CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification:

mecoprop-P (ISO) [1] and its salts; (*R*)-2-(4-chloro-2-methylphenoxy)propionic acid [1] and its salts

EC Number: **240-539-0**

CAS Number: **16484-77-8**

Index Number: **607-434-00-5**

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Chemicals Regulation Division

Health and Safety Executive

United Kingdom

Version number: 2 **Date: July 2018**

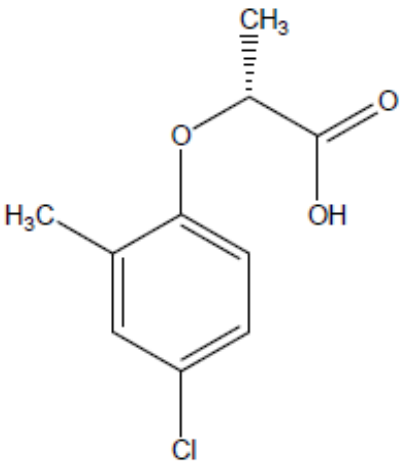
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Mecoprop-P (ISO) [1] and its salts; (*R*)-2-(4-chloro-2-methylphenoxy)propionic acid [1] and its salts.

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	(R)- 2-(4-chloro-2-methylphenoxy)propionic acid
Other names (usual name, trade name, abbreviation)	Mechlorprop-P, Mécoprop-P, MCPP-P, CMPP-P
ISO common name (if available and appropriate)	Mecoprop-P
EC number (if available and appropriate)	240-539-0
EC name (if available and appropriate)	(R)-2-(4-chloro-2-methylphenoxy)propionic acid
CAS number (if available)	16484-77-8
Other identity code (if available)	CIPAC 475
Molecular formula	C10H11ClO3
Structural formula	
SMILES notation (if available)	Not available
Molecular weight or molecular weight range	214.65
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	R enantiomer of mecoprop
Description of the manufacturing process and identity of the source (for UVCB substances only)	N/A
Degree of purity (%) (if relevant for the entry in Annex VI)	≥ 89%

The information reported in the table above includes information specifically on (R)-2-(4-chloro-2-methylphenoxy)propionic acid

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
Mecoprop-p	**89%**	**Acute Tox. 4*; H302 Eye Dam. 1; H318 Aquatic Chronic 2; H411**	**In addition to the harmonised classification, there are also notifications for Aquatic Chronic 1; H411.**

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Confidential				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
None					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	607-434-00-5	mecoprop-P [1] and its salts (R)-2-(4-chloro-2-methylphenoxy)propionic acid	240-539-0	16484-77-8	Acute Tox. 4* Eye Dam. 1 Aquatic Chronic 2	H302 H318 H411	GHS07 GHS05 GHS09 Dgr	H302 H318 H411			
Dossier submitters proposal	607-434-00-5	mecoprop-P (ISO) [1] and its salts; (R)-2-(4-chloro-2-methylphenoxy)propionic acid [1] and its salts	240-539-0 [1]	16484-77-8 [1]	Retain Eye Dam. 1 Modify Acute Tox. 4 Aquatic Chronic 3	Retain H302 H318 Modify H412	Retain GHS07 GHS05 Dgr Remove GHS09	Retain H302 H318 Modify H412		Add oral: ATE = 431 mg/kg bw	
Resulting entry in Annex VI if adopted by RAC and agreed by Commission	Existing or TBD	mecoprop-P (ISO) [1] and its salts; (R)-2-(4-chloro-2-methylphenoxy)propionic acid [1] and its salts	240-539-0 [1]	16484-77-8 [1]	Acute Tox. 4 Eye Dam. 1 Aquatic Chronic 3	H302 H318 H412	GHS07 GHS05 Dgr	H302 H318 H412		oral: ATE = 431 mg/kg bw	

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier	No
Oxidising gases	Hazard class not assessed in this dossier	No
Gases under pressure	Hazard class not assessed in this dossier	No
Flammable liquids	Hazard class not assessed in this dossier	No
Flammable solids	Hazard class not assessed in this dossier	No
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not assessed in this dossier	No
Pyrophoric solids	Hazard class not assessed in this dossier	No
Self-heating substances	Hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not assessed in this dossier	No
Oxidising solids	Hazard class not assessed in this dossier	No
Organic peroxides	Hazard class not assessed in this dossier	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	**Harmonised classification proposed**	**Yes**
Acute toxicity via dermal route	Hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	Hazard class not assessed in this dossier	No
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	Hazard class not assessed in this dossier	No
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity	Hazard class not assessed in this dossier	No
Reproductive toxicity	**Data conclusive but not sufficient for classification**	**Yes**
Specific target organ toxicity-single exposure	Hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	**Data conclusive but not sufficient for classification**	**Yes**
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	**Harmonised classification proposed**	**Yes**
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

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.

Mecoprop-P has an existing entry in Annex VI of CLP (Acute Tox. 4*: H302, Eye Dam. 1: H318, Aquatic Chronic 2: H411).

