lowest NOAEL in the short term studies on mecoprop-P was 50 ppm (4.4 mg/kg b.w/day (males)) in the 7 weeks (49 days) rat study (Kirsch et al. 1986) and in one of the rat 90-day studies (Kirsch et al. 1985). Studies comparing the toxicity of the racemate and the D-isomer have shown similar toxicity behaviour of the two substances. The LOAEL in the 90 day rat studies was 400 ppm. The highest NOAEL below the lowest LOAEL should be taken as the endpoint for short-term toxicity.

- Short-term toxicity endpoint = 4 mg/kg b.w/day

The 90 day and one year dog studies also confirm that the lowest NOAEL is 4 mg/kg bw/day.

#### **Current proposal for AOEL for this renewal review:**

The RMS for this renewal review agrees with the AOEL set during the previous review.

In conclusion the RMS proposes the AOEL should remain at 0.04 mg/kg bw/day based on a critical NOAEL of 4 mg/kg bw/day (from the 7 week rat study and supported by findings in the dog studies) and applying a standard 100 uncertainty factor.

No adjustment is necessary for oral absorption as mecoprop-P in the rats exceeds 80% (based on urinary excretion).

*Applicant: Proposes an AOEL of 0.16 mg/kg bw/day based on the 90 day rat study (Reinert (1979)).*

### 2.6.14. Summary of product exposure and risk assessment

Operator exposure estimates using the German model indicate that the proposed uses of 'Mecoprop-P K 600' will result in an acceptable risk to operators (as detailed in Table 2.6.14 -1).

Operator exposure estimates using UK POEM indicate that the proposed uses of 'Mecoprop-P K 600' will result in an unacceptable risk to operators at 102% of the AOEL when gloves are worn during mixing/loading and application.

**Table 2.6.14 -1 Operator exposure to mecoprop-P resulting from the proposed use of 'Mecoprop-P K 600': summary of German model estimate indicating an acceptable risk**

Proposed use	Application method	Model/data	Operator protection	% of AOEL
Cereals	Tractor-mounted field crop boom sprayer	German model	Gloves when mixing/loading, and gloves, coveralls and sturdy footwear during application	14%

On the basis of the German model estimates and considering the classification of the formulation with respect to human health, the risk to operators resulting from the proposed use of 'Mecoprop-P K 600' is considered to

be acceptable (subject to an operator wearing coveralls, gloves and face protection (faceshield) when mixing/loading, and gloves, coveralls and sturdy footwear during application).

On the basis of UK POEM estimates, the risk to operators resulting from the proposed use of ‘Mecoprop-P K 600’ is considered to be unacceptable.

Bystander, resident and worker exposure assessments also indicate an acceptable level of risk, as summarised in Tables 2.6.14 -2 and 2.6.14 -3.

**Table 2.6.14 -2 Bystander and resident exposure to mecoprop-P resulting from the proposed use of ‘Mecoprop-P K 600’: summary of estimates indicating an acceptable risk for unprotected bystanders and residents**

Proposed use	Application method	Model/data	% of AOEL
Cereals	Tractor-mounted field crop boom sprayer	UK approach – vapour exposure Californian EPA surrogate study	10% adults 21% children
Cereals	Tractor-mounted field crop boom sprayer	UK approach – drift exposure Simulated bystander exposure measurements (Lloyd and Bell)	3%
Cereals	Tractor-mounted field crop boom sprayer	UK approach – exposure to drift fallout US EPA values for residential exposure	2%

**Table 2.6.14 -3 Worker exposure to mecoprop-P resulting from the proposed use of ‘Mecoprop-P K 600’: summary of estimate indicating an acceptable risk for unprotected workers undertaking crop inspection activities**

Proposed use	Application method	Model/data	% of AOEL
Cereals	Tractor-mounted field crop boom sprayer	EUROPOEM II worker re-entry model	75%



## 2.7. RESIDUE

### 2.7.1. Summary of storage stability of residues

Appropriate storage stability data conducted on wheat (grain, straw and whole plant) was evaluated and deemed acceptable in Addendum II of the original DAR (Perny, A., 2002). This demonstrated that mecoprop-P residues were stable in wheat grain, straw and foliage samples at -18°C for 12 months. This storage period accommodates the storage of the specimens in the residue trials. An additional freezer storage study (Anding, C., 2001) was submitted, but was not relied upon. No data on the stability of metabolites HMCPP and CCPP in plant matrices were provided. This has been identified as a data gap.

Residues of mecoprop-P, HMCPP and CCPP in all animal matrices (whole milk, skimmed milk, cream, muscle, liver, kidney and fat) are considered stable following frozen (< -18°C) storage 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. Also, 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.

### 2.7.2. Summary of metabolism, distribution and expression of residues in plants, poultry, lactating ruminants, pigs and fish

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 main metabolic pathway for the degradation of mecoprop-P in wheat was hydroxylation of the 2-methyl group on the aromatic ring. Parent mecoprop-P and primary metabolites from the main pathway were, as a percent of the total radioactive residue (TRR):

	Parent (mecoprop-P)	HMCPP*	CCPP**
Whole plants	4.1%	14.9%	9.9%
Grain	2.4%	not detected	6.1%
Straw	22.0%	12%	14.3%

\*2-hydroxymethyl-4-chloro-phenoxypropionic acid

\*\*2-carboxy-4-chloro-phenoxypropionic acid

The greater TRR observed in straw compared to whole plant is attributed to the drying out of the commodity and thus a concentration of radioactivity.

A poultry metabolism study is not required since the dietary intake is calculated to be below the trigger value of 0.004 mg/kg bw/day in NEU and the exceedance in the SEU dietary burden has been mitigated. No poultry metabolism study was submitted.

A lactating goat metabolism study originally evaluated in the DAR was found acceptable according to the OECD guideline 503. The majority of radioactivity was rapidly excreted in urine and faeces (combined ca. 90% at both doses). After 7 days of dosing the positively identified component of the radioactivity in urine and faeces was parent mecoprop-P (> 75% TRR). Further identification of metabolites was not considered necessary. Radioactive residues in milk and tissues were minimal.

### 2.7.3. Definition of the residue

The current plant residue definition for risk assessment [mecoprop (sum of isomers)] is not supported by the data evaluated. The absolute levels of the metabolites 2-hydroxymethyl-4-chloro-phenoxypropionic acid (HMCPP) and 2-carboxy-4-chloro-phenoxypropionic acid (CCPP) in grain are low, but they occur at more



significant levels in straw, which raises concerns regarding metabolism in animals. CRD are in agreement with EFSA (Reasoned Opinion 2013;11(4):3191) that these metabolites should be included in the residue definition for risk assessment (see Vol.3CA B7):

**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.

The residue for monitoring/enforcement is: **Mecoprop-P**.

The residue definition for animal products should be: **Mecoprop-P** both for enforcement and risk analysis.

#### 2.7.4. Summary of residue trials in plants and identification of critical GAP

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. A reduced data set is acceptable for NEU cereal grain trials, as residues < LOQ were observed. For straw, NEU and SEU trials were combined, as the Mann-Whitney U-Test confirmed populations were similar. The residue trials have been evaluated and deemed acceptable to support the proposed GAP.

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 CCPP. 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 trials data these are currently deemed sufficient to represent the contribution of the additional metabolites for risk assessment. A summary of the trials data and residue levels relevant to the proposed GAP is shown in Table 2.7-1.

**Table 2.7-1 Summary of residue levels of mecoprop-P following application to cereal relevant to the proposed GAP**

<b>Crop</b>	<b>Region/ Indoor (a)</b>	<b>Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs</b>	<b>Residue levels (mg/kg) observed in the supervised residue trials relevant to the supported GAPs</b>	<b>Recommendations/comments (OECD calculations)</b>	<b>MRL proposals (mg/kg)</b>	<b>HR<sup>1</sup> (mg/kg)</b>	<b>STMR<sup>1</sup> (mg/kg)</b>
		<b>Monitoring RD</b>	<b>Risk assessment RD<sup>1</sup></b>				
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

\* LOQ

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

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 are required complying with the GAP of mecoprop-P on wheat and/or barley 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. The trials should be accompanied by appropriate storage stability studies on the plant metabolites HMCPP and CCPP and a validated analytical method.

### 2.7.5. Summary of feeding studies in poultry, ruminants, pigs and fish

An assessment of the maximum dietary burden by domestic animals from the consumption of cereal (grain and straw) which may contain residues of mecoprop-P has been made in accordance with OECD guidance 73. The following assumptions have been made:

- 1) The highest likely inclusion rate of all crops which may have been treated has been used with the proviso that the aggregate does not exceed 100% diet;
- 2) All produce eaten which may have been treated, has been treated and contains residues at the HR and/or the STMR found in the trials considered to support the SEU and NEU GAP, as given below:

Mecoprop-P (SEU):

Commodity	HR <sup>1</sup> (mg/kg)	STMR <sup>1</sup> (mg/kg)
Cereal (wheat, barley, oats, rye and triticale) grain	STMR used in accordance with OECD 73.	0.2
Cereal (wheat, barley, oats, rye and triticale) straw	0.704	0.231

<sup>1</sup>Including tentative conversion factors of 4 (grain) and 2.2 (straw).

Mecoprop-P (NEU):

Commodity	HR <sup>1</sup> (mg/kg)	STMR <sup>1</sup> (mg/kg)
Cereal (wheat, barley, oats, rye and triticale) grain	STMR used in accordance with OECD 73.	0.04
Cereal (wheat, barley, oats, rye and triticale) straw	0.704	0.231

<sup>1</sup>Including tentative conversion factors of 4 (grain) and 2.2 (straw).

- 3) There is no loss of residue during transport, storage, preparation of feed or processing prior to consumption.

Table 2.7-2 Dietary burden of mecoprop-P by domestic animals 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

Table 2.7-3 Dietary burden of mecoprop-P by domestic animals 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

In NEU (Table 2.7-3) animal intakes for dairy and beef cattle, sheep and poultry layer are above the trigger of 0.004 mg/kg bw/day. In SEU (Table 2.7-2) animal intakes for dairy cattle, beef cattle, pig, sheep and chicken are above the trigger of 0.004 mg/kg bw/day. The inputs for the dietary burden are significantly worst case. They have incorporated worst-case conversion factors for the metabolites and in SEU these conversion factors have been applied to an LOQ of 0.05 mg/kg. This LOQ in itself represents a worst-case, as residue levels are realistically expected to be well below the LOQ, even < 0.01 mg/kg. Hence it can confidently be concluded that pig and chicken dietary burdens could be expected to be much lower than those shown in Tables 2.7-2 and 2.7-3, their intakes will not realistically be of concern and therefore no further consideration will be required.

A ruminant feeding study was submitted and evaluated, although it was significantly over-dosed (538X compared to beef cattle in SEU) as was originally designed to take into account animal intakes from grassland use of mecoprop-P. Residues of mecoprop-P were found in all matrices, but no residues of HMCPP and CCPP were detected in any specimens in any treatment group.

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. In accordance with the guidelines on residues in livestock, OECD 505, the livestock should be dosed with the representative components of the residue definition for feed. This feeding study only dosed with parent mecoprop-P, but as the metabolites HMCPP and CCPP are included in the plant residue definition and are significant residue components in straw, a consideration of the effect of dosing with these metabolites is necessary. A case was provided (B.7.2.3) that used the metabolic behaviour or CCPA to represent that of CCPP. Sufficient evidence was 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 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 HMCPP 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.

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, 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.

The following endpoints were derived from the study for use in the consumer risk assessments:

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

<sup>1</sup>These values are estimated from the metabolism study.

<sup>2</sup>These 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.

### 2.7.6. Summary of effects of processing

In accordance with the data requirements 283/2013, if residues  $\geq 0.01$  mg/kg are observed in the unprocessed commodities, 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 wheat grain. Additionally, in the original 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 mins), 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 in processed commodities and no further information on the nature of mecoprop-P residues during processing is required.

### 2.7.7. Summary of residues in rotational crops

Metabolism studies in rotational crops are not required, since mecoprop-P is not persistent in soil (DT<sub>50</sub> 10.12 days). Additionally, there are no soil metabolites.

### 2.7.8. Summary of other studies

Not applicable.

## 2.7.9. Estimation of the potential and actual exposure through diet and other sources

### 2.7.9.1. Acute and chronic EU dietary intake estimates – EU MS national NESTIs and EU MS national TMDIs

The following toxicological reference values have been used in the consumer risk assessments:

ADI (mg/kg bw/day)	0.01	Two year rat study, safety factor x100
ARfD (mg/kg bw)	0.5	Developmental rabbit study, safety factor x100

The EU MS national NESTIs and EU MS national TMDIs for the active and commodities listed below have been calculated using PRIMo – Pesticide Residues Intake Model (revision 2).

The following assumptions have been made:

- 1) All produce eaten which may have been treated, has been treated and contains residues at the proposed MRL, as given below.

Mecoprop-P:

Commodity	MRL inputs <sup>1</sup> (mg/kg)
Wheat (including triticale)	0.2
Barley	0.2
Rye	0.2
Oats	0.2
Bovine muscle, liver, fat	0.04
Bovine kidney	0.04
Sheep muscle, liver, fat	0.04
Sheep kidney	0.04
Goat muscle, liver, fat	0.04
Goat kidney	0.04
Milk	0.04

<sup>1</sup> Including a tentative conversion factor of 4.

- 2) There is no loss of residue during transport or storage, or processing of foods prior to consumption.

A full description of PRIMo and the underlying assumptions is in the document: 'Reasoned opinion on the potential chronic and acute risks to consumers' health arising from proposed temporary EC MRLs, 15 March 2007' – see PRIMo, instructions worksheet, cell B7.

The relevant intakes are presented in Tables 2.7-4 and Table 2.7-5. The critical consumer group for chronic intakes is the NL child with intakes of 22.4 % of the ADI and the critical consumer group for acute intakes are UK infants with intakes of 1.0 % of the ARfD. Chronic and acute intakes for all consumer groups are below the ADI (0.01 mg/kg bw/day) and ARfD (0.5 mg/kg bw) respectively and therefore no health effects due to either chronic or acute dietary exposure are expected in EU consumers.