At the Meeting of the Commission Working Group on the Classification and Labelling of Dangerous Substances in 1999, it was agreed that mecoprop-P warranted classification with Xn; R22 and Xi; R41. A proposal by one Member State to classify with Repr. Cat. 3; R63 was discussed in October 2000. The Dossier Submitter argued that the slight increase in late resorptions in rabbits was not convincingly different from the control and not dose dependent. The Group agreed on no classification for developmental toxicity.

At the time the substance was reviewed by the TC C&L Group, a 2 generation reproduction study on the mecoprop racemate was available. However, some regulatory authorities rejected this study because of the very minimal parental toxicity. As a result, a dose-range finding study for a 2 generation study on mecoprop-P was conducted subsequently. The toxicity shown in the dose-range finding study was comparable to that observed in the existing 2 generation study on the mecoprop racemate and therefore a 2 generation study on mecoprop-P was not conducted. It was considered that the existing 2 generation study on the racemate and the one generation study on mecoprop-P were sufficient to assess any potential adverse effects of mecoprop-P on sexual function and fertility.

Since the substance was discussed by the TC C&L Group, an acute oral toxicity study in mice has been conducted. In addition there is a recently conducted 2 year chronic toxicity study in rats.

During the Annex I renewal process in 2017, a concern for developmental toxicity was raised at the Pesticides Peer Review Meeting. The experts proposed classification with Repr. 2; H361d based on increased late resorptions in the rabbit.

This proposal seeks to amend the existing entry in Annex VI of CLP to take account of data that do not appear to have been considered during the original discussions on classification and labelling, and to confirm the existing classification that was derived by translation from Directive 67/548/EEC (DSD).

At the time of submission, the substance is registered as an intermediate under REACH.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Mecoprop-P is a plant protection product in the scope of Regulation EC 1107/2009. As mecoprop-P already has an existing entry in Annex VI of CLP, this proposal is targeted to confirm the existing classification and to take account of additional information.

5 IDENTIFIED USES

Mecoprop-P is used as a herbicide on winter and spring wheat, barley, rye, oats and triticale.

6 DATA SOURCES

Renewal Assessment Report (RAR) – Mecoprop-P, 2017

Draft Assessment Report – Mecoprop-P – Volume 3, Annex B.2: Physical and Chemical Properties, 2016

Draft Assessment Report – Mecoprop-P – Volume 3, Annex B.6: Toxicology and Metabolism, 2016

Draft Assessment Report – Mecoprop-P – Volume 3, Annex B.8: Fate and Behaviour, 2016

Draft Assessment Report – Mecoprop-P – Volume 3, Annex B.9: Ecotoxicology, 2016

Draft Assessment Report – Mecoprop-P – Volume 4 – Confidential Information, 2016

7 PHYSICOCHEMICAL PROPERTIES

Studies are taken from the Draft Assessment Report (DAR) – Volume 3 – B.2 (AS).

Table 7: Summary of physicochemical properties

<table>
<tr><th>Property</th><th>Value</th><th>Reference</th><th>Comment (e.g. measured or estimated)</th></tr>
<tr><td>Physical state at 20°C and 101,3 kPa</td><td>(Mecoprop-P pure 99.8 % w/w) White solid at 20°C
N 9.25/84.2% R on Munsell Colour system

(Mecoprop-P TGAI) Dark cream solid at 20°C
2.5Y 9/2 on Munsell Colour system</td><td>Comb, A.L. NUF004/993523 (2000a)

Comb, A.L NUF002/993274 (2000b)</td><td>OPPTS 830.6302

OPPTS 830.6303</td></tr>
<tr><td>Melting/freezing point</td><td>Melting point 93.5 - 97.5°C</td><td>Comb, A.L. NUF004/993523 (2000a)</td><td>EEC A1
OPPTS 830.7200</td></tr>
<tr><td>Boiling point</td><td>Boiling point could not be determined. Decomposes above 240°C without boiling</td><td>Comb, A.L. NUF004/993523 (2000a)</td><td>EEC A2
OPPTS 830.7220</td></tr>
<tr><td>Relative density</td><td>D422 = 1.31</td><td>Comb, A.L. NUF004/993523 (2000a)</td><td>EEC A3 OPPTS 830.7300</td></tr>
<tr><td>Vapour pressure</td><td>1.4 x 10^{-3} Pa at 25°C</td><td>Comb, A.L. NUF004/993523 (2000a)</td><td>EEC A4
OPPTS 830.7950</td></tr>
<tr><td>Surface tension</td><td>50.0 mN/m (90% saturated solution) at 20ºC.
As surface tension is < 60 mN/m at 20ºC it is surface active.</td><td>Comb, A.L. NUF004/993523 (2000a)</td><td>EEC A5</td></tr>
<tr><td>Water solubility</td><td>Measured at 20°C

<table><tr><td>Purified water (pH 3)</td><td>880 mg/L</td></tr><tr><td>pH 4 buffer</td><td>6.65g/L</td></tr><tr><td>pH 7 buffer</td><td>> 250g/L</td></tr><tr><td>pH 10 buffer</td><td>>250 g/L</td></tr></table></td><td>Comb, A.L. NUF004/993523 (2000a)</td><td>EEC A6 OPPTS 830.7840</td></tr>
<tr><td>Partition coefficient n-octanol/water</td><td>Measured at 20°C

<table><tr><td>pH4 buffer</td><td>log10Pow = 2.19, Pow = 156</td></tr><tr><td>pH 7 buffer</td><td>log10Pow = -0.19, Pow = 0.64</td></tr><tr><td>pH 10 buffer</td><td>log10Pow = -0.64, Pow = 0.23</td></tr></table>Calculated values of log10Pow:
mecoprop-P = 2.94
HMCPP = 1.47
CCPP = 1.93</td><td>Comb, A.L. NUF004/993523 (2000a)</td><td>EEC A8
OPPTS 830.7550</td></tr>
<tr><td>Flash point</td><td>The flash point is not applicable, since Mecoprop-P is a solid.</td><td>-</td><td>Case</td></tr>
<tr><td>Flammability</td><td>Mecoprop-P TGAI is not flammable. At ignition, localized combustion with no spreading. Mecoprop-P charred and melted but failed to ignite.</td><td>Comb, A.L NUF002/993274 (2000b)</td><td>OPPTS 830.6315/ EEC A10</td></tr>
</table>

Property	Value	Reference	Comment (e.g. measured or estimated)
Explosive properties	Mecoprop-P technical material is not explosive. Tests for thermal sensitivity and mechanical sensitivity (shock and friction) were negative.	Comb, A.L NUF002/993274 (2000b)	EEC A14
Self-ignition temperature	Mecoprop-P TGAI did not self-ignite prior to melting. No exothermic reaction of mecoprop-P technical grade below its melting point at *ca.* 90 - 100°C was observed.	Comb, A.L NUF002/993274 (2000b)	EEC 16
Oxidising properties	Mecoprop-P technical grade is not oxidising.	Comb, A.L NUF002/993274 (2000b)	EEC A17
Granulometry	No data		
Stability in organic solvents and identity of relevant degradation products	Solvent solubility at 20± 1°C Acetone: > 250 g/L Dichloromethane: > 250 g/L Ethyl acetate: > 250 g/L Methanol: > 250 g/L Heptane: 7.69 g/L Toluene: > 250 g/L	Wilson. I, 14/0866 (2014) Wilson, I., 2015 15/0969 (heptane result)	CIPAC Method MT181 & modified MT157 with validated method (heptane)
Dissociation constant	At 25 °C dissociation constant = 2.0 x 10-4 pKa = 3.7 (acidic)	Comb, A.L. NUF004/993523 (2000a)	OECD 112 OPPTS 830.7370
Viscosity	Not relevant, solid		

8 EVALUATION OF PHYSICAL HAZARDS

Not addressed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 8: Summary table of toxicokinetic studies

Method	Results	Reference
Absorption, distribution, metabolism and excretion in the rat Wistar rats (5/sex/group) Oral route 5 mg or 100 mg (^{14}C)-mecoprop-P, Batch 469-05, radiochemical purity 99.5%, chemical purity 98.6% Broadly follows OECD 417	• Single and repeat oral doses of 5 mg (^{14}C)-mecoprop-P/kg bw were rapidly and extensively absorbed and distributed and were eliminated within 24 hours of administration - around 90% with the urine and 3-7.5% with faeces. Elimination half-life ($T_{½\ elim}$) was around 4 hours (females) and 6 hours (males) • After a single oral dose of 100 mg ^{14}C-mecoprop-P/kg bw the time course was extended to about 48 hours for the same excretion - 77% and 85% via urine for females and males, respectively and 9-12% via the faeces for females and males respectively. $T_{½\ elim}$ was around 8 hours (both sexes). • No radioactivity in expired air. • Little radioactivity in the tissues 7 days after dosing - only about 3% of the high dose (mainly in the fat) and < 1% of the low dose, whether single or repeat. • Peak plasma concentrations of approximately 30 to 400 µg /gram ^{14}C-mecoprop-P were reached around 2 to 4 hours after dosing for rats receiving single oral doses of 5 or 100 mg ^{14}C-mecoprop- P/kg bw respectively. • One major metabolite (2-hydroxy-mecoprop-P). >30% of the excreted radioactivity was attributable to this metabolite in repeat dose males. • Major part of radioactivity in urine (> 60% and > 85% from males and females, respectively) was attributable to unchanged - and unconjugated - parent compound.	Anonymous (1997a) EU RAR B.6.1.1.1

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Absorption

Mecoprop-P was rapidly and extensively absorbed. In a study with rats, peak blood levels were reached 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 (between 80 and 95% depending on dose or repeated exposure).

Metabolism

The only major metabolite was hydroxymethyl-mecoprop-P (HMCPP), which 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).

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 was remarkably slower than for other tissues.

Elimination

Mecoprop-P was largely excreted as parent material. Following oral administration, mecoprop-P was rapidly excreted, predominantly via the urine. The elimination half-life was less than 8 hours at both the low and high doses.

There is no information on the biliary excretion of mecoprop-P. The only available studies included in the 1998 Draft Assessment Report (DAR) were on the mecoprop racemate. These studies indicated extensive biliary excretion and evidence of significant enterohepatic recirculation. Therefore, biliary excretion and enterohepatic recirculation may also be important for mecoprop-P.