Table 2.7-4 EFSA model (PRIMo) for chronic risk assessment - rev. 2 for mecoprop-P

				<b>Mecoprop-P</b>				<b>Prepare workbook for refined calculations</b>			
				Status of the active substance:		Code no.					
				LOQ (mg/kg bw):		proposed LOQ:					
				<b>Toxicological end points</b>				<b>Undo refined calculations</b>			
				ADI (mg/kg bw/day):		ARfD (mg/kg bw):					
				Source of ADI:		Source of ARfD:					
				Year of evaluation:		Year of evaluation:					
<p>Explain choice of toxicological reference values.</p> <p>The risk assessment has been performed on the basis of the MRLs collected from Member States in April 2006. For each pesticide/commodity the highest national MRL was identified (proposed temporary MRL = pTMRL). The pTMRLs have been submitted to EFSA in September 2006.</p>											
<b>Chronic risk assessment</b>											
				TMDI (range) in % of ADI minimum - maximum							
				22							
				No of diets exceeding ADI:				---			
	Highest calculated TMDI values in % of ADI	MS Diet		Highest contributor to MS diet (in % of ADI)	Commodity / group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity / group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity / group of commodities	pTMRLs at LOQ (in % of ADI)	
	22.4	NL child		11.7	Milk and milk products: Cattle	9.5	Wheat	0.5	Bovine: Meat		
	20.7	DK child		11.0	Wheat	8.8	Rye	0.8	Oats		
	19.6	WHO Cluster diet B		17.1	Wheat	1.2	Milk and milk products: Cattle	0.6	Barley		
	16.7	WHO cluster diet D		13.0	Wheat	1.9	Milk and milk products: Cattle	0.8	Rye		
	16.1	DE child		8.2	Wheat	5.7	Milk and milk products: Cattle	1.6	Rye		
	14.5	ES child		8.9	Wheat	5.0	Milk and milk products: Cattle	0.6	Bovine: Meat		
	13.3	IT kids/toddler		13.3	Wheat	0.0	Barley	0.0	Oats		
	12.2	WHO Cluster diet F		7.2	Wheat	1.6	Milk and milk products: Cattle	1.5	Rye		
	12.2	FR infant		10.3	Milk and milk products: Cattle	1.7	Wheat	0.2	Bovine: Meat		
	12.1	WHO cluster diet E		7.9	Wheat	1.6	Barley	1.2	Milk and milk products: Cattle		
	11.9	SE general population 90th percentile		6.4	Wheat	5.0	Milk and milk products: Cattle	0.6	Rye		
	9.3	IE adult		4.6	Wheat	2.5	Barley	1.1	Milk and milk products: Cattle		
	9.2	WHO regional European diet		5.9	Wheat	1.9	Milk and milk products: Cattle	0.7	Barley		
	8.3	IT adult		8.3	Wheat	0.0	Barley	0.0	Oats		
	8.2	PT General population		7.8	Wheat	0.3	Rye	0.1	Barley		
	8.0	ES adult		4.7	Wheat	2.0	Milk and milk products: Cattle	1.0	Barley		
	8.0	NL general		4.1	Wheat	2.6	Milk and milk products: Cattle	0.7	Barley		
	8.0	UK Toddler		7.8	Wheat	0.1	Oats	0.0	Barley		
	7.9	FR all population		6.6	Wheat	1.1	Milk and milk products: Cattle	0.2	Bovine: Meat		
	6.3	LT adult		2.2	Rye	2.1	Wheat	1.6	Milk and milk products: Cattle		
	5.9	DK adult		4.0	Wheat	1.4	Rye	0.2	Oats		
	5.8	FR toddler		5.2	Wheat	0.5	Bovine: Meat	0.0	Bovine: Edible offal		
	5.8	UK Infant		5.2	Wheat	0.5	Oats	0.0	Bovine: Liver		
	4.3	UK vegetarian		4.1	Wheat	0.1	Oats	0.0	Barley		
	3.6	FI adult		2.0	Wheat	1.4	Rye	0.2	Oats		
	3.5	UK Adult		3.4	Wheat	0.1	Barley	0.0	Oats		
		PL general population			FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)		FRUIT (FRESH OR FROZEN)		
<p><b>Conclusion:</b></p> <p>The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI.</p> <p>A long-term intake of residues of Mecoprop-P is unlikely to present a public health concern.</p>											

Table 2.7-5 EFSA model (PRIMO) for acute risk assessment - rev. 2 for mecoprop-P

Acute risk assessment /children						Acute risk assessment / adults / general population						
The acute risk assessment is based on the ARfD.												
For each commodity the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.												
In the IESTI 1 calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002), for lettuce a variability factor of 5 was used.												
In the IESTI 2 calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variability factor of 3.												
Threshold MRL is the calculated residue level which would leads to an exposure equivalent to 100 % of the ARfD.												
Unprocessed commodities	No of commodities for which ARfD/ADI is exceeded (IESTI 1):			No of commodities for which ARfD/ADI is exceeded (IESTI 2):			No of commodities for which ARfD/ADI is exceeded (IESTI 1):			No of commodities for which ARfD/ADI is exceeded (IESTI 2):		
	---			---			---			---		
	IESTI 1		*)	**) (								



### 2.7.9.2. Chronic (long term) UK dietary intake estimates – UK NEDIs

The UK NEDIs for the active and commodities listed below have been calculated for ten consumer groups as detailed in the Regulatory Update 21/2005. The following assumptions have been made:

- 1) Upper range of normal (97.5th percentile) consumption of each individual crop which may have been treated.
- 2) All produce eaten which may have been treated has been treated and contains residues at the median residue (STMR) found in the SEU trials to represent a worst case, as given below.

Mecoprop-P:

Commodity	STMR inputs <sup>1</sup> (mg/kg)
Wheat (including triticale)	0.2
Barley	0.2
Rye	0.2
Oats	0.2
Bovine muscle, liver, fat	0.04
Bovine kidney	0.04
Sheep muscle, liver, fat	0.04
Sheep kidney	0.04
Goat muscle, liver, fat	0.04
Goat kidney	0.04
Milk	0.04

<sup>1</sup>Including a tentative conversion factor of 4.

- 3) There is no loss of residue during transport or storage, or processing of foods prior to consumption.

The relevant intake estimates are presented in Table 2.7-6. **Error! Reference source not found.**

Chronic intakes for all consumer groups are below the ADI of 0.01 mg/kg bw/day ( $\leq 46\%$  ADI) therefore no health effects are expected.

Table 2.7-6 UK NEDIs for 10 consumer groups (calculated using chronic consumer version 1.1) for mecoprop-P

Active substance:	Mecoprop-P	ADI:	0.01	mg/kg bw/day	Source:	AIR3					
		TOTAL INTAKE based on 97.5th percentile									
		ADULT	INFANT	TODDLER	4-6 YEARS	7-10 YEARS	11-14 YEARS	15-18 YEARS	VEGETARIAN	ELDERLY (OWN HOME)	ELDERLY (RESIDENTIAL)
	mg/kg bw/day	0.00109	0.00458	0.00400	0.00302	0.00213	0.00151	0.00122	0.00126	0.00104	0.00120
	% of ADI	11%	46%	40%	30%	21%	15%	12%	13%	10%	12%
	STMR	P	COMMODITY INTAKES								
Commodity	(mg/kg)		(mg/kg bw/day)								
Oats	0.2		0.00007	0.00044	0.00024	0.00015	0.00009	0.00007	0.00013	0.00013	0.00011
Barley	0.2		0.00005	L/C	0.00007	0.00007	0.00016	0.00004	0.00005	0.00005	0.00005
Wheat	0.2		0.00072	0.00056	0.00170	0.00178	0.00135	0.00100	0.00081	0.00085	0.00065
Rye	0.2		0.00010	0.00027	0.00008	0.00009	0.00009	0.00005	0.00002	0.00012	0.00009
Meat fat	0.04		0.00001	0.00002	0.00003	0.00002	0.00001	0.00001	0.00001	0.00000	0.00001
Meat excl. poultry & offal	0.04		0.00008	0.00016	0.00017	0.00014	0.00012	0.00008	0.00008	0.00002	0.00007
All types of kidney	0.04		0.00001	0.00002	0.00005	0.00001	0.00001	0.00001	0.00001	L/C	0.00002
All types of Liver	0.04		0.00002	0.00009	0.00010	0.00001	0.00002	0.00002	0.00001	L/C	0.00003
Other types of offal	0.04		0.00003	0.00006	0.00009	0.00004	0.00004	0.00004	0.00002	0.00001	0.00003
Milk	0.04		0.00033	0.00390	0.00223	0.00118	0.00073	0.00047	0.00037	0.00039	0.00047
* 0.00000 corresponds to <0.000005 mg/kg bw/day (any value ≥0.000005 is rounded to 0.00001)											
L/C Low consumption (<0.1 g/day) or low number of consumers (<4)											

### 2.7.9.3. Acute (short term) UK dietary intake estimates – UK NESTIs

The UK NESTIs for the active and commodities listed below have been calculated for ten consumer groups as detailed in the Regulatory Update 21/2005. The following assumptions have been made:

- 1) Upper range of normal (97.5th percentile) consumption of each individual crop which may have been treated.
- 2) All produce eaten which may have been treated has been treated and contains residues at the MRL / highest residue found in the SEU to represent a worst case, as given below.

Mecoprop-P:

Commodity	MRL inputs <sup>1</sup> (mg/kg)
Wheat (including triticale)	0.2
Barley	0.2
Rye	0.2
Oats	0.2
Bovine muscle, liver, fat	0.04
Bovine kidney	0.04
Sheep muscle, liver, fat	0.04
Sheep kidney	0.04
Goat muscle, liver, fat	0.04
Goat kidney	0.04
Milk	0.04

<sup>1</sup>Including a tentative conversion factor of 4.

- 3) There is no loss of residue during transport or storage, or processing of foods prior to consumption.

The standard set of assumptions as given in the Regulatory Update 21/2005 applies unless stated otherwise.

The relevant intake assessment is presented in Table 2.7-7.

Acute intakes for all consumer groups are below the ARfD of 0.5 mg/kg bw ( $\leq 1.0$  % ARfD) therefore no health effects are expected.

Acute Intakes (97.5th percentiles)			Goto Inputs									
			adult		infant		toddler		4-6 year old child		7-10 year old child	
commodity	HR	P	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD
Oats	0.20		0.00018	0.0	0.00063	0.1	0.00062	0.1	0.00037	0.1	0.00041	0.1
Barley	0.20		0.00014	0.0	0.00000	0.0	0.00014	0.0	0.00035	0.1	0.00112	0.2
Wheat	0.20		0.00121	0.2	0.00257	0.5	0.00264	0.5	0.00289	0.6	0.00218	0.4
Rye	0.20		0.00026	0.1	0.00126	0.3	0.00023	0.0	0.00040	0.1	0.00029	0.1
Meat fat	0.04		0.00003	0.0	0.00008	0.0	0.00007	0.0	0.00008	0.0	0.00005	0.0
Meat excl.poultry & offal	0.04		0.00020	0.0	0.00047	0.1	0.00041	0.1	0.00036	0.1	0.00031	0.1
All types of kidney	0.04		0.00007	0.0	0.00010	0.0	0.00015	0.0	0.00010	0.0	0.00007	0.0
All types of liver	0.04		0.00011	0.0	0.00032	0.1	0.00027	0.1	0.00007	0.0	0.00010	0.0
Other types of offal	0.04		0.00012	0.0	0.00029	0.1	0.00028	0.1	0.00023	0.0	0.00022	0.0
Milk	0.04		0.00052	0.1	0.00497	1.0	0.00293	0.6	0.00186	0.4	0.00119	0.2
			11-14 year old child		15-18 year old child		vegetarian		Elderly - own home		Elderly - residential	
commodity	HR	P	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD	NESTI	%ARfD
Oats	0.20		0.00018	0.0	0.00029	0.1	0.00024	0.0	0.00014	0.0	0.00013	0.0
Barley	0.20		0.00009	0.0	0.00012	0.0	0.00015	0.0	0.00010	0.0	0.00007	0.0
Wheat	0.20		0.00177	0.4	0.00168	0.3	0.00156	0.3	0.00092	0.2	0.00091	0.2
Rye	0.20		0.00014	0.0	0.00016	0.0	0.00032	0.1	0.00017	0.0	0.00006	0.0
Meat fat	0.04		0.00004	0.0	0.00004	0.0	0.00002	0.0	0.00002	0.0	0.00002	0.0
Meat excl.poultry & offal	0.04		0.00023	0.0	0.00023	0.0	0.00011	0.0	0.00015	0.0	0.00013	0.0
All types of kidney	0.04		0.00005	0.0	0.00008	0.0	0.00000	0.0	0.00007	0.0	0.00005	0.0
All types of liver	0.04		0.00017	0.0	0.00008	0.0	0.00000	0.0	0.00009	0.0	0.00008	0.0
Other types of offal	0.04		0.00018	0.0	0.00009	0.0	0.00004	0.0	0.00010	0.0	0.00010	0.0
Milk	0.04		0.00083	0.2	0.00070	0.1	0.00059	0.1	0.00044	0.1	0.00057	0.1
	Pesticide	Mecoprop-P										
	ARfD	0.500 mg/Kg bw/day										
	Source	AIR3										
* 0.00000 corresponds to <0.000												

### 2.7.10. Proposed MRLs and compliance with existing MRLs

The current MRL for mecoprop-P on cereals is 0.05\* mg/kg and there are no animal MRLs set on a residue definition of “mecoprop (sum of mecoprop-P and mecoprop expressed as mecoprop)”. The proposed residue definition for monitoring (plant and animal) is mecoprop-P, therefore the following MRLs are proposed based on the representative uses:

#### Proposed MRLs

Code	Commodity	Current MRL	Proposed MRL	Comment
0500000	Cereals	0.05*	0.05*	No change required in value, but RD-Mo should be updated.
1012010	Bovine muscle	-	0.01	Default MRL
1012030	Bovine liver	-	0.01	Default MRL
1012020	Bovine fat	-	0.01	Default MRL
1012040	Bovine kidney	-	0.01	Default MRL
1020000	Milk	-	0.01	Default MRL
1013010	Sheep muscle	-	0.01	Extrapolated from bovine commodities
1013030	Sheep liver	-	0.01	
1013020	Sheep fat	-	0.01	
1013040	Sheep kidney	-	0.01	
1014010	Goat muscle	-	0.01	
1014030	Goat liver	-	0.01	
1014020	Goat fat	-	0.01	
1014040	Goat kidney	-	0.01	

These are the proposed MRLs based on a residue definition (monitoring) of mecoprop-P. It is the view of the RMS that a formal change in MRL is not considered appropriate until the data gap for further residue trials is addressed. Currently the trials data available is only suitable for monitoring, not risk assessment and official conversion factors have not been determined.

### 2.7.11. Proposed import tolerances and compliance with existing import tolerances

Not relevant.

## 2.8. FATE AND BEHAVIOUR IN THE ENVIRONMENT

### 2.8.1. Summary of fate and behaviour in soil

#### Route and rate of degradation in soil

No new aerobic soil degradation studies were submitted. An acceptable aerobic soil degradation study was assessed in Addendum 1 to the DAR (2000). The aerobic degradation of mecoprop-P was investigated at 20°C and 75% FMC (1/3 bar) in one American sandy loam (Timmerman) over 191 days and three German standard soils (Speyer 2.1, 2.2 and 2.3) over 100 days. A clear decline in the concentration of mecoprop-P was observed in all four soils, with final concentrations of mecoprop-P reaching less than 10 %AR in all soils studied. Mecoprop-P degraded directly to non-extractable residues or indirectly via minor degradation products to CO<sub>2</sub>. No metabolites were identified that require further consideration. Data from the aerobic soil degradation study were re-analysed according to FOCUS kinetics guidance and modelling endpoints were normalised to pF2. Mecoprop-P degrades quickly in soil (Worst case DT<sub>50</sub>; best-fit 7.0 days, modelling 10.12 days).

For the representative use (spring/summer use on cereals), anaerobic conditions are considered unlikely, therefore an anaerobic soil degradation study on mecoprop-P is not required.

A new soil photolysis study on mecoprop-P was submitted. The photo transformation of mecoprop-P was studied on a sandy loam soil over 30 days at 25°C under artificial sunlight. The metabolite 4-chloro-2-methylphenol (PCOC) was detected at up to 3.23% AR. In the dark controls, extractable radioactivity remained constant and PCOC was not detected. Data from the soil photolysis study were re-analysed according to FOCUS kinetics guidance and degradation rates under natural sunlight at 42°N were estimated (DT<sub>50</sub>; artificial light 73.8 days, 42°N 20.7 days)

Soil dissipation and soil accumulation studies are not required. For mecoprop-P, DT<sub>50,lab</sub> are all less than 60 days, and DT<sub>90,lab</sub> are all less than 200 days.

#### Adsorption and desorption in soil

In the DAR for the original approval (1998), two adsorption and desorption studies were assessed and considered acceptable: Matla & Vonk (1991) assessed sorption of mecoprop-P to soils with pH <5 whilst Obrist (1986) assessed sorption of racemic mecoprop to soils with pH >5.5. One study was submitted for the purpose of renewal: Simmonds (2010), which assessed sorption of mecoprop-P to soils with pH >5.5. Results from the study on racemic mecoprop on soils with pH >5.5 were within the same range as those in the newly submitted study (pH >5.5) indicating that the adsorption process is not stereoselective. Mecoprop-P is highly mobile with K<sub>f</sub> observed from 0.298 ml/g to 4.5 ml/g in 10 soils. Only a weak correlation between K<sub>f</sub> and organic carbon content is evident. Both K<sub>oc</sub> and 1/n were found to have pH dependency, with values clustered above (7 soils) and below (3 soils) pH<sub>(H2O)</sub> 5.5. Below pH 5.5 (pH<sub>(H2O)</sub> range 5.2-5.3), K<sub>oc</sub> ranged from 135 to 167 ml/g and 1/n ranged from 0.66 to 0.75. Above pH 5.5 (pH<sub>(H2O)</sub> range 5.7-7.6), K<sub>oc</sub> ranged from 12 to 34 ml/g and 1/n ranged from 0.852 to 1.012.

#### Mobility in soil

Column leaching studies are not required as reliable batch equilibrium adsorption studies are available.

In the DAR for original approval (1998) a lysimeter study on mecoprop-P was assessed and considered acceptable (Herrchen, 1991). This study provides supporting information for renewal purposes. The fate of <sup>14</sup>C-mecoprop-P (ring label, >97% pure) in two outdoor lysimeters consisting of undisturbed sandy loam soil monoliths and its uptake by plants was investigated over two years. The study was performed on acidic sandy loam at Fraunhofer in Germany. Applications of 1.2 kg a.s/ha were made on 18th May 1989. Lysimeters were successively seeded with summer wheat, winter wheat and winter rape. Neither mecoprop-P nor the metabolite 4-chloro-2-methylphenol could be detected in any leachate sample in concentrations > 0.03 µg/l. Unidentified compounds were present at 0.4-0.5 and 0.1-0.2 µg/l (expressed as mecoprop-P equivalents) 1 and 2 years after application, respectively.

### 2.8.2. Summary of fate and behaviour in water and sediment

#### Route and rate of degradation in aquatic systems (chemical and photochemical degradation)

In the DAR for original approval (1998) two aqueous hydrolysis studies were considered acceptable. Both studies were conducted on racemic mecoprop, however differences in hydrolysis between mecoprop and mecoprop-P are not expected. Mecoprop was found to be stable to hydrolysis at pH 5, 7 and 9 at both 70°C over 8 days and 25°C over 31 days.

A new aqueous photolysis study was submitted for the purpose of renewal. In irradiated samples (artificial light), degradation of mecoprop-P was observed at pHs 5, 7 and 9, reaching <10%AR within the 30 day study period. The metabolite *o*-cresol was detected at up to 30.4 % of the applied radioactivity on day 30 at pH 7. Photo-degradate data were not reported for pH 5 and 9 systems. Degradation of mecoprop-P was not observed in dark control samples. Data from the study were re-analysed according to FOCUS kinetics guidance and degradation rates under natural sunlight at 42°N were estimated (Mecoprop-P DT<sub>50</sub> at 42°N; pH 5 3.39 days, pH 7 4.65 days, pH 9 4.21 days).

#### Route and rate of biological degradation in aquatic systems

A new study was conducted to determine the ready biodegradability of mecoprop-P in a manometric respirometry test over 28 days in accordance with OECD test guideline 301 F. At the end of the 28-day incubation period, mecoprop-P was 85% biodegraded under the test conditions. The pass level for ready biodegradability (biodegradation  $\geq 60\%$  of the chemical oxygen demand [COD] of the test item in a 10-day window within the 28-day test period) was reached. Mecoprop-P can therefore be classified as readily biodegradable under the test conditions.

A new aerobic mineralisation in surface water study was submitted for the purpose of renewal.  $^{14}\text{C}$ -Mecoprop-P was applied at two test concentrations of 10  $\mu\text{g/L}$  and 100  $\mu\text{g/L}$  to surface water taken from Rhineland-Palatinate (Germany, 49°31'N, 08°32'O). The mineralisation rate was negligible for both tested concentrations. For both concentrations no metabolites were formed during the incubation period (58 days). The test system was validated using reference substance sodium benzoate; 82-87% mineralised after 13 days demonstrating the surface water contained an active microbial population. Due to the negligible mineralisation of mecoprop-P, degradation rates could not be reliably calculated. Mecoprop-P is considered persistent in surface water.

Data from four water sediment systems are available from two studies: In the first study (Cooper & Unsworth, 1996), the degradation of  $^{14}\text{C}$ -mecoprop-P was investigated under aerobic conditions at 20°C in two contrasting water/sediment systems (Manningtree and Ongar).  $^{14}\text{C}$ -mecoprop-P was applied to the water phase at an application rate of 0.449 mg/L and the systems were incubated for 100 days. Some partitioning to sediment was observed (max 14.77%AR and 6.58%AR in Manningtree and Ongar systems respectively). Unknown metabolite 1 was identified at  $>5\%$  at two time points in the Ongar system and at  $>5\%$  at one time point in the Manningtree system. At the time of the original assessment metabolites were not considered relevant at this level and were therefore not identified. A second water/sediment study was undertaken to identify the metabolites (Roohi, 2015) for the purpose of renewal. In Roohi, 2015, the degradation of  $^{14}\text{C}$ -mecoprop-P was investigated under aerobic conditions at 20°C in two contrasting water/sediment systems (Calwich Abbey and Swiss Lake).  $^{14}\text{C}$ -Mecoprop-P was applied to the water surface of individual water sediment systems at a target application rate of 0.138 mg/L in the water phase and the systems incubated for 98 days. Some partitioning to sediment was observed (max 22.73%AR and 14.91%AR in Calwich Abbey and Swiss Lake systems respectively). In both the Calwich Abbey and Swiss Lake systems, the applied mecoprop-P degraded to form minor metabolites, none exceeding 5% AR. The RMS considers the dose rate of mecoprop-P applied to the Calwich Abbey and Swiss Lake systems (0.138 mg/L) to be appropriate for the representative use, therefore, the higher levels of metabolites observed in the Manningtree and Ongar systems could be ascribed to the higher dose rate applied (0.449 mg/L).

The dissipation of mecoprop-P from the water phase and degradation in the total systems was evaluated according to FOCUS (2006) guidance. In the Manningtree, Ongar and Calwich Abbey systems,  $^{14}\text{C}$ -mecoprop-P dissipated rapidly from the water phase after an initial lag phase with best-fit overall  $\text{DT}_{50}$  values of 51.4, 23.2 and 72.5 days respectively (HS model). Dissipation from the water phase was slower in the Swiss Lake system with a  $\text{DT}_{50}$  of 171 days (SFO). Degradation in the total water/sediment systems also occurred rapidly following an initial lag phase in three of the systems. Best fit overall  $\text{DT}_{50}$  values of 58.9 (SFO), 23.4 and 83.2 days (HS model) were obtained for the Manningtree, Ongar and Calwich Abbey systems respectively. Degradation from the total system was slower in the Swiss Lake system with a best fit  $\text{DT}_{50}$  of 244 days (SFO).

### 2.8.3. Summary of fate and behaviour in air

Seven studies were assessed for the original approval of mecoprop-P in the DAR (1998) and Addendum II to the DAR (2002). No new data has been submitted. Mecoprop-P has a relatively low vapour pressure indicating a minor volatilization ( $1.4 \times 10^{-3}$  Pa at 25°C). In laboratory studies the volatilization of formulated products from plant surfaces was  $< 0.1\%$  of applied and the volatilization from soil surfaces was  $< 1\%$ . In a field study mecoprop-P was concluded to volatilize to some (not quantified) extent. The photochemical oxidative degradation of mecoprop-P in air is rapid (half-life 21 hours calculated using Atkinson method, 24 hour day,  $5 \times 10^6$  OH  $\text{cm}^{-3}$ ). Therefore, although volatilisation from soil and plant surfaces may occur, long-range transport is not considered likely. No data are provided on local and global effects. Due to the rapid photochemical oxidative degradation in air of mecoprop-P; local and global effects are expected to be negligible.

#### 2.8.4. Summary of monitoring data concerning fate and behaviour of the active substance, metabolites, degradation and reaction products

A survey of the occurrence of mecoprop-P in groundwater, surface freshwater and drinking water was carried out from monitoring programmes in the 28 European Union Member States plus Norway and Switzerland. Information was collected for the period 2009 to 2014.

Groundwater: mecoprop-P is monitored in three countries (Luxembourg, Norway and the Netherlands). In total over 267 sites were monitored with over 1047 samples analysed. Mecoprop-P exceeded 0.1µg/l in 11 samples. Maximum reported concentrations were in Luxembourg (1.438µg/l).

Surface freshwater: mecoprop-P is monitored in seven countries (Ireland, Italy, Luxembourg, Norway, Slovakia, Switzerland and the Netherlands). In total over 341 sites were monitored and 4169 samples were analysed. Mecoprop-P exceeded 0.1µg/l in more than 43 samples in Luxembourg, Norway and Slovakia. The maximum reported concentration in surface freshwater was 1.8µg/l in Norway.

Drinking water; mecoprop-P is monitored in two countries (Ireland and the Netherlands). In total over 103 sites were monitored and 574 samples analysed. No exceedances of the 0.1µg/l drinking water limit were reported.

A further 11 countries reported that mecoprop is monitored in at least one of the compartments (groundwater, surface freshwater and drinking water), however the analytical methods do not distinguish between isomers. Therefore, data from these monitoring programmes were not reported.

#### 2.8.5. Definition of the residues in the environment requiring further assessment

Compartment	Compound
Soil	mecoprop-P
Surface water	mecoprop-P, o-cresol
Sediment	mecoprop-P
Ground water	mecoprop-P
Air	mecoprop-P

#### 2.8.6. Summary of exposure calculations and product assessment

No studies were submitted on the formulation Mecoprop-P K 600, code CA3015. Exposure calculations were carried out using values determined for the active substance, mecoprop-P.

##### Predicted environmental concentration in soil

The RMS calculated the PECs for use on spring cereals (1 x 1.2 kg a.s/ha, 0% crop interception) using a simple Excel spread sheet. The longest non-normalised laboratory DT<sub>50</sub> was used – pseudo-SFO DT<sub>50</sub> 10.12 days, Speyer 2.2 soil. A soil layer of 5cm depth with density of 1.5g/cm<sup>3</sup> was assumed. Initial PEC<sub>soil</sub> is 1.600 mg/kg.

The DT<sub>90</sub> of mecoprop-P in soil is less than 1 year, therefore plateau concentrations have not been calculated.

There are no soil metabolites to consider.

##### Predicted environmental concentration in groundwater

The RMS carried out groundwater modelling using soil DT<sub>50</sub>, K<sub>foc</sub> and 1/n as determined for the active substance, mecoprop-P, with PEARL v4.4.4, PELMO v5.5.3 and MACRO v4.4.2 (Chateaudun). Sorption values for pH > 5.5 were used to represent the most conservative case. The application date selected for use within the models was 1<sup>st</sup> March. The applicant considers this represents worst-case timing for applications made in spring based on dates predicted using PELMO AppDate calculator which demonstrate that BBCH 13 for spring cereals is likely to occur after 1<sup>st</sup> March. Applications from 1<sup>st</sup> March for both spring and winter



cereals are specified in the GAP table for the representative uses. PELMO AppDate calculator predicts winter cereals BBCH 20 will occur between 15<sup>th</sup> November and 3<sup>rd</sup> January and BBCH 32 will occur between 9<sup>th</sup> January and 27<sup>th</sup> May. Therefore, Member States may wish to consider whether applications from 1<sup>st</sup> March will be appropriate for winter cereals between BBCH 20 and 32. For application to spring cereals, PEC<sub>GW</sub> are <0.1 µg/l following application on 1<sup>st</sup> March for all scenarios (max PEC<sub>GW</sub> 0.056 µg/l, PELMO v5.5.3, Okehampton). Following application to winter cereals on 1<sup>st</sup> March, 0.1 µg/l is exceeded in one scenario (Okehampton) with one model (PELMO v5.5.3). PEC<sub>GW</sub> are below 0.1 µg/l for all other scenarios and models (max PEC<sub>GW</sub> 0.076 µg/l, PELMO v5.5.3, Jokioinen). Member States should consider the protection of groundwater when the active substance is applied in regions with vulnerable soil and/or climatic conditions.

There are no metabolites requiring consideration for groundwater.

### Predicted environmental concentration in surface water and sediment

The RMS carried out surface water modelling at FOCUS Steps 1, 2, 3 and 4 for mecoprop-P and FOCUS Steps 1 and 2 for the aqueous photolysis metabolite, *o*-cresol, for the representative uses on spring and winter cereals.

For mecoprop-P at FOCUS Step 3 (SWASH v3.1): 1 application of 1200 g a.s/ha was assessed for both winter and spring cereals. Sorption values for pH > 5.5 were used to represent the most conservative case. The application window was set to 7 days post emergence to 31<sup>st</sup> July for spring cereals and from 1<sup>st</sup> March to 31<sup>st</sup> July for winter cereals. For spring cereals max PEC<sub>SW</sub> was 32.316 µg/l (R4, Stream) and max PEC<sub>SED</sub> was 8.248 µg/kg (D1, Ditch). For winter cereals max PEC<sub>SW</sub> was 184.278 µg/l (D2, Ditch) and max PEC<sub>SED</sub> was 54.830 µg/kg (D1, Ditch). At Step 4 the following mitigation measures were assessed using SWAN for both spring and winter cereals: 5m and 10m no spray buffer zones, 5m, 10m and 20m vegetative filter strips (5m VFS were calculated using VFSmod) and 50%, 75% and 95% drift reduction.