10 EVALUATION OF HEALTH HAZARDS

Table 9: Summary table of animal studies used for the evaluation of health hazards, and details of the substance tested (mecoprop-P or racemic mecoprop)

Hazard Class	Available studies	
	mecoprop-P	**mecoprop racemate**
Acute toxicity via oral route	OECD 401 Mecoprop-P, purity 94.4% Rat, SD 100, 180, 320 and 580 mg/kg bw	No acute toxicity studies available with the racemate
	OECD 401 Mecoprop-P, purity not known Rat, CD 450, 567, 714 and 900 mg/kg bw	
	Similar to OECD 401 Mecoprop-P, purity not known Rat, Wistar 681, 1000, 1470 and 2150 mg/kg bw	
	OECD 425 Mecoprop-P potassium salt Mouse, CD1 3993 mg/kg bw	
Reproductive toxicity and adverse effects on or via lactation – oral route	One generation reproduction study (dose range finding study), OECD 415 Mecoprop-P, purity 92.8% Rat, Han Wistar 0, 500, 800 or 1200 ppm	Two generation study reproduction study, OECD 416 Mecoprop racemate, 92.7% Rat, Wistar 0, 20, 100 or 500 ppm
Developmental toxicity – oral route - rats	Developmental toxicity, OECD 414 Mecoprop-P, purity >92.2% Rat, Wistar	No developmental toxicity studies in rats available

Hazard Class	Available studies	
	mecoprop-P	**mecoprop racemate**
	0, 20, 50 or 100 mg/kg bw/d	
Developmental toxicity – oral route - rabbits	Developmental toxicity , OECD 414 Mecoprop-P, purity >92.2% Rabbit, Himalayan 0, 5, 20 or 50 mg/kg bw/day	Developmental toxicity (non-guideline) Mecoprop racemate, purity not known Rabbit, Dutch-belted 0, 12, 30 and 72 mg/kg bw/d
	Preliminary dose range-finding study Mecoprop-P, purity not known Rabbit, Himalayan 0, 40, 80 and 120 mg/kg bw/day	
Developmental toxicity – oral route - mice	Non-guideline study, oral route Mecoprop-P (purity not known) and mecoprop racemate (purity not known) Mice, NMRI 0, 200, 300, 400 or 500 mg/kg bw/d (mecoprop-p) or 0, 100, 200, 300, 400, 500 or 700 mg mecoprop racemate	
STOT-RE – oral route - rats	28 day study, OECD 407 Mecoprop-p, purity 99.4% Rat, Wistar 0, 50 and 400 ppm	49 day study, OECD 407 Mecoprop racemate, purity 92.7% Rat, Wistar 0, 50 and 400 ppm
	90 day study, Similar to OECD 408 Mecoprop-p, purity 100% Rats, SD 0, 200, 400, 800, 1600 and 3200 ppm	90 day study, OECD 408 Mecoprop racemate, purity 93% Rat, SD 0, 200, 800 and 3200 ppm
	Supplementary 3 month study Mecoprop-P, purity 99.9% Rat, SD 800, 1600 and 3200 ppm	Supplementary 3 month study Mecoprop racemate, purity 93% Rats, SD 0, 800 and 3200 ppm
		90 day study, OECD 408 Mecoprop racemate, purity 92.7% Rat, Wistar 0, 50, 150 or 450 ppm
	2 year carcinogenicity study, OECD 451 Mecoprop-P, purity not known Rat, Han Wistar 0, 100, 600 or 1200 ppm	2 year carcinogenicity study, OECD 453 Mecoprop racemate, purity 92.7% Rat, Wistar 0, 20, 100 and 400 ppm
STOT-RE –	90 day study, OECD 408	No repeated dose studies in mice by the oral

Hazard Class	Available studies	
	mecoprop-P	**mecoprop racemate**
oral route - mice	Mecoprop-P, purity 96.5% Mice, B6C3F1 0, 100, 1000 and 2500 ppm	route are available
	18 month carcinogenicity study, OECD 451 Mecoprop-P, purity 92.7% 0, 25, 250 and 2500 ppm	
	18 month supplementary study, OECD 451 Mecoprop-P, purity 92.7% Mice, B6C3F1 0 or 700 ppm	
STOT-RE – oral route - dogs	1 year study, OECD 452 Mecoprop-P, purity 89.9% Dog, beagle 0, 60, 180 and 600 ppm	90 day study, OECD 409 Mecoprop racemate, purity 93.3% Dog, beagle 0, 4, 16 and 64 mg/kg bw/d
STOT-RE – dermal route - rabbits	21 day study, OECD 410 Mecoprop-P, purity 92.6% Rabbit, New Zealand White 0, 10, 100 or 1000 mg/kg bw/d	No repeated dose studies in rabbits by the dermal route are available
Other studies	No other studies are available	Non-guideline immunotoxicity study (acute, 14 day and 90 day) Mecoprop racemate potassium salt, purity 97% Rats, Wistar 0, 320, 800 and 1300 mg/kg bw/d for the acute study 0, 100, 320 and 800 mg/kg bw/d for the 14 day study 0, 0.8, 8, 80 and 320 mg/kg bw/d for the 90 day study
		Non-guideline immunotoxicity study Mecoprop racemate, purity 97% Rats, Wistar up to 500 mg/kg bw/d
		Non-guideline haematology study Mecoprop racemate, purity >99%

Hazard Class	Available studies	
	mecoprop-P	**mecoprop racemate**
		In vitro study Up to 2.0 mg/ml

Acute toxicity

10.1 Acute toxicity - oral route

Two standard OECD 401 oral toxicity studies in rats are available. In addition, there is a non-standard toxicity study in rats and a dietary OECD 424 limit test in mice.