For *o*-cresol at FOCUS Step 1 and 2: max formation was 30.4% in water and sediment. *O*-Cresol is not observed in soil studies. No crop interception (0%) was selected for spring cereals and minimal crop cover (25% interception) was selected for winter cereals. As no data is available for *o*-cresol, DT<sub>50s</sub> were set to conservative defaults of 1000 days for all compartments and Koc was set to 1 ml/g. PEC<sub>SW</sub> and PEC<sub>SED</sub> were calculated for applications in March to May in North and South EU. At Step 2 max PEC<sub>SW</sub> was 1.68 µg/l (spring and winter cereals, N+SEU) and max PEC<sub>SED</sub> was 0.017 µg/kg (spring and winter cereals, N+SEU).

### Predicted environmental concentration in air

See Section 2.8.3. No additional calculations were performed or are considered necessary.

### Other routes of exposure

Environmental exposure is not expected to occur via other routes. The product, Mecoprop-P K 600, is a soluble concentrate formulation; therefore dust drift is not considered a relevant route of exposure. Indirect surface water exposure via a sewage treatment plant is not considered relevant as mecoprop-P was determined to be readily biodegradable.

## 2.9. EFFECTS ON NON-TARGET SPECIES

### 2.9.1. Summary of effects on birds and other terrestrial vertebrates

Based on an available 4 acute avian studies with the active substance (in either technical or DMA salt form) a geometric mean LD<sub>50</sub> of 532.7 mg a.s./kg body weight was calculated and utilised to assess the acute risk to birds. On the basis of a single reproductive study an avian NOAEL of 70.9 mg a.s./kg bw/day was defined. As the LD<sub>50</sub> divided by a factor of 10 was lower than this long-term NOAEL, the long-term endpoint for use in the avian risk assessment was set as 53.3 mg a.s./kg bw/day.

On the basis of 4 available acute oral studies with the rat, a geometric mean LD50 = 703.9 mg a.s./kg bw was calculated and used in the mammalian acute risk assessment. A further acute dietary study with the mouse (Lowe, 2009) did not indicate increased acute toxicity to this mammalian species. For defining an

ecotoxicologically relevant NOAEL detailed consideration of an available 7 long-term, reproduction and teratogenicity studies with mammalian species was made (See Volume 3, (CP) B.9.1.2). An overall mammalian NOAEL was concluded by the RMS to be 34.5 mg a.s./kg bw/day.

### 2.9.2. Summary of effects on aquatic organisms

Toxicity to aquatic organisms was addressed via a combination of original Annex I data and newly submitted data with the active substance and representative formulation. For some groups data with previous representative formulations BAS 037 29 H ('Duplosan KV') and 'Optica MP' were considered as suitable to support the renewal representative formulation 'Mecoprop-P K 600 g/L'. New representative formulation data was submitted with each acute organism group: Fish, *Daphnia*, algae, and 2 aquatic plant species; *Lemna gibba* and *Myriophyllum spicatum*. The aquatic plant *Myriophyllum* was shown to be the most sensitive organism group, with a critical ErC<sub>50</sub> endpoint of 26.9 µg a.s./L, based on study Gonsoir (2015). No toxicity data with this group was available with the technical active substance, so the risk assessment for *Myriophyllum* was considered to address the risk from both mecoprop-P and the representative formulation. Representative formulation toxicity was expressed in terms of active substance content to aid use in the risk assessment.

A single potentially relevant metabolite was identified for the surface water environment: O-cresol. No specific toxicity data was generated by the notifier in support of this metabolite. However, a position paper (Simmons, 2015) was provided which argued loss of the toxophore from the parent and thus expected lower toxicity to non-target organisms. The paper additionally presented toxicity data for some aquatic organism groups based on either QSAR modelling or from the REACH registration of o-cresol (on [www.ECHA.com](http://www.ECHA.com)). The lower endpoint per organism group from these 2 methods of toxicity data generation was applied by the RMS in the aquatic risk assessment.

### 2.9.3. Summary of effects on arthropods

In addition to acute adult oral and contact toxicity data with mecoprop-P, the notifier provided an acute larval toxicity study conducted in accordance with OECD guideline 237, and a bee brood field study, both testing the representative formulation Mecoprop-P K 600 g/L. Acute oral and contact LD<sub>50</sub> values for adult acute exposure were > 83 µg a.s./bee. Due to the composition of the representative formulation it was considered by the RMS as appropriate to extrapolate active substance data to support the conclusion of risk from Mecoprop-P K 600 g/L. The larval LD<sub>50</sub> was found to be 89.4 µg a.s./bee, equivalent to 2.636 g a.s./kg food. In the bee brood field trial no significant effects on adults or brood development parameters were seen at 0.15 g a.s./L food.

First tier laboratory studies were conducted with the representative formulation Mecoprop-P K 600 g/L on the 2 sensitive indicator species *Aphidius rhopalosiphii* and *Typhlodromus pyri*. The resultant LR<sub>50</sub> values were 447.6 and >1468 g a.s./ha, respectively. Higher tier data with *A.rhopalosiphii* and *C.carnea* was generated using exposure on natural substrates, and previous Annex I data with the representative formulations 'Duplosan KV' and 'Optica MPK' were also available with *A.rhopalosiphii* and *A.bilineata*. It was confirmed under Volume 3 (CA) B.2 of the assessment report that data with these formulations are also supportive of Mecoprop-P K 600 g/L.

### 2.9.4. Summary of effects on non-target soil meso- and macrofauna

Valid studies were provided demonstrating the long-term toxicity of mecoprop-P to earthworms (NOEC = 10.8 mg a.s./kg soil, EC<sub>10</sub> = 9.0 mg a.s./kg soil) and also toxicity to soil macro-organisms *F.candida* and *H.Aculeifer* from the representative formulation. *F.candida* 28-day NOEC = 52.9 mg a.s./kg and *H.aculeifer* NOEC = 1000 mg a.s./kg.

There were no metabolites identified as potentially relevant in soil. As mecoprop-P has a Log Pow of < 2 no correction of endpoints was required to account for the high organic matter content typically found in laboratory artificial soils.

### 2.9.5. Summary of effects on soil nitrogen transformation

Only a single study was available in support of this data requirement, which was originally submitted for Annex I inclusion. Evaluation of the study by the RMS at renewal concluded that it was not of sufficient quality to be

included for use in the regulatory risk assessment. As such no valid data is available with regards to the toxicity of mecoprop-P or the representative formulation to nitrogen-transforming soil micro-organisms.

### 2.9.6. Summary of effects on terrestrial non-target higher plants

As mecoprop-P has a herbicidal mode of action no screening data was provided in support of active substance approval. Tier 2 vegetative vigour and seedling emergence studies were submitted at renewal testing the active substance in a 0.4% aqueous solution. Additionally, three valid laboratory tier II studies were available with the previous representative formulation (deemed suitable to support Mecoprop-P K 600 g/L): BAS 037 32 H. Across these 5 studies the lowest pre-emergence ER<sub>50</sub> endpoint was 19.2 g a.s./ha, for inhibitory effects to oilseed rape. The corresponding post-emergence ER<sub>50</sub> was 19.9 g a.s./ha, for effects on cucumber.

Due to the availability of suitable ER<sub>50</sub> endpoints from  $\geq 6$  species per exposure type, a HC<sub>5</sub> endpoint was generated in accordance with the probabilistic methods described in the SANCO terrestrial guidance document (2002). These were calculated using software at [www.webfram.com](http://www.webfram.com) to be:

- Pre-emergence median HC<sub>5</sub> = 19.8 g a.s./ha
- Post-emergence median HC<sub>5</sub> = 22.6 g a.s./ha

### 2.9.7. Summary of effects on other terrestrial organisms (flora and fauna)

No additional studies were submitted for the purpose of renewal.

### 2.9.8. Summary of effects on biological methods for sewage treatment

Results of a single OECD 209 test (Falk, 2013) submitted for renewal purposes indicate that technical mecoprop-P is of low toxicity to aerobic waste water bacteria, having an estimated EC<sub>50</sub> value of 319 mg/L.

### 2.9.9. Summary of product exposure and risk assessment

#### 2.9.9.1. Birds and other terrestrial vertebrates

The risk assessment for birds and other terrestrial vertebrates was conducted in adherence with the EFSA guidance (2009)<sup>1</sup>. The acute and long-term risk to birds from dietary intake of mecoprop-P residues on food items was assessed to first-tier where a low risk was demonstrated for the representative uses on winter and spring cereals. As 2 metabolites were found to be formed in plant material in a metabolism study with wheat, but no avian metabolism study was available, the risk to birds from these 2 plant metabolites HMCPP and CCPP was assessed according to EFSA (2009). A conservative estimation of 10 times parent toxicity was applied, as well as predicted exposure based on the representative use application rates and maximum metabolite formation percentage in the wheat metabolism study. A low risk to birds was demonstrated under first tier assumptions.

The acute and long-term risk to mammals was also assessed according to the EFSA (2009) guidance document. At first tier a low acute risk was demonstrated, but there was an outstanding risk found for the first tier crop scenario 'cereals early (shoots)' for which the generic focal species is the large herbivorous "lagomorph" (TER = 2.4). No further assessment (refinement to the risk) was provided by the notifier and the RMS has considered that 'early (shoot)' in cereals may correspond to up to BBCH 29. As such there is an unaddressed long-term risk to mammals for both representative uses. In the same manner as for birds, the risk to mammals from metabolites formed in plant food items was assessed. However, no consideration of metabolite HMCPP was made, due to available rat metabolism data (volume 3 (CA) B.6.1.3) showing formation and excretion of this metabolite in rats in excess of the percentage formation in wheat plants. The acute and long-term risks to mammals from the other plant metabolite CCPP could not be addressed for all generic focal species under first tier assumptions (Acute TERs = 9.7 – 47.6, repro TERs = 1.7 - 9.6) and no further assessment was provided by the notifier.

A low risk to birds and mammals via drinking water was demonstrated using the screening step of EFSA (2009): When comparing the effective application rate for the proposed uses to the toxicity endpoints for birds

<sup>1</sup> EFSA Journal 2009; 7(12):1438

and mammals the ratio was found to be below the trigger of 50 (as mecoprop-P has a mean Koc value of 21) indicating a low risk via this route of exposure. The Log Kow of mecoprop-P is less than 3, meaning no assessment for secondary poisoning is required and a low risk can be concluded via this route of exposure.

Overall a low risk to mammals from the active substance (long-term risk only) and plant metabolite CCP (acute and long-term risk) could not be concluded for the representative uses on winter and spring cereals.

### 2.9.9.2. Aquatic organisms

The assessment was conducted in line with Guidance document on Aquatic Ecotoxicology SANCO/3268/2002, with reference made to the scientific principles of the 2013 EFSA aquatic guidance document<sup>2</sup> as appropriate.

The proposed representative uses of mecoprop-P are on winter (spring application) and spring cereals for a single application at 1.2 kg a.s./ha (2 L formulation/ha). At FOCUS step 1 assessment the overall worst-case exposure for both uses across the entire EU was considered in the risk assessment. At FOCUS steps 2-4 the individual representative uses were assessed separately.

At FOCUS step 1 a maximum PEC<sub>SW</sub> of 400.14 µg a.s./L was modelled for the active substance (also used to assess the risk from the representative formulation), and 1.68 µg a.s./L for the metabolite o-cresol. At this first step a low risk was demonstrated to all groups from the metabolite o-cresol. With regards to mecoprop-P and the representative formulation a low risk was demonstrated for all organism groups EXCEPT *Lemna* (technical a.s. toxicity endpoint only) and *Myriophyllum*.

**Table 2.9.9-01 : Summary of FOCUS step 1 aquatic risk assessment for mecoprop-P**

Test substance	Organism group	Time scale	Toxicity end point (µg a.s./L)	PEC <sub>sw,max</sub> Global max (µg a.s./L)	TER	Trigger
a.s.	Fish	Acute	>93 000	400.14	232	100
O-cresol	Fish	Acute	6200	1.68	3690	100
Mecoprop-P K 600 g/L	Fish	Acute	>58 700	400.14	147	100
a.s.	Fish	Chronic	11 100	400.14	28	10
O-cresol	Fish	Chronic	1700	1.68	1012	10
a.s.	Aquatic invertebrate	Acute	>91 000	400.14	227	100
O-cresol	Aquatic invertebrate	Acute	5200	1.68	3095	100
Mecoprop-P K 600 g/L	Aquatic invertebrate	Acute	>58 700	400.14	147	100
a.s.	Aquatic invertebrate	Chronic	50 000	400.14	125	10
a.s.	Aquatic invertebrate	Chronic	22 200	400.14	55	10
O-cresol	Aquatic invertebrate	Chronic	1000	1.68	595	10
a.s.	Algae	Growth	23 900	400.14	60	10
O-cresol	Algae	Growth	23 900	1.68	14226	10
Mecoprop-P K 600 g/L	Algae	Growth	>58 700	400.14	147	10
a.s.	Aquatic plant ( <i>Lemna</i> )	Growth	1600	400.14	<b>4</b>	10
O-cresol	Aquatic plant ( <i>Lemna</i> )	Growth	11 900	1.68	7083	10
Mecoprop-P K 600 g/L	Aquatic plant ( <i>Lemna</i> )	Growth	34 700	400.14	87	10
Mecoprop-P K 600 g/L	Plant ( <i>Myriophyllum</i> )	Growth	26.9	400.14	<b>0.07</b>	10

<sup>2</sup> EFSA Journal 2013;11(7):3290

At FOCUS step 2 (considering both Northern and Southern Europe maximum PEC<sub>sw</sub> values) the TER values with regards to the active substance and the aquatic plant group *Lemna spp.* were greater than 10 for both representative uses of mecoprop-P. As such a low risk to this group was concluded for the representative uses.

With regards to the aquatic plant *Myriophyllum* all step 2 calculated PEC<sub>sw</sub> values resulted in a TER less than 10. As such an outstanding risk to this group remained following both representative GAPs and further risk assessment was required at FOCUS step 3.

FOCUS step 3 considered the various relevant scenarios for each of the 2 representative uses proposed for mecoprop-P. Under risk assessment using firstly the critical (lowest) toxicity endpoint for *Myriophyllum*, and then the geometric mean of 2 comparable study endpoints (second study: Seeland-Fremer and Mosch (2015)) there was still an unresolved risk to this group for the majority of the FOCUS step 3 scenarios as follows:

**Table 2.9.9-02 : Scenarios at FOCUS step 3 aquatic risk assessment for mecoprop-P with outstanding risk identified**

Representative use	FOCUS step 3 scenarios with outstanding risk identified
Winter cereals 1 x 2L/ha at BBCH 20-32	<ul style="list-style-type: none"> <li>- D1 ditch + stream</li> <li>- D2 ditch + stream</li> <li>- D3 ditch</li> <li>- D4 stream</li> <li>- D5 stream</li> <li>- D6 ditch</li> <li>- R1 stream</li> <li>- R3 stream</li> <li>- R4 stream</li> </ul>
Spring cereals 1 x 2L/ha at BBCH 13-32	<ul style="list-style-type: none"> <li>- D1 ditch + stream</li> <li>- D3 ditch</li> <li>- D4 stream</li> <li>- D5 stream</li> <li>- R4 stream</li> </ul>

To further assess the risk to *Myriophyllum* from the active substance and representative formulation Mecoprop-P K 600 g/L the risk assessment was conducted using FOCUS step 4 PEC<sub>sw</sub> values, considering a variety of risk mitigation options and directly comparing them against the RAC for this aquatic group of 2.97 µg a.s./L (geometric mean ErC<sub>50</sub> toxicity endpoint for *Myriophyllum* divided by the regulatory trigger of 10). There is required risk mitigation and some outstanding FOCUS scenarios for all representative GAPs:

A low risk for most FOCUS scenarios could be demonstrated following application to spring cereals when the following mitigation measures were applied:

- 5m no spray buffer zone and 5m vegetative filter strip

However, the following FOCUS scenario could not be addressed via provision of risk mitigation:

- D1 ditch + stream

A low risk for most FOCUS scenarios could be demonstrated following application to winter cereals when the following mitigation measures were applied:

- 5m no spray buffer zone and 5m vegetative filter strip

However, the following FOCUS scenario could not be addressed via provision of risk mitigation:

- D1 ditch + stream
- D2 ditch + stream

Overall a low risk could not be demonstrated for all FOCUS scenarios for either representative use of mecoprop-P on the basis of the illustrative risk assessment undertaken; meaning further consideration of the risk to aquatic plants will be required by individual Member States.

### 2.9.9.3. Bees and other arthropods

The acute risk to adult honeybees was assessed in accordance with the SANCO Terrestrial guidance document<sup>3</sup>. The critical acute contact and oral LD<sub>50</sub> values were compared with the maximum individual application rate for the representative uses to derive a Hazard Quotient (HQ) for each exposure route. HQ values of  $\leq 50$  indicate a low acute risk to honeybees. Both acute HQ values were calculated to be  $<14.5$  meaning a low risk to honeybees was concluded for the representative uses of mecoprop-P, considering current EU-agreed guidance.

The notifier submitted a bee brood study conducted with the representative formulation under field conditions according to the Oomen et al (1992) guideline. The study has been evaluated under (CA) B.9.3.1.3 and was concluded to be valid by the RMS. However due to the lack of an EU-agreed risk assessment scheme and the difficulty relating exposure in this study to mecoprop-P exposure in the field, the risk to bee brood has not been considered further.

The risk to non-target arthropods other than bees was assessed using the Guidance Document on Regulatory Testing and Risk Assessment Procedures for Plant Protection Products with Non-Target Arthropods from the ESCORT 2 workshop (Candolphi et al, 2000). At first tier the LD<sub>50</sub> endpoints from standard laboratory studies with *Aphidius rhopalosiphi* and *Typhlodromus pyri* were compared to in-field and off-field Predicted Environmental Rates following the representative uses of mecoprop-P. Calculated off-field Hazard Quotients (HQ) for both species were below the trigger of 2, indicating a low risk to off-field populations of non-target arthropods. The in-field Hazard Quotient for the species *T. pyri* was below the trigger of 2, but the HQ with regards to the first tier in-field risk assessment for *A. rhopalosiphi* was 2.7, indicating a potential in-field risk and requirement for higher tier consideration to the ESCORT II scheme.

In accordance with the guidance of ESCORT II (Candolfi et al), where an indicator species fails the tier I in-field risk assessment, further testing is required with that species, and at least one further species. An extended laboratory study with *A. rhopalosiphi* was provided, testing exposure on natural substrates (whole plant). There were also data available with 2 further species; *C. carnea* (foliar dwelling green lacewing) and ground dwelling rove beetle *A. bilineata*. The exposure in-field (PER<sub>in-field</sub>) was calculated as per tier I. At higher tier both lethal and sub-lethal effects were considered directly against the predicted exposure, with a threshold of 50% adverse effects at the PER<sub>in-field</sub> defining a low/high risk. A low in-field risk was demonstrated for the species *Aphidius rhopalosiphi* and *Chrysoperla carnea*. However, available data from the original DAR with *A. bilineata* did not result in an acceptable risk, due to the limit tested rate of the study not exceeding the PER<sub>in-field</sub> for the representative uses of mecoprop-P.

However, the RMS presented a case supporting a conclusion of low in-field risk to non-target arthropods other than bees, based on the following:

- A low risk was shown with the indicator species failing the tier I risk assessment plus the required 1 additional species.
- At the limit tested rate in the previous study with *Aleochara bilineata* there was only a 2.8% reduction in reproductive output (as successfully hatched F1 generation). Given that this is such a minor variation from the control group, and the small difference in tested rate from the maximum PER<sub>in-field</sub> it is likely that no adverse effects to this species in excess of the 50% threshold would occur at exposure to the PER<sub>in-field</sub>.
- Only a single application of mecoprop-P per year is proposed. The DT<sub>50</sub> of the active substance in soil is 10.12 days (as used to calculate PEC<sub>soil</sub>), and a default foliar DT<sub>50</sub> of 10 days can be conservatively assumed. On this basis it would be expected that in-field residues of mecoprop-P would drop below the tested 1064 g a.s./ha shown to have negligible effects on *A. bilineata* well within the maximum of 1 year allowed for recolonisation of the in-field according to ESCORT II.

The RMS therefore proposes that a low risk to non-target arthropods other than bees can be concluded following the representative uses of mecoprop-P.

#### 2.9.9.4. Soil meso- and macrofauna

The risk assessment for these groups was conducted following the guidance of the SANCO terrestrial guidance document (2002). Toxicity endpoints expressed in terms of the active substance (as reported in table B.2.9.4-

<sup>3</sup> Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC - SANCO/10329/2002

01) were compared against the initial Predicted Environmental Concentration of the active substance in soil ( $PEC_{soil}$ ). Due to the short half-life of mecoprop-P in soil (10.12 days) no accumulation in soil following year-on-year application was anticipated for the representative uses. A chronic trigger of  $\geq 5$  indicated a low risk to this organism group. When utilising either the statistically defined NOEC or the dose-response-modelled  $EC_{10}$  toxicity endpoint a low risk ( $TER > 5$ ) was concluded for earthworms, *Folsomia candida* and *Hypoaspis aculeifer*.

#### **2.9.9.5. Soil micro-organisms involved in nitrogen transformation**

Due to the lack of any toxicity data from a valid study for this data requirement, no conclusion of the risk to this group could be made. The RMS therefore proposes that a data gap be set to provide a valid study with the active substance or representative formulation.

#### **2.9.9.6. Terrestrial non-target higher plants**

The risk assessment for terrestrial non-target higher plants was conducted in accordance with the SANCO terrestrial guidance document (2002). Due to the known herbicidal action of mecoprop-P no screening data was generated, so a tier II risk assessment was conducted using both the deterministic and probabilistic approaches.

Under the deterministic approach the critical (lowest)  $ER_{50}$  from the available seedling emergence studies (representing pre-emergence exposure) and vegetative vigour studies (post-emergence exposure) are compared to the Predicted Environmental Rate (PER) reaching the off-field via spray drift. A resultant TER of  $\geq 5$  is used as an indication of low risk. Both the pre- and post-emergence TER values were found to be less than the trigger of 5 at a standard 1m and at mitigated 5m spray distance, and a low risk was only demonstrated when consideration was given to a 10m distance between spraying and the off-field environment ( $TER$  at 10m = 5.52 and 5.72 for pre- and post-emergence exposure routes).

Using the modelled  $HC_5$  values for pre- and post-emergence exposure (see method described under 2.9.6) compared to the  $PER_{off-field}$  in a tier II probabilistic approach; a low risk could only be demonstrated at a 5m spray distance.

Overall the conclusion of the RMS is that a low risk to terrestrial non-target plants can be demonstrated following the representative uses of mecoprop-P, but risk mitigation measures are required and would need consideration at Member State level for subsequent product registration.

#### **2.9.9.7. Summary of effects on other terrestrial organisms (flora and fauna)**

No data submitted

#### **2.9.9.8. Summary of effects on biological methods for sewage treatment**

Endpoints from the newly submitted study were used to perform a risk assessment. The effects of mecoprop-P on activated sludge showed an acceptable risk to biological methods of sewage treatment. No Member State issues were identified.

## 2.10. CLASSIFICATION AND LABELLING

**Proposed classification according to Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures**

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification <sup>1)</sup>	Reason for no classification <sup>2)</sup>
2.1.	Explosives	Not classified		Not classified	Conclusive but not sufficient for classification
2.2.	Flammable gases	N/A		N/A	
2.3.	Flammable aerosols	N/A		N/A	
2.4.	Oxidising gases	N/A		N/A	
2.5.	Gases under pressure	N/A		N/A	
2.6.	Flammable liquids	N/A		N/A	
2.7.	Flammable solids	Not classified		Not classified	Conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	N/A		N/A	
2.9.	Pyrophoric liquids	N/A		N/A	
2.10.	Pyrophoric solids	Not classified		Not classified	Conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	Not classified		Not classified	Conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	Not classified		Not classified	Conclusive but not sufficient for classification
2.13.	Oxidising liquids	N/A		N/A	
2.14.	Oxidising solids	Not classified		Not classified	Conclusive but not sufficient for classification
2.15.	Organic peroxides	N/A		N/A	
2.16.	Substance and mixtures corrosive to metals	N/A		N/A	
3.1.	Acute toxicity - oral	H302		H302	N/A
	Acute toxicity - dermal	Not classified		Not classified	Conclusive but not sufficient for classification
	Acute toxicity - inhalation	Not classified		Not classified	Conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	Not classified		Not classified	Conclusive but not sufficient for classification



CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification <sup>1)</sup>	Reason for no classification <sup>2)</sup>
3.3.	Serious eye damage / eye irritation	H318		H318	N/A
3.4.	Respiratory sensitisation	Not classified		Not classified	Data lacking
3.4.	Skin sensitisation	Not classified		Not classified	Conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	Not classified		Not classified	Conclusive but not sufficient for classification
3.6.	Carcinogenicity	Not classified		Not classified	Conclusive but not sufficient for classification
3.7.	Reproductive toxicity	Not classified		Not classified	Conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	Not classified		Not classified	Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	Not classified		Not classified	Conclusive but not sufficient for classification
3.10.	Aspiration hazard				
4.1.	Hazardous to the aquatic environment	H400 H410	Acute M-factor = 10 Chronic M-factor = 1	H411	N/A
5.1.	Hazardous to the ozone layer				

<sup>1)</sup> Including specific concentration limits (SCLs) and M-factors

<sup>2)</sup> Data lacking, inconclusive, or conclusive but not sufficient for classification

#### **Labelling:**

##### **Signal word:**

‘Warning’

##### **Pictogram:**

GHS09

GHS07

##### **Hazard statements:**

‘Harmful if swallowed’

‘Causes serious eye damage’

‘Very toxic to aquatic life’

‘Very toxic to aquatic life with long lasting effects’

##### **Precautionary statements:**

P264: Wash hands thoroughly after handling.

P270: Do not eat, drink or smoke when using this product.

P273: Avoid release to the environment.

P280: Wear protective gloves/protective clothing/eye protection/face protection.

P301 + P312 + P330: IF SWALLOWED: Call a doctor: Rinse mouth.

P305 + P351 + P338 + P310: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses if present and easy to do. Continue rinsing. Call a doctor.

P391: Collect spillage.

P405: Store locked up

P501: Dispose of contents/container to... in accordance with local/regional/national/international regulation (to be specified).

**Proposed notes assigned to an entry:**

Notes in accordance with CLP Regulation, Annex VI, Section 1.1.3

## **2.11. RELEVANCE OF METABOLITES IN GROUNDWATER**

There are no metabolites to consider for groundwater.

### **2.11.1. STEP 1: Exclusion of degradation products of no concern**

N/A

### **2.11.2. STEP 2: Quantification of potential groundwater contamination**

N/A

### **2.11.3. STEP 3: Hazard assessment – identification of relevant metabolites**

2.11.3.1 STEP 3, Stage 1: screening for biological activity

2.11.3.2 STEP 3, Stage 2: screening for genotoxicity

2.11.3.3 STEP 3, Stage 3: screening for toxicity

N/A

### **2.11.4. STEP 4: Exposure assessment – threshold of concern approach**

N/A

### **2.11.5. STEP 5: Refined risk assessment**

N/A

### **2.11.6. Overall conclusion**

N/A

## **2.12. CONSIDERATION OF ISOMERIC COMPOSITION IN THE RISK ASSESSMENT**

### **2.12.1. Identity and physical chemical properties**

Technical grade mecoprop-P is a single enantiomer (R-). The (S-) enantiomer is herbicidally inactive. The tests for the physical chemistry properties were conducted on the single mecoprop-P isomer and further consideration of the isomeric composition is not required.

### **2.12.2. Methods of analysis**

A method has been submitted to determine the optical ratio of the technical grade active substance. This is presented in Volume 4 Confidential section. Further consideration of the isomeric composition is not required.

### 2.12.3. Mammalian toxicity

Most of the studies in this submission have been conducted on mecoprop-P. However studies on the racemate (mixture of both isomers) are also included where there is limited information on the P isomer. Overall the studies on the racemate are considered also to be applicable to mecoprop-P as the toxicity and target organs are very similar.

### 2.12.4. Operator, Worker, Bystander and Resident exposure

Exposure estimates considered the resolved isomer mecoprop-P using appropriate endpoints and further consideration of isomeric composition is not required.

### 2.12.5. Residues and Consumer risk assessment

Technical grade mecoprop-P is a single enantiomer (R-). The (S-) enantiomer is herbicidally inactive. The residue trials were conducted with the single mecoprop-P isomer and further consideration of the isomeric composition is not required.

### 2.12.6. Environmental fate

Studies relied on for the risk assessment used the single isomer mecoprop-P. Further consideration of the isomeric composition is not required.

### 2.12.7. Ecotoxicology

Studies relied on were conducted with mecoprop-P (R-isomer), the racemic mixture (containing both isomers) or the DMA salt form of mecoprop-P. As discussed elsewhere in the dossier, the S-isomer is herbicidally inactive and of no greater toxicity to other non-target organism groups. Therefore endpoints from studies with the racemic mixture or with the DMA Salt are suitable for generation of relevant data with the active substance, but all endpoints were expressed in terms of MCPP-P (i.e. the R-isomer) content for use in the regulatory risk assessments.

## 2.13. RESIDUE DEFINITIONS

### 2.13.1. Definition of residues for exposure/risk assessment

**Food of plant origin:** Mecoprop-P, 2-carboxy-4-chloro-phenoxypropionic acid (CCPP) and 2-hydroxymethyl-4-chloro-phenoxypropionic acid (HMCPP), expressed as mecoprop-P.