Table 10: Summary table of animal studies on acute oral toxicity of mecoprop-P

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50} (mg/kg bw)	Reference
OECD 401 (1987) Oral administration GLP	Rat, SD 5/sex/group	Mecoprop-P (purity 94.4%) suspended in 0.5% aqueous carboxymethyl cellulose Single oral administration of 10ml/kg bw	100, 180, 320, and 580 mg/ kg bw	Males: 431 Females: 431	Anonymous (1994) EU RAR B.6.2.1.1/02
OECD 401 (1987) Gavage GLP	Rat, CD 5/sex/group	Mecoprop-P (technical grade, purity not stated) suspended in 0.5% aqueous carboxymethyl cellulose A volume of 20ml/kg was administered.	450, 567, 714, and 900 mg/ kg bw	Males: 803 Females: 756 Combined: 775	Anonymous (1990a) EU RAR B.6.2.1.1/03
Broadly similar to OECD 401 (1981) Gavage Non-GLP	Rat, Wistar 5/sex/group	Mecoprop-P (purity not stated) suspended in 0.5% aqueous carboxymethyl cellulose A volume of 10ml was administered by gavage.	681, 1000, 1470, and 2150 mg/kg bw	Males: 1327 (interpolation) Females: 681< LD50 < 1000 Combined: 1050	Anonymous (1983) EU RAR B.6.2.1.1/01

Table 11: Summary table of animal studies on acute oral toxicity of mecoprop-P salts

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50} (mg/kg bw)	Reference
OECD 425 (2001) as a limit test Dietary administration	Mouse, CD1 (Swiss derived), albino 5 females	Mecoprop-P potassium salt	20000 ppm (3993mg/kg bw/day) Dose administered in the diet over 24 hours to provide information on acute effects on small mammals for ecotoxicity assessment.	>3993	Anonymous (2009) EU RAR B.6.2.1.2

The potential of mecoprop-P to elicit acute toxic effects via the oral route has been investigated in rats and mice.

Anonymous (1994)

Mecoprop-P (suspended in 0.5% aqueous CMC) was administered to SD rats (5/sex/group) at doses of 100, 180, 320, and 580 mg/kg bw in a GLP-compliant study (OECD TG 401). Under the conditions of this study, the LD_{50} value was 431mg/kg bw in both sexes.

At 180 and 320 mg/kg bw, piloerection, reduced motor activity and hunched posture were observed on days 1 and 2. At the top dose, piloerection, dyspnoea, prostration, absence of traction and grasping reflex, muscular atony, reduced motor activity and unconsciousness were reported.

Anonymous (1990a)

Mecoprop-P (suspended in 0.5% aqueous CMC) was administered to CD rats (5/sex/group) by gavage at 450, 567, 714, and 900 mg/kg bw in compliance with OECD 401 and under GLP conditions. In this study, the LD_{50} values were 803 and 756 mg/kg bw in males and females, respectively.

Lethargy, unconsciousness, decreased motor activity, prone posture, ataxia, clonic convulsion, muscle tremor, breathing irregularities, ungroomed appearance, pigmented orbital secretion and hunched posture were observed, although unconsciousness and clonic convulsions were not observed in surviving animals. Animals at the lowest dose were reported to be less severely affected.

In the animals that died from the treatment, altered stomach and jejunum content, dark thymic lymph nodes and pale perineal staining were observed.

Anonymous (1983a)

Mecoprop-P was suspended in 0.5% aqueous carboxymethyl cellulose (CMC) and administered to Wistar rats (5/sex/group) by gavage at dose levels of 681, 1000, 1470, and 2150 mg mecoprop-P /kg bw. The rats were then observed for 14 days. Under the conditions of this study, the LD_{50} value was 1327 mg/kg bw in males and 681 - 1000mg/kg bw in females. All deaths occurred in the 2 days that followed dosing.

Dyspnoea, apathy, abnormal position, staggering, atonia, paresis, absence of pain reflex and corneal reflex, narcotic-like state, tremors, twitching, spastic gait, piloerection, exsiccosis, lacrimation, blood in urine, and poor general state were observed in the rats. However, information relating to incidences and severity is not available. At the lowest dose, blood was observed in the urine. At necropsy, general congestive hyperaemia and bloody ulcerations in the glandular stomach were noted in 2 animals at 1000 mg/kg bw. The intestine was

found to be slightly atonic in some cases, and the urinary bladder was described as being strikingly full in a number of cases. No abnormalities were reported in the surviving animals sacrificed after day 14.

Anonymous (2009)

Five female CD-1 mice were exposed to 20000ppm mecoprop-P potassium salt in the diet in a GLP-compliant limit test, which was described as following OECD TG 425. The treated diet was provided for 24 hours, before the mice were fed a standard diet during a 14 day observation period. It is noted that the dose was administered via the diet rather than by gavage and therefore this study is considered to be non-standard.