**Food of animal origin:** Mecoprop-P

**Soil:** Mecoprop-P

**Groundwater:** Mecoprop-P

**Surface water:** Mecoprop-P

**Sediment:** Mecoprop-P

**Air:** Mecoprop-P

### 2.13.2. Definition of residues for monitoring

**Food of plant origin:** Mecoprop-P

**Food of animal origin:** Mecoprop-P

**Soil:** Mecoprop-P

**Groundwater:** Mecoprop-P

**Surface water:** Mecoprop-P

**Sediment:** Mecoprop-P

**Air:** Mecoprop-P

# **Level 3**

## **MECOPROP-P**

### 3. PROPOSED DECISION WITH RESPECT TO THE APPLICATION

#### 3.1. BACKGROUND TO THE PROPOSED DECISION

##### 3.1.1. Proposal on acceptability against the decision making criteria – Article 4 and annex II of regulation (EC) No 1107/2009

<b>3.1.1.1. Article 4</b>			
		Yes	No
i)	It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with. Specifically the RMS considers that authorisation in at least one Member State is expected to be possible for at least one plant protection product containing the active substance for at least one of the representative uses.	Yes	<p>It is considered that Article 4 of Regulation (EC) No 1107/2009 is complied with for mecoprop-P for use as a herbicide on winter and spring cereals (refer to Level 1, Table 1.5.1 for details of the representative use considered).</p> <p>The long-term risk to mammals from the active substance, the acute and long-term risk to mammals from the plant metabolite CCPP and the risk to soil micro-organisms involved in nitrogen transformation (from the active substance or representative formulation) could not be resolved for the representative uses and further information/data are required.</p> <p>Overall a low risk could not be demonstrated for all FOCUS scenarios for either representative use of mecoprop-P on the basis of the illustrative risk assessment undertaken; meaning further consideration of the risk to aquatic plants will be required by individual Member States.</p> <p>Low risk to terrestrial non-target plants can be demonstrated following the representative uses of mecoprop-P, but risk mitigation measures are required and would need consideration at Member State level for subsequent product registration.</p>
<b>3.1.1.2. Submission of further information</b>			
		Yes	No
i)	It is considered that a complete dossier has been submitted		No
ii)	It is considered that in the absence of a full dossier the active substance may be approved even though certain information is still to be submitted because: (a) the data requirements have been amended or refined after the submission of the dossier; or	Yes	<p>There are data gaps identified (see Level 3.1.4)</p> <p>The identified data gaps at Level 3.1.4 are considered to be confirmatory in nature.</p>

	(b) the information is considered to be confirmatory in nature, as required to increase confidence in the decision.			
<b>3.1.1.3. Restrictions on approval</b>				
		Yes	No	
	It is considered that in line with Article 6 of Regulation (EC) No 1107/2009 approval should be subject to conditions and restrictions.	Yes		<p>(a) the minimum degree of purity of the active substance; Minimum purity 890 g/kg</p> <p>(b) the nature and maximum content of certain impurities; Maximum level of relevant impurity, 4-chloro-2-methylphenol, is 5 g/kg.</p> <p>(c) restrictions arising from the evaluation of the information referred to in Article 8 of 1107/2009 taking account of the agricultural, plant health and environmental, including climatic, conditions in question; N/A</p> <p>(d) type of preparation; N/A</p> <p>(e) manner and conditions of application; N/A</p> <p>(f) submission of further confirmatory information to Member States, the Commission and the European Food Safety Authority, (the Authority), where new requirements are established during the evaluation process or as a result of new scientific and technical knowledge; N/A</p> <p>(g) designation of categories of users, such as professional and non-professional; N/A</p> <p>(h) designation of areas where the use of plant protection products, including soil treatment products, containing the active substance may not be authorised or where the use may be authorised under specific conditions;</p>

				<p>N/A</p> <p>(i) the need to impose risk mitigation measures and monitoring after use;</p> <p>Member States should consider the protection of groundwater if the substance is applied under vulnerable soil or climatic conditions.</p> <p>Member States should consider the risk to aquatic organisms (aquatic plants) and other non-target organisms (flora and fauna), ensuring that conditions of authorisation include risk mitigation measures, where appropriate.</p> <p>Member states should consider the risk to non-target terrestrial higher plants, ensuring that conditions of authorisation include risk mitigation measures, where appropriate.</p> <p>(j) any other particular conditions that result from the evaluation of information made available in the context of Regulation 1107/2009.</p> <p>N/A</p>
<b>3.1.1.4. Criteria for the approval of an active substance</b>				
<b>Dossier</b>				
		Yes	No	
	It is considered the dossier contains the information needed to establish, where relevant, Acceptable Daily Intake (ADI), Acceptable Operator Exposure Level (AOEL) and Acute Reference Dose (ARfD).	Yes		The data submitted are sufficient to establish an Acceptable Daily Intake (ADI), an Acceptable Operator Exposure Level (AOEL) and an Acute Reference Dose (ARfD).
	<p>It is considered that the dossier contains the information necessary to carry out a risk assessment and for enforcement purposes (relevant for substances for which one or more representative uses includes use on feed or food crops or leads indirectly to residues in food or feed). In particular it is considered that the dossier:</p> <p>(a) permits any residue of concern to be defined;</p> <p>(b) reliably predicts the residues in food and feed, including succeeding crops</p> <p>(c) reliably predicts, where relevant, the corresponding residue level reflecting the effects of processing and/or mixing;</p> <p>(d) permits a maximum residue level to be defined and to be</p>		No	Sufficient information has been provided to allow residue definitions to be set, consumer risk assessments to be conducted and the effects of processing to be determined. However, the dossier is considered deficient in relation to the residue trials on the representative cereal use. The potential for the metabolites HMCPP and CCPP to be found in commodities destined for human and livestock consumption has not been adequately addressed (refer to section 2.7.4).



	determined by appropriate methods in general use for the commodity and, where appropriate, for products of animal origin where the commodity or parts of it is fed to animals; (e) permits, where relevant, concentration or dilution factors due to processing and/or mixing to be defined.			
	It is considered that the dossier submitted is sufficient to permit, where relevant, an estimate of the fate and distribution of the active substance in the environment, and its impact on non-target species.	Yes		Yes (for both of the representative uses).
<b>Efficacy</b>				
		Yes	No	
	It is considered that it has been established for one or more representative uses that the plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use is sufficiently effective.	Yes		The applicant has addressed all the Efficacy related points outlined in Guidance Document on the renewal of approval of active substances to be assessed in compliance with Regulation (EU) No 844/2012 (the Renewal Regulation), SANCO/2012/11251 rev. 4, 12 December 2014. Refer to Volume 1 Level 2.1.3 for details.
<b>Relevance of metabolites</b>				
		Yes	No	
	It is considered that the documentation submitted is sufficient to permit the establishment of the toxicological, ecotoxicological or environmental relevance of metabolites.	N/A	N/A	There are no soil metabolites to consider. There are no metabolites requiring consideration for groundwater.
<b>Composition</b>				
		Yes	No	
	It is considered that the specification defines the minimum degree of purity, the identity and maximum content of impurities and, where relevant, of isomers/diastereo-isomers and additives, and the content of impurities of toxicological, ecotoxicological or environmental concern within acceptable limits.		No	A new reference specification has been proposed, as although the minimum purity of the new source complies with the Implementing Regulation, a relevant impurity must now be included.  There is no batch analysis for the majority of the batches used in the toxicity studies (see Table C.10 in Volume 4). It is not possible to conclude if the impurities in the proposed specification were present in the batches used in the toxicity studies. Therefore the toxicity studies cannot be relied on to determine the toxicity profile of the impurities present in the proposed specification. Further information is required to address the toxicity of the impurities in the specification. Information requirements are listed in Table C.6 in the confidential section.  From an ecotoxicology perspective the proposed specification of mecoprop-P is confirmed as equivalent to the previous specification set at first EU review. As

				such the original Annex I data set with the technical active substance is suitable to support the specification proposed at renewal. However, no batch specification was provided for the studies conducted with the technical active substance and submitted for the purposes of renewal. Nor could it be confirmed that these ecotoxicology-tested batches were included in the 7-batch analysis used to propose the specification at renewal. As such it cannot be confirmed whether studies with the technical a.s. for the purposes of renewal are suitable to support the proposed specification of mecoprop-P.
	It is considered that the specification is in compliance with the relevant Food and Agriculture Organisation specification, where such specification exists.	N/A	N/A	No FAO specification exists.
	It is considered for reasons of protection of human or animal health or the environment, stricter specifications than that provided for by the FAO specification should be adopted	N/A	N/A	No FAO specification exists.
<b>Methods of analysis</b>				
		Yes	No	
	It is considered that the methods of analysis of the active substance, safener or synergist as manufactured and of determination of impurities of toxicological, ecotoxicological or environmental concern or which are present in quantities greater than 1 g/kg in the active substance, safener or synergist as manufactured, have been validated and shown to be sufficiently specific, correctly calibrated, accurate and precise.	Yes		Methods of analysis have been submitted to determine the active substance, optical ratio and impurities in the technical material. These are generally HPLC-UV methods and they have been fully validated in accordance with SANCO/3030/99 rev. 4.
	It is considered that the methods of residue analysis for the active substance and relevant metabolites in plant, animal and environmental matrices and drinking water, as appropriate, shall have been validated and shown to be sufficiently sensitive with respect to the levels of concern.	Yes		Enforcement methods of analysis for detection of total mecoprop-P, present as acid, ethylhexyl ester or glycine conjugate in cereals (grain, straw and foliage), animal matrices, olives and orange have been provided using a QeChERS LC-MS/MS method. These methods were validated in accordance with the requirements of SANCO 825/00 rev. 8.1.  Methods have also been validated for mecoprop-P in soil, water and air in accordance with the requirements of SANCO 825/00 rev. 8.1. No method for determining mecoprop-P in body fluids and tissues is required, as mecoprop-P is not classified as toxic or highly toxic.
	It is confirmed that the evaluation has been carried out in accordance with the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	Yes		Refer to Level 2, Section 2.5 for further details.
<b>Impact on human health</b>				

Impact on human health – ADI, AOEL, ARfD			
		Yes	No
	It is confirmed that (where relevant) an ADI, AOEL and ARfD can be established with an appropriate safety margin of at least 100 taking into account the type and severity of effects and the vulnerability of specific groups of the population.	Yes	No
			<p>The ADI of <b>0.01 mg/kg/day</b> is proposed based on the application of a standard assessment factor of 100 to the NOAEL of 1.1 mg/kg bw, identified for males in the rat 2-yr chronic toxicity and carcinogenicity study.</p> <p>The ARfD of <b>0.5 mg/kg bw/day</b> is proposed based on the application of a standard assessment factor of 100 to the NOAEL of 50 mg/kg bw/day identified in the rat developmental study.</p> <p>The AOEL of <b>0.04 mg/kg/day</b> is proposed based on the application of an assessment factor of 100 to the NOAEL of 4 mg/kg bw/day, identified in males and females in the 7 week rat study. No correction factor for oral absorption is required.</p>
Impact on human health – proposed genotoxicity classification			
		Yes	No
	It is considered that, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements and other available data and information, including a review of the scientific literature, reviewed by the Authority, <b>the substance SHOULD BE classified or proposed for classification</b> , in accordance with the provisions of Regulation (EC) No 1272/2008, as <b>mutagen category 1A or 1B</b> .		No
			Mecoprop-P was negative for mutagenicity in bacterial cells. In mammalian cells <i>in vitro</i> mecoprop-P was negative for gene mutations but equivocal for clastogenicity at cytotoxic doses. Mecoprop-P was negative for genotoxicity <i>in vivo</i> . Taking a weight of evidence approach classification for mutagenicity is not warranted.
Impact on human health – proposed carcinogenicity classification			
		Yes	No
i)	It is considered that, on the basis of assessment of the carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, <b>the substance SHOULD BE classified or proposed for classification</b> , in accordance with the provisions of Regulation (EC) No 1272/2008, as <b>carcinogen category 1A or 1B</b> .		No
			Mecoprop-P does not currently have a harmonised classification for carcinogenicity. In the two year rat study conducted on mecoprop-P there was increased incidence of benign lipoma in male rats. In mice there was increased incidence of hepatocellular carcinoma in females. These findings are not considered sufficient evidence of a carcinogenic effect therefore classification for carcinogenicity is not warranted.
ii)	Linked to above classification proposal. It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener		
			Not applicable.

	or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			
<b>Impact on human health – proposed reproductive toxicity classification</b>				
		Yes	No	
i)	It is considered that, on the basis of assessment of the reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, <b>the substance SHOULD BE classified or proposed for classification</b> , in accordance with the provisions of Regulation (EC) No 1272/2008, as <b>toxic for reproduction category 1A or 1B</b> .		No	The reproductive toxicity of mecoprop-P has been adequately investigated in rat multigeneration studies and in rat and rabbit developmental toxicity studies. These studies demonstrate that mecoprop-P does not possess hazardous properties in relation to fertility, reproductive performance or development. Classification for reproductive toxicity is not warranted.
ii)	Linked to above classification proposal.  It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			Not applicable.
<b>Impact on human health – proposed endocrine disrupting properties classification</b>				
		Yes	No	
i)	It is considered that <b>the substance SHOULD BE classified or proposed for classification</b> in accordance with the provisions of Regulation (EC) No 1272/2008, as <b>carcinogenic category 2 and toxic for reproduction category 2 and on that basis shall be considered to have endocrine disrupting properties</b>		No	As indicated above mecoprop-P is not currently classified as a Cat 2 carcinogen or Cat 2 for reproductive toxicity. Following the current review it is considered that mecoprop-P does not require classification as a carcinogen or for reproductive toxicity. Therefore it does not meet the interim criteria for endocrine disrupting properties.
ii)	It is considered that <b>the substance SHOULD BE classified or proposed for classification</b> in accordance with the provisions of Regulation (EC) No 1272/2008, as <b>toxic for reproduction category 2 and in addition the RMS considers the substance has toxic effects on the endocrine organs and on that basis shall be considered to have endocrine disrupting properties</b>		No	As indicated above classification for reproductive toxicity is not warranted. Furthermore, no evidence of endocrine system effects were identified in standard repeated dose toxicity studies.



iii)	Linked to either i) or ii) immediately above.  It is considered that exposure of humans to the active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.			Not applicable.
<b>Fate and behaviour in the environment</b>				
<b>Persistent organic pollutant (POP)</b>				
		Yes	No	
	It is considered that the active substance <b>FULFILS</b> the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 Annex II Section 3.7.1.		No	Mecoprop-P fulfils 1 out of 3 of the criteria of a persistent organic pollutant (POP) as laid out in Regulation 1107/2009 (see below).

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Persistent, bioaccumulative and toxic substance (PBT)																						
	Yes	No																				
It is considered that the active substance <b>FULFILS</b> the criteria of a persistent, bioaccumulative and toxic (PBT) substance as laid out in Regulation 1107/2009 Annex II Section 3.7.2.		No	Mecoprop-P fulfils 2 out of 3 of the criteria of a persistent, bioaccumulative and toxic substance (PBT) as laid out in Regulation 1107/2009.																			
			<table><tr><th>Criterion</th><th>Mecoprop-P data</th><th>Criteria met?</th></tr><tr><td><u>Persistence</u> — the half-life in marine water is higher than 60 days, — the half-life in fresh or estuarine water is higher than 40 days, — the half-life in marine sediment is higher than 180 days, — the half-life in fresh or estuarine water sediment is higher than 120 days, or — the half-life in soil is higher than 120 days. Assessment of persistency in the environment shall be based on available half-life data collected under appropriate conditions, which shall be described by the applicant.</td><td><u>Soil</u> DT50 10.12d (longest non-normalised laboratory DT50, FOMC DT90/3.32)  <u>Water</u> From aerobic water-sediment studies:<table><tr><td>Water/sediment system</td><td>DegT50 Whole system (best fit model) (days)</td></tr><tr><td>Manningtree</td><td>58.9 (SFO)</td></tr><tr><td>Ongar</td><td>8.31 (HS DT90/3.32)</td></tr><tr><td>Calwich Abbey</td><td>29.1 (HS DT90/3.32)</td></tr><tr><td>Swiss Lake</td><td>244 (SFO)</td></tr></table> From aerobic mineralisation in surface water study: fresh water without suspended sediment – no degradation observed after 58 days (DT50 &gt;1000 days default value)  <u>Sediment</u> No half-life in marine water or sediment available.</td><td>Yes  Mecoprop-P meets the criteria for 'Persistence' in water</td></tr><tr><td><u>Bioaccumulation</u> BCF &gt; 2000, or in absence log K<sub>ow</sub> &gt; 5, or evidence that the substance, presents other reasons for concern, such as high bioaccumulation in other non-target species, high toxicity or ecotoxicity.</td><td>BCF value = 3.0  Measured at 20 C pH 4; log<sub>10</sub>P<sub>ow</sub> = 2.19 pH 7; log<sub>10</sub>P<sub>ow</sub> = -0.19 pH 10; log<sub>10</sub>P<sub>ow</sub> = -0.64</td><td>No</td></tr></table>	Criterion	Mecoprop-P data	Criteria met?	<u>Persistence</u> — the half-life in marine water is higher than 60 days, — the half-life in fresh or estuarine water is higher than 40 days, — the half-life in marine sediment is higher than 180 days, — the half-life in fresh or estuarine water sediment is higher than 120 days, or — the half-life in soil is higher than 120 days. Assessment of persistency in the environment shall be based on available half-life data collected under appropriate conditions, which shall be described by the applicant.	<u>Soil</u> DT50 10.12d (longest non-normalised laboratory DT50, FOMC DT90/3.32)  <u>Water</u> From aerobic water-sediment studies: <table><tr><td>Water/sediment system</td><td>DegT50 Whole system (best fit model) (days)</td></tr><tr><td>Manningtree</td><td>58.9 (SFO)</td></tr><tr><td>Ongar</td><td>8.31 (HS DT90/3.32)</td></tr><tr><td>Calwich Abbey</td><td>29.1 (HS DT90/3.32)</td></tr><tr><td>Swiss Lake</td><td>244 (SFO)</td></tr></table> From aerobic mineralisation in surface water study: fresh water without suspended sediment – no degradation observed after 58 days (DT50 >1000 days default value)  <u>Sediment</u> No half-life in marine water or sediment available.	Water/sediment system	DegT50 Whole system (best fit model) (days)	Manningtree	58.9 (SFO)	Ongar	8.31 (HS DT90/3.32)	Calwich Abbey	29.1 (HS DT90/3.32)	Swiss Lake	244 (SFO)	Yes  Mecoprop-P meets the criteria for 'Persistence' in water	<u>Bioaccumulation</u> BCF > 2000, or in absence log K <sub>ow</sub> > 5, or evidence that the substance, presents other reasons for concern, such as high bioaccumulation in other non-target species, high toxicity or ecotoxicity.	BCF value = 3.0  Measured at 20 C pH 4; log <sub>10</sub> P <sub>ow</sub> = 2.19 pH 7; log <sub>10</sub> P <sub>ow</sub> = -0.19 pH 10; log <sub>10</sub> P <sub>ow</sub> = -0.64	No
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				<u>Toxicity</u> - the long-term no-observed effect concentration for marine or freshwater organisms is < 0.01 mg/l, - substance is classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2) pursuant to Regulation (EC) No 1272/2008, or - there is other evidence of chronic toxicity, as identified by the classifications STOT RE 1 or STOT RE 2 pursuant to Regulation (EC) No 1272/2008.	Lowest NOEC with active substance = 0.00937 mg/L ( <i>M.spicatum</i> )  Substance is <u>not</u> classified as carcinogenic (category 1A or 1B), mutagenic (category 1A or 1B), or toxic for reproduction (category 1A, 1B or 2) pursuant to Regulation (EC) No 1272/2008, and - there is <u>no</u> other evidence of chronic toxicity, as identified by the classifications STOT RE 1 or STOT RE 2 pursuant to Regulation (EC) No 1272/2008.	Yes Mecoprop-P meets the criteria for 'Toxicity'.  No														
Very persistent and very bioaccumulative substance (vPvB).																				
		Yes	No																	
	It is considered that the active substance <b>FULFILS</b> the criteria of a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009 Annex II Section 3.7.3.		No	Mecoprop-P fulfils 1 out of 2 criteria of a very persistent and very bioaccumulative substance (vPvB) as laid out in Regulation 1107/2009.																
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Swiss Lake	244 (SFO)																			



					>1000 days default value)	
					<u>Sediment</u> No half-life in marine water or sediment available.	
				<u>Bioaccumulation</u> BCF > 5000	BCF value = 3.0	No
<b>Ecotoxicology</b>						
		Yes	No			
	It is considered that the risk assessment demonstrates risks to be acceptable in accordance with the criteria laid down in the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) under realistic proposed conditions of use of a plant protection product containing the active substance, safener or synergist. The RMS is content that the assessment takes into account the severity of effects, the uncertainty of the data, and the number of organism groups which the active substance, safener or synergist is expected to affect adversely by the intended use.		No	<p>A low risk was demonstrated to birds, aquatic organisms other than aquatic plants, bees, non-target arthropods, soil meso- and macrofauna and sewage treatment organisms, without the requirement for risk mitigation.</p> <p>The risk to aquatic plants and terrestrial non-target plants could be demonstrated as low, but Member State considerations of risk mitigation and relevant surface water modelling scenarios is required to comprehensively conclude a low risk.</p> <p><b>The long-term risk to mammals from the active substance, and the acute and long-term risk to mammals from plant metabolite CCPP could NOT be resolved for the representative uses on the basis of available data and risk assessment.</b></p> <p><b>The risk to soil micro-organisms involved in nitrogen transformation could NOT be resolved due to a lack of valid data to meet the data requirement.</b></p>		
	It is considered that, on the basis of the assessment of Community or internationally agreed test guidelines, the substance <b>HAS</b> endocrine disrupting properties that may cause adverse effects on non-target organisms.	N/A	N/A	<p>No consideration of endocrine disruption has been performed by the RMS as the approach and definition criteria are still under consideration by the European Commission.</p> <p>Nevertheless from a toxicology perspective no evidence of a reproductive toxicity hazard was seen in the standard reproductive toxicity tests. Furthermore, no evidence of endocrine system effects were identified in standard repeated dose toxicity studies. There is currently no concern regarding endocrine disruption.</p>		
	Linked to the consideration of the endocrine properties immediately above.  It is considered that the exposure of non-target organisms to the active substance in a plant protection product under realistic proposed conditions of use is negligible.	N/A	N/A	See above. Mecoprop-P is <u>not</u> considered an endocrine disruptor.		

	It is considered that it is established following an appropriate risk assessment on the basis of Community or internationally agreed test guidelines, that the use under the proposed conditions of use of plant protection products containing this active substance, safener or synergist:  — will result in a negligible exposure of honeybees, or  — has no unacceptable acute or chronic effects on colony survival and development, taking into account effects on honeybee larvae and honeybee behaviour.	Yes		A low acute risk to honeybees under the EU-agreed risk assessment scheme is concluded for the representative uses of mecoprop-P.  Chronic effects on behaviour, colony development and effects on larvae were assessed in a submitted acute larval toxicity test and bee brood field study. Both studies were evaluated as valid by the RMS. Currently there is no EU-agreed risk assessment scheme to utilize these data.
Residue definition				
		Yes	No	
	It is considered that, where relevant, a residue definition can be established for the purposes of risk assessment and for enforcement purposes.	Yes		Refer to Vol.3 CA B7 for full discussion.  The residue definition for risk assessment is: Mecoprop-P, 2-carboxy-4-chloro-phenoxypropionic acid (CCPP) and 2-hydroxymethyl-4-chloro-phenoxypropionic acid (HMCPP), expressed as mecoprop-P.  The residue definition for monitoring/enforcement is: Mecoprop-P.
Fate and behaviour concerning groundwater				
		Yes	No	
	It is considered that it has been established for one or more representative uses, that consequently after application of the plant protection product consistent with realistic conditions on use, the predicted concentration of the active substance or of metabolites, degradation or reaction products in groundwater complies with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products referred to in Article 29(6) of Regulation 1107/2009.	Yes		Groundwater modelling with PEARL v4.4.4, PELMO v5.5.3 and MACRO v4.4.2 (Chateaudun).  Spring cereals; 1 x 1200 g a.s/ha, 0% crop interception, PEC <sub>GW</sub> are all <0.1 µg/l following application on 1 <sup>st</sup> March (max 0.056 µg/l, PELMO, Okehampton).  Winter cereals; 1 x 1200 g a.s/ha, 20% crop interception, 0.1 µg/l is exceeded in one scenario (0.115 µg/l, Okehampton) with one model (PELMO v5.5.3) following application on 1 <sup>st</sup> March.  There are no metabolites requiring consideration for groundwater.

## 3.1.2. Proposal – Candidate for substitution

Candidate for substitution			
	Yes	No	
It is considered that the active substance shall be approved as a candidate for substitution	Yes		<p><i>[If yes identify the criteria considered met by the substance i.e.</i></p> <p><i>its ADI, ARfD or AOEL is significantly lower than those of the majority of the approved active substances within groups of substances/use categories, - No</i></p> <p><i>— it meets two of the criteria to be considered as a PBT substance -</i></p> <p><b>Mecoprop-P fulfils 2 out of 3 of the criteria of a persistent, bioaccumulative and toxic substance (PBT) as laid out in Regulation 1107/2009 (for persistence and toxicity – see 3.1.1.4 above).</b></p> <p><i>— there are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones), <b>No</b></i></p> <p><i>— it contains a significant proportion of non-active isomers, No</i></p> <p><i>— it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, if the substance has not been excluded in accordance with the criteria laid down in point 3.6.3, -No</i></p> <p><i>— it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.4, - No</i></p>

				<p>— if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have endocrine disrupting properties that may cause adverse effects in humans if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5. ] - <b>No</b></p>
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### 3.1.3. Proposal – Low risk active substance

Low-risk active substances				
		Yes	No	
	<p>It is considered that the active substance <b>shall be considered of low risk.</b></p> <p>In particular it is considered that the substance <b>should NOT be classified or proposed for classification</b> in accordance with Regulation (EC) No 1272/2008 as at least one of the following:</p> <ul style="list-style-type: none"> <li>— carcinogenic,</li> <li>— mutagenic,</li> <li>— toxic to reproduction,</li> <li>— sensitising chemicals,</li> <li>— very toxic or toxic,</li> <li>— explosive,</li> <li>— corrosive.</li> </ul> <p>In addition it is considered that <b>the substance is NOT:</b></p> <ul style="list-style-type: none"> <li>— persistent (half-life in soil more than 60 days),</li> <li>— has a bioconcentration factor higher than 100,</li> <li>— is deemed to be an endocrine disrupter, or</li> <li>— has neurotoxic or immunotoxic effects.</li> </ul>		No	<p>Mecoprop-P cannot be considered a low risk substance because it is persistent in surface water when sediment is not present.</p> <ul style="list-style-type: none"> <li>— carcinogenic, - No classification proposed</li> <li>— mutagenic, - No classification proposed</li> <li>— toxic to reproduction, - No classification proposed</li> <li>— sensitising chemicals, - No classification proposed</li> <li>— very toxic or toxic, - No classification proposed</li> <li>— explosive, - No classification proposed</li> <li>— corrosive. - No classification proposed</li> </ul> <ul style="list-style-type: none"> <li>— persistent (half-life in soil more than 60 days), - persistent in surface water when sediment is not present.</li> <li>— has a bioconcentration factor higher than 100, - No</li> <li>— is deemed to be an endocrine disrupter, or - No</li> <li>— has neurotoxic or immunotoxic effects - No</li> </ul>

## 3.1.4. List of studies to be generated, still ongoing or available but not peer reviewed

Data gap	Relevance in relation to representative use(s)	Study status		
		No confirmation that study available or on-going.	Study on-going and anticipated date of completion	Study available but not peer-reviewed
3.1.4.1. Identity of the active substance or formulation				
<p>There is no batch analysis for the majority of the batches used in the toxicity studies (see Table C.10 Volume 4). Further information is required to address the toxicity of the impurities in the specification. Information requirements are listed in Table C.6 in the confidential section.</p> <p>Data to confirm that the batches of technical mecoprop-P used in ecotoxicology studies submitted for the purposes of renewal are reflective of the ecotoxicity of the proposed active substance specification.</p>		X		
3.1.4.2. Physical and chemical properties of the active substance and physical, chemical and technical properties of the formulation				
<p>Data point 2.7 for the chemical active has not been fully addressed. The n-octanol/water partition coefficient is required for all components of the residue definition (plant metabolites HMCPP and CCPP).</p>		X		
3.1.4.3. Data on uses and efficacy				
<p>None.</p>				

<b>3.1.4.4. Data on handling, storage, transport, packaging and labelling</b>				
None.				
<b>3.1.4.5. Methods of analysis</b>				
None.				
<b>3.1.4.6. Toxicology and metabolism</b>				
An <i>in vitro</i> comparative metabolism study has been commissioned but is not yet submitted for evaluation.			X Expected January 2016	
<b>3.1.4.7. Residue data</b>				
Trials are required complying with the GAP of mecoprop-P on wheat and/or barley 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. The trials should be accompanied by appropriate storage stability studies on the plant metabolites HMCPP and CCPP and a validated analytical method.		X		
<b>3.1.4.8. Environmental fate and behaviour</b>				
None				
<b>3.1.4.9. Ecotoxicology</b>				
A valid study is required to address data requirement 8.3 of (EU) 283/2013: Nitrogen transformation.		X		



### 3.1.5. Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) No 546/2011, and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

Area of the risk assessment that could not be finalised on the basis of the available data	Relevance in relation to representative use(s)
The risk to soil micro-organisms involved in nitrogen transformation from the active substance	Relevant for all representative uses
The suitability of the mammalian toxicology tested batches of the technical a.s. to support the proposed specification of mecoprop-P	Relevant for all representative uses
The suitability of the ecotox-tested batches of the technical a.s. to support the proposed specification of mecoprop-P	Relevant for all representative uses
Further consideration at a Member State level of the risk from the active substance to aquatic plants	Relevant for all representative uses – certain FOCUS scenarios only (please refer to 2.9.9.2)

### 3.1.6. Critical areas of concern

An issue is listed as a critical area of concern:

(a) where the substance does not satisfy the criteria set out in points 3.6.3, 3.6.4, 3.6.5 or 3.8.2 of Annex II of Regulation (EC) No 1107/2009 and the applicant has not provided detailed evidence that the active substance is necessary to control a serious danger to plant health which cannot be contained by other available means including non-chemical methods, taking into account risk mitigation measures to ensure that exposure of humans and the environment is minimised, or

(b) where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles, as laid out in Commission Regulation (EU) 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

Critical area of concern identified	Relevance in relation to representative use(s)
The long-term risk to mammals from the active substance	Relevant for all representative uses

The acute and long-term risk to mammals from the plant metabolite CCPP	Relevant for all representative uses
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### 3.1.7. Overview table of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in 3.3.1, has been evaluated as being effective, then 'risk identified' is not indicated in this table.)