There were no reports of clinical signs of gross toxicity, adverse pharmacologic effects, abnormal behaviour or macroscopic abnormalities. No deaths were observed. Therefore under the conditions of this study, the LD_{50} value in mice was greater than 3393 mg/kg bw.

The results of this study seem to imply that the salt is less toxic than mecoprop-P. However, the salt was administered via the diet over a period of 24 hours whereas mecoprop-P was administered via a single gavage dose. Historically, the toxicity of mecoprop-P and its salts have been considered equal and the result from *Anonymous (2009)* is not considered to cast any doubt on the way the substances have been considered in the past.

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

In rats, LD_{50} values ranged from 431 to 1327 mg/ kg bw in 3 separate studies. Mecoprop-P was not acutely toxic to mice in a limit test. Therefore the rat appears to be more sensitive than the mouse to the acute effects of mecoprop-P via the oral route. The reason for the species difference is unclear. However, it is noted that mice were exposed to the mecoprop-P potassium salt via the diet rather than a pure form of mecoprop-P via gavage. Therefore, the rat studies are used to support classification for acute oral toxicity.

No human information that would support classification of mecoprop-P and its salts for acute oral toxicity is available.

10.1.2 Comparison with the CLP criteria

In rats, the LD_{50} values ranged from 431 to 1327mg mecoprop-P/ kg bw. These values all fall within the range for Acute Oral Toxicity Category 4 ($300 < ATE \leq 2000$ mg/kg bw).

Therefore mecoprop-P meets the criteria for classification in Category 4 for Acute Oral Toxicity.

Based on the lowest LD_{50} value obtained in rats, an Acute Toxicity Estimate (ATE) of 431 mg/kg bw is proposed.

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Acute Toxicity (oral) Category 4; H302: Harmful if swallowed.
ATE (Acute oral toxicity): 431 mg/kg bw

10.2 Acute toxicity - dermal route

This hazard class was not evaluated.

10.3 Acute toxicity - inhalation route

This hazard class was not evaluated.

10.4 Skin corrosion/irritation

This hazard class was not evaluated.

10.5 Serious eye damage/eye irritation

This hazard class was not evaluated.

10.6 Respiratory sensitisation

This hazard class was not evaluated.

10.7 Skin sensitisation

This hazard class was not evaluated.

10.8 Germ cell mutagenicity

This hazard class was not evaluated.

10.9 Carcinogenicity

This hazard class was not evaluated.

10.10 Reproductive toxicity

Studies on both mecoprop-P and racemic mecoprop have been considered in the assessment of reproductive toxicity. As discussed in section 3, this has been the practice for some time. The 2 generation study with racemic mecoprop is regarded as sufficient to assess the reproductive toxicity profile of mecoprop-P. Studies on both racemic mecoprop and mecoprop-P have been taken into account to assess whether mecoprop-P meets the criteria for a classification as a developmental toxicant.

10.10.1 Adverse effects on sexual function and fertility

For the purposes of assessing the potential of mecoprop-P to adversely affect sexual function and fertility, there are 2 guideline studies available: a 2-generation study on the mecoprop racemate and a preliminary 1-generation study on mecoprop-P.

Table 12: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**
Non-standard one-generation reproductive toxicity study in the rat Rats, Han Wistar	Mecoprop-P, batch 91-1, purity 92.8% 0, 500, 800 or 1200 ppm	**P0** Statistically significant, dose-related reduction in the mean numbers of implantation sites in all treated groups compared with control The mean number of pups born was lower in all treated groups compared with the controls.

<table>
<tr><th>Method, guideline, deviations if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results</th></tr>
<tr>
<td>12/sex/dose, 7-9 weeks old at the start of the study

Oral (dietary)

OECD 415 (1983)

GLP

Only 12 animals per dose group instead of 20. Gross pathology should be performed on the P generation but in this study, gross pathology was conducted only on P and F1 animals which had external abnormalities.

Anonymous (2003) EU RAR B.6.6.1.2</td>
<td>mecoprop-P

Lactation period: the females were given diets containing nominal concentrations of 0, 300, 530 and 790 ppm mecoprop-P</td>
<td>
<table>
<tr><td>Dose (ppm)</td><td>0</td><td>500</td><td>800</td><td>1200</td><td rowspan="2">HCD[a] Range</td></tr>
<tr><td>mg/kg bw/day (females)</td><td>0</td><td>38.2</td><td>60.6</td><td>88.8</td></tr>
<tr><td>Mean implantation sites</td><td>13.8</td><td>12.5**</td><td>12.4**</td><td>10.9***</td><td>10.3-11.7</td></tr>
<tr><td>% implantation sites compared with control</td><td>N/A</td><td>9%↓</td><td>10%↓</td><td>21%↓</td><td></td></tr>
<tr><td>Mean pups born</td><td>12.7</td><td>11.2*</td><td>11.7</td><td>10.0**</td><td>9.3-11.1</td></tr>
<tr><td>% pups born compared with control</td><td>N/A</td><td>12%↓</td><td>8%↓</td><td>21%↓</td><td></td></tr>
<tr><td>Mean pups alive day 1</td><td>12.3</td><td>10.7</td><td>11.2</td><td>9.8</td><td></td></tr>
<tr><td>Mean pups alive day 4</td><td>11.1</td><td>9.7</td><td>11.0</td><td>9.0</td><td>9.1-10.8</td></tr>
</table>
* statistically significant compared to control: * = P<0.05, ** = P<0.01, *** = P<0.001
[a] HCD = historical control data (from 5 studies) for Han Wistar rats at Covance. Dates of these studies have not been provided.

No information on corpora lutea is available.

1200ppm

Males
↓ bodyweight gain during the first 5 weeks of treatment (by 18% weeks 0 to 18 and 20% weeks 0 to 10
Females
↓ bodyweight gain during the pre-mating period (by 26% weeks 0 to 10)
↓ bodyweight gain during gestation (by 50% days 0-7, 30% days 7-14, 20% days 14-20)

<u>F1</u>

No effects at lower concentrations

1200ppm

↓ (slight) group mean food intake (both sexes) during the 4 weeks of this generation, particularly females during the last week.

↓ body weight gain during pre-mating and gestation: males by 16% on days 0 to 18; females by 50% days 0-7, 30% days 7-14, 20% days 14-20.

Maternal/paternal NOAEL[a] = 800ppm
Reproductive NOAEL[a] = 800ppm
Offspring NOAEL[a] > 1200ppm
</td>
</tr>
</table>

<table>
<tr><th>Method, guideline, deviations if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results</th></tr>
<tr>
<td>2-generation reproduction study in rats

Wistar

25/sex/group

35 days old at the start of the study

OECD 416 (1983)

Sperm parameters and oestrus cycle length, vaginal opening, preputial separation, anogenital distance and number of implantation sites were not determined in this study as they were not required in the 1983 version of the OECD 416 test guideline.

Organ weights of pups and parental animals were not required in the 1983 version of the OECD 416 test guideline, so only the liver, kidney and testes from parental animals were weighed.

No histopathological examination of the female reproductive organs of pups or parental animals. No examination of the post lactational ovary.

Anonymous</td>
<td>Mecoprop racemate, purity 92.7%, TPH batch Racemic form

0, 20, 100, or 500 ppm

Continuous dietary administration over 2 generations starting when the P0 generation were 35 days old</td>
<td><u>P0</u>
No treatment-related differences in mating and fertility indices

500ppm
↑ absolute and relative kidney weights (relative 12% /9% in males/females, respectively).

<u>F1a, F1b, F2 Pups</u>
No treatment-related differences in F1a and F1b pup numbers and status at delivery

<table>
<tr><th>Litter type</th><th colspan="4">Total dead pups day 4 (dead day 0 + dead day 1-4)</th></tr>
<tr><td></td><td>0 ppm</td><td>20 ppm</td><td>100 ppm</td><td>500 ppm</td></tr>
<tr><td>F1a</td><td>8 (1+7)</td><td>6 (0+6)</td><td>15 (2+13)</td><td>23 (3+20##)</td></tr>
<tr><td>F1b</td><td>5 (1+4)</td><td>8 (1+7)</td><td>13 (4+9)</td><td>17 (6+11)</td></tr>
<tr><td>F2</td><td>17 (1+16)</td><td>22 (2+20)</td><td>22 (0+22)</td><td>32 (13##+19)</td></tr>
<tr><td></td><td colspan="4">Mean number of pups delivered per litter</td></tr>
<tr><td>F1a</td><td>14.5</td><td>13.1</td><td>14.6</td><td>14.9</td></tr>
<tr><td>F1b</td><td>15.8</td><td>15.0</td><td>15.3</td><td>15.7</td></tr>
<tr><td>F2</td><td>13.0</td><td>11.6</td><td>13.3</td><td>14.9</td></tr>
<tr><td></td><td colspan="4">Mean live pups/ litter Day 0</td></tr>
<tr><td>F1a</td><td>14.0</td><td>12.9</td><td>14.1</td><td>14.1</td></tr>
<tr><td>F1b</td><td>15.4</td><td>14.7</td><td>14.7</td><td>15.2</td></tr>
<tr><td>F2</td><td>12.9</td><td>11.4</td><td>12.9</td><td>14.4</td></tr>
<tr><td></td><td colspan="4">Mean live pups/ litter Day 4 (pre-culling)</td></tr>
<tr><td>F1a</td><td>13.6</td><td>12.6</td><td>13.5</td><td>13.2</td></tr>
<tr><td>F1b</td><td>15.2</td><td>14.3</td><td>14.1</td><td>14.5</td></tr>
<tr><td>F2</td><td>12.2</td><td>10.5</td><td>12.0</td><td>13.1</td></tr>
<tr><td></td><td colspan="4">Viability Index (%)</td></tr>
<tr><td>F1a</td><td>98</td><td>98</td><td>96</td><td>93</td></tr>
<tr><td>F1b</td><td>99</td><td>98</td><td>96</td><td>96</td></tr>
<tr><td>F2</td><td>95</td><td>92</td><td>93</td><td>91</td></tr>
</table>
significance level 0.05, ## significance level 0.01

<u>F1a pups</u>
500ppm:
↓ body weight gain of pups (significant ($p<0.05$) ↓ 6% on days 7-14 in the F1a generation)
The number of pups which died or were cannibalized from day 1 to day 4 post-partum (before culling) was significantly increased ($p<0.01$) therefore the viability index of this group was significantly reduced ($p<0.01$).