All columns are grey as the material tested in the toxicological studies has not been demonstrated to be representative of the technical specification.

Representative use		Winter Cereals (X <sup>1</sup> )	Spring Cereals (X <sup>1</sup> )
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Bystander risk	Risk identified		
	Assessment not finalised		
Consumer risk	Risk identified		
	Assessment not finalised		
Risk to wild non target terrestrial vertebrates	Risk identified	X - A low long-term risk to the large herbivorous mammal "lagomorph" could not be confirmed for the active substance. Additionally a low acute and long-term risk to mammals from the plant metabolite CCPP could not be confirmed	X - A low long-term risk to the large herbivorous mammal "lagomorph" could not be confirmed for the active substance. Additionally a low acute and long-term risk to mammals from the plant metabolite CCPP could not be confirmed
	Assessment not finalised		
Risk to wild non target terrestrial organisms other than vertebrates	Risk identified		
	Assessment not finalised	X - No valid study and hence no risk assessment to address the risk to soil micro-organisms	X - No valid study and hence no risk assessment to address the risk to soil micro-organisms
Risk to aquatic organisms	Risk identified	X – For FOCUS scenarios D1 ditch + stream D2 Ditch + stream	X – for FOCUS scenarios D1 ditch +stream
	Assessment not finalised		
Groundwater exposure active substance	Legal parametric value breached	PEC <sub>GW</sub> >0.1µg/l in 1/9 FOCUS <sub>GW</sub> scenarios	
	Assessment not finalised		
Groundwater exposure	Legal parametric value breached		



<b>metabolites</b>	Parametric value of 10µg/L <sup>(a)</sup> breached		
	Assessment not finalised		
<b>Comments/Remarks</b>			

The superscript numbers in this table relate to the numbered points indicated within chapter 3.1.5 and 3.1.6. Where there is no superscript number, see level 2 for more explanation.

(a): Value for non relevant metabolites prescribed in SANCO/221/2000-rev 10-final, European Commission, 2003

### 3.1.8. Area(s) where expert consultation is considered necessary

It is recommended to organise a consultation of experts on the following parts of the assessment report:

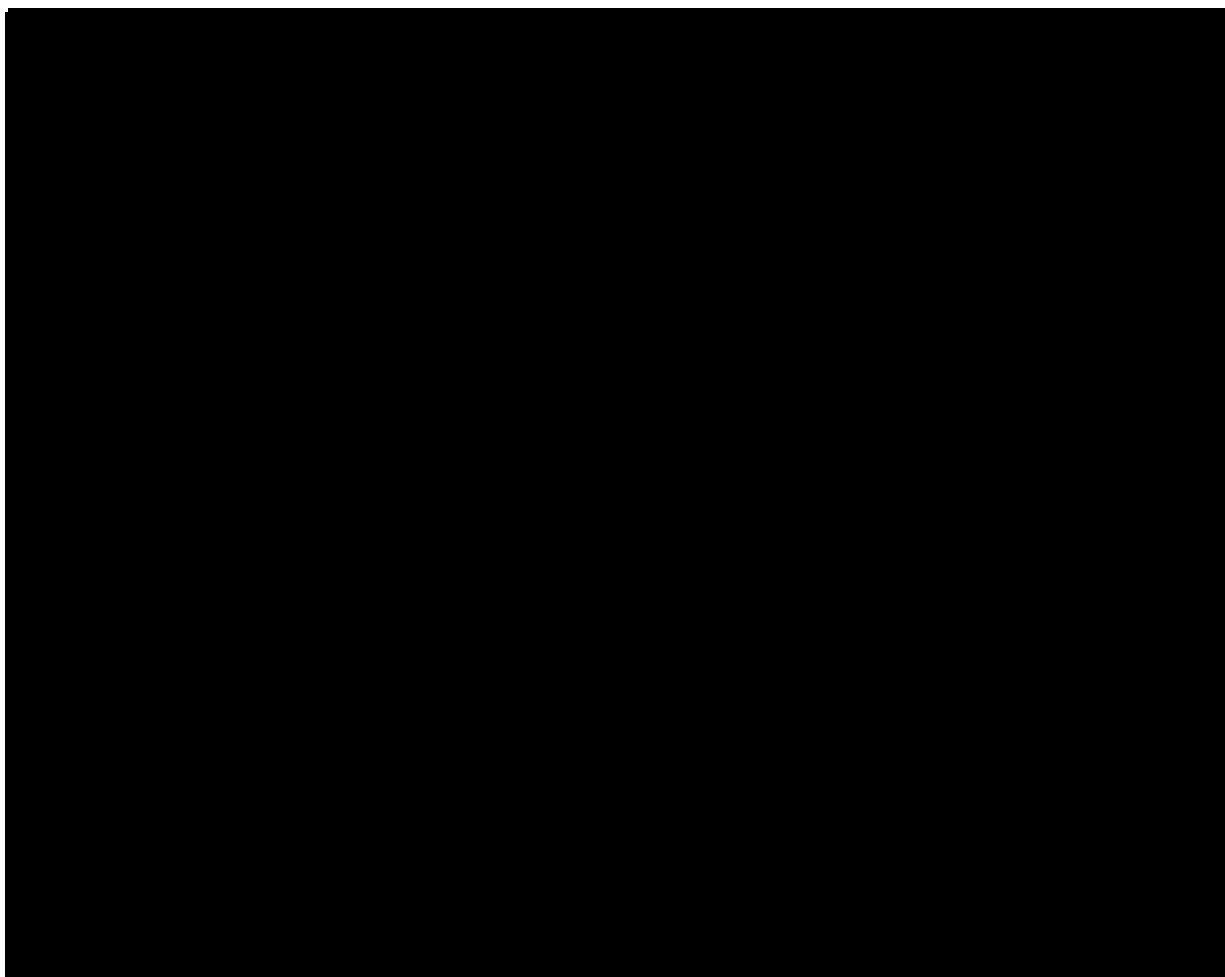
<b>Area(s) where expert consultation is considered necessary</b>	<b>Justification</b>
Persistence criteria : POP, PBT and vPvB classification	For PBT classification: the P criteria is fulfilled for fresh or estuarine water in 2 out of 4 water/sediment systems and the aerobic mineralisation in surface water study. For POP and vPvB classification: the P criteria is fulfilled for water in 1 out of 4 water/sediment systems and the aerobic mineralization in surface water study. As the aerobic mineralisation in surface water study is a new data requirement, expert discussion would be appreciated to confirm correct interpretation of how to use the results in relation to the PBT criteria.

### 3.1.9. Critical issues on which the Co RMS did not agree with the assessment by the RMS

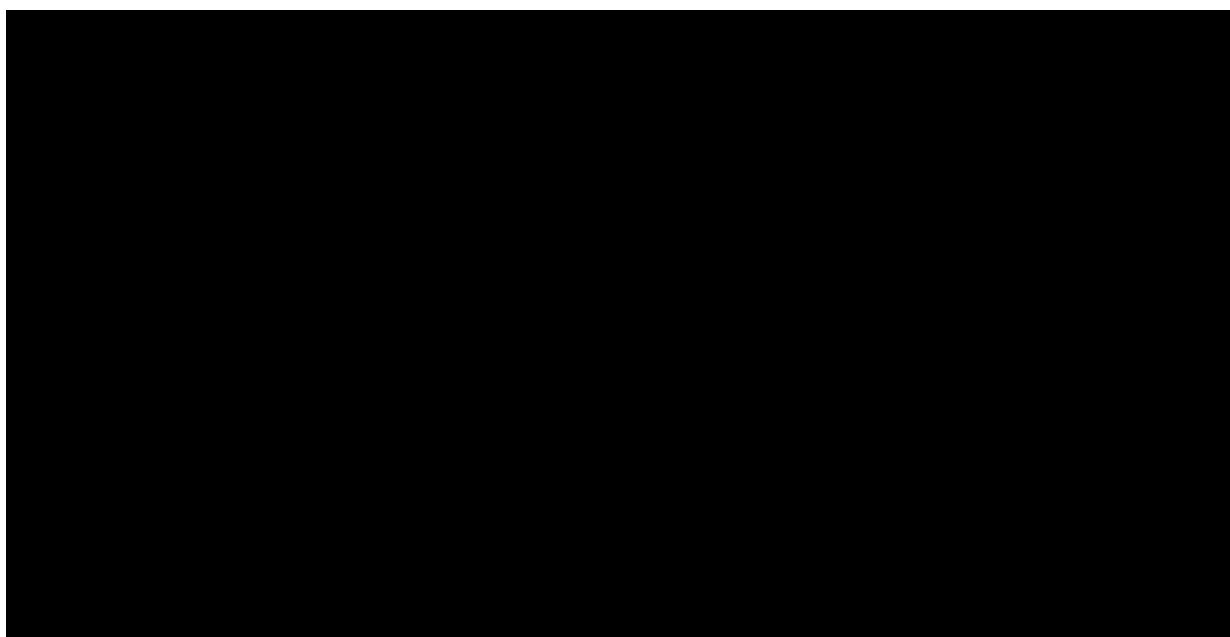
Points on which the co-rapporteur Member State did not agree with the assessment by the rapporteur member state. Only the points relevant for the decision making process should be listed.

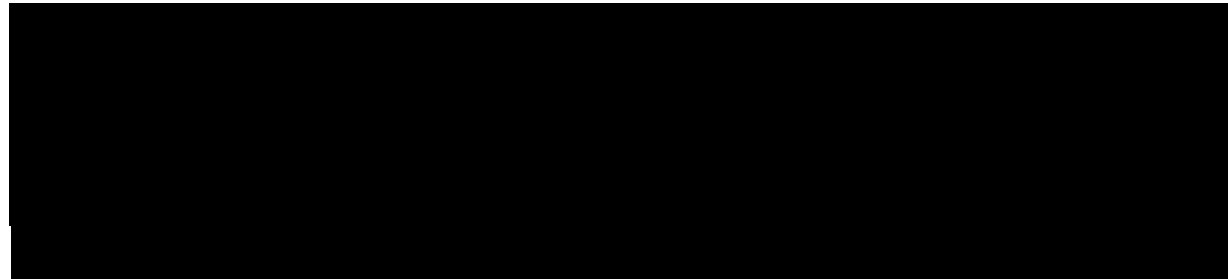
<b>Issue on which Co-RMS disagrees with RMS</b>	<b>Opinion of Co-RMS</b>	<b>Opinion of RMS</b>

### **3.2. PROPOSED DECISION**



### **3.3. RATIONALE FOR THE CONDITIONS AND RESTRICTIONS TO BE ASSOCIATED WITH THE APPROVAL OR AUTHORISATION(S), AS APPROPRIATE**





### 3.4. APPENDICES

#### GUIDANCE DOCUMENTS USED IN THIS ASSESSEMENT

##### Chemistry, methods of analysis and residues

- Guidance document on pesticide residue analytical methods, SANCO/825/00 rev. 8.1.
- Residues: Guidance for generating and reporting methods of analysis in support of pre-registration data requirements for Annex II (part A, Section 4) and Annex III( part A, Section 5) of Directive 91/414: SANCO/3029/99/ rev.4.
- Technical material and preparations: Guidance for generating and reporting methods of analysis in support of pre- and post- registration data requirements for Annex II (part A, Section 4) and Annex III( part A, Section 5) of Directive 91/414: SANCO/3030/99/ rev.4.
- Guidance Document: guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs: SANCO 7525/VI/95 – rev.9
- OECD guidelines for the testing of chemicals 503: Metabolism in livestock.
- OECD guidelines for the testing of chemicals 505: Residues in livestock.
- OECD guidelines for the testing of chemicals 507: Nature of the pesticide residues in processed commodities – high temperature hydrolysis.

##### Environmental Fate and Behaviour

- Guidance document on estimating persistence and degradation kinetics from environmental fate studies on pesticides in EU registration; SANCO/10058/2005, version 2.0, June 2006.
- Guidance document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil; SANCO/12117/2014-final
- FOCUS groundwater scenarios in the EU review of active substances; SANCO/321/2000 rev. 2.
- Generic guidance for Tier 1 FOCUS groundwater assessments; Version 2.2, May 2014.
- FOCUS surface water scenarios in the EU evaluation process under 91/414/EEC. SANCO/4802/2001- rev.2 final, May 2003.
- Generic guidance for FOCUS surface water scenarios; Version 1.1, March 2012.
- Landscape and mitigation factors in aquatic ecological risk assessment SANCO/10422/2005, version 2.0, September 2007.
- ECHA guidance on information requirements and chemical safety assessment Chapter R11: PBT/vPvB Assessment v2.0, November 2014.
- Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009. EFSA Journal 2011; 9(2): 2092.

##### Ecotoxicology:

- Guidance of EFSA : Risk Assessment for Birds and Mammals: EFSA Journal 2009; 7(12):1438
- Guidance Document on Aquatic Ecotoxicology in the context of the Directive 91/414/EEC: Sanco/3268/2001
- Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters: EFSA Journal 2013;11(7):3290
- Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods ESCORT II (2000)

- Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC: SANCO/10329/2002
- Guidance of EFSA: Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009: EFSA Journal 2011;9(2):2092

#### Efficacy

- SANCO/2012/11251 Guidance Document on the renewal of approval of active substances

#### Toxicology

- Guidance on Dermal Absorption, EFSA Journal 2012;10(4):2665
- Draft guidance on setting and application of acceptable operator exposure levels (AOELs) SANCO 7531 rev.10 (July 2006)
- Guidance document on the assessment of the equivalence of technical materials of substances regulated under Regulation (EC) No 1107/2009, SANCO/10597/2003-rev. 10.1 (July 2012)

#### General

- Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009, EFSA Journal 2011;9(2):2092
- ECHA Guidance on the application of the CLP criteria, version 4.1, June 2015.

### **3.5. REFERENCE LIST**

EFSA Reasoned opinion on the review of the existing maximum residue levels (MRLs) for mecoprop and mecoprop-p according to Article 12 of Regulation (EC) No 396/2005 [EFSA Journal 2013;11(4):3191].