<u>F1b pups</u>

500ppm
↑ number of pup deaths from day 1 to day 4 (non-significant)

<u>F1 parental animals</u>
500ppm
↑ absolute and relative kidney weights (relative 10%/8% in males/females, respectively).</td>
</tr>
</table>

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results
(1992a) EU RAR B.6.6.1.1		**F2 pups** **500ppm** The number of dead pups on day 0 was significantly increased ($p<0.01$) ↓ body weight gain of pups, 8-11% over days 4-14 post-partum Delayed auditory canal opening (93% cf. 99% in controls) Maternal/paternal NOAEL[a] = 100ppm Offspring NOAEL[a] = 100ppm Reproductive/fertility NOAEL[a] > 500ppm

[a] NOAEL values have been taken from the EU Risk Assessment Report

One-generation reproductive toxicity study

A limited dose-range finding study for a modern 2-generation study was conducted in Wistar rats (12/sex/group) with mecoprop-P (purity 92.8%).

Method

At 7-9 weeks old, 0, 500, 800 or 1200 ppm mecoprop-P was administered to rats via the diet. Administration of the test substance at these dose levels continued until the lactation period. After 70 days of exposure to mecoprop-P, males and females mated. The females were allowed to litter and rear their offspring. During lactation, 0, 300, 530 and 790 ppm mecoprop-P was administered to dams in the diet. On day 4 post-partum, all litters were culled to a maximum of 8 pups with an equal sex distribution where possible. At weaning (day 21 post-partum), allocation of the F1 generation was by random selection of 10 males and 10 females from the available litters. Post-weaning, the F1 generation received mecoprop-P at the original concentrations.

The intake of mecoprop-P (mg/kg bw/day) achieved in each generation is shown in Table 13.

Table 13: Test substance intake in the one-generation reproductive toxicity study

	Mean dose received mg mecoprop-P/kg/day for the P0 generation		
	500 ppm	**800 ppm**	**1200 ppm**
Males, pre-pairing	34.5	53.7	82.9
Females, pre-pairing	41.0	64.7	98.4
Females, gestation	38.2	60.6	88.8
	300 ppm	**530 ppm**	**790 ppm**
Females, lactation	48.1	85.8	130.2
Mean P generation female	42.4	70.4	105.8
Sexes combined	38.5	62.1	94.4
	Mean dose received mg mecoprop-P/kg/day for the F1 generation		
	500 ppm	**800 ppm**	**1200 ppm**
Males	59.6	98.0	148.4
Females	61.1	101.5	147.7
Sexes combined	60.4	99.8	148.1

Results

No parental deaths were reported. There were no treatment-related clinical signs in P and F1 adults.

Bodyweight

During the pre-mating period, reduced bodyweight gain was observed in top dose males (by 18% weeks 0 to 18 and 20% weeks 0 to 10) and top dose females (by 26% weeks 0 to 10). Bodyweight gain of top dose females was lower than in controls throughout gestation (by 50% days 0-7, 30% days 7-14, 20% days 14-20).

Group mean body weight and food intake were slightly lower than the controls in the F1 generation (high dose group, both sexes) for the 4 weeks of this generation, particularly during the last week. The body weight gain of the males over the 4 weeks was statistically significantly lower (↓ 14%).

Reproductive toxicity

There were no treatment-related effects on mating performance, mean duration of gestation or post-implantation survival index.

The mean body weight gain of pups in the treatment groups was slightly lower than in controls, particularly in the high dose group (days 7-21 post-partum), but this was not dose-related or statistically significant.

There were significant reductions in number of pups born at 500 and 1200ppm but no dose-response relationship was evident. A statistically significant dose-related reduction in the mean numbers of implantation sites compared to controls was observed in all treated groups. As this was only a limited study, corpora lutea were not measured. However, at around the time implantation occurs (day 5 of gestation in rats), maternal bodyweight gain was particularly affected. During days 0-7 of gestation, maternal bodyweight gain was lower than controls by 18.2%, 17.6% and 49.7% at the low, mid and high doses, respectively. On this basis, the reduction in implantation sites is considered to be secondary to maternal toxicity. The absence of an adverse effect on any other fertility parameters provides reassurance that the reduction in the number of implantation sites is not a biologically relevant treatment-related adverse effect.

Two generation reproductive study

A 2 generation GLP-compliant rat study is available (OECD 416, 1983).

Method

At 35 days of age, rats (25/sex/group) were first administered 0, 20, 100, or 500 ppm mecoprop (racemic form) via the diet and dosing continued throughout the study period. At least 70 days after the beginning of treatment, the rats were allowed to mate in a 1:1 ratio. Females were allowed to litter and rear their pups (F1a generation pups) to weaning on day 21 after parturition. On day 4 litters were culled to 8 pups/litter preferably with 4 males and 4 females/litter). At least 10 days after the last weaning of the F1a generation pups, the F0 parental animals were mated again in a ratio of 1:1 for the F1b generation and the females were allowed to rear their pups. After the F1b generation had been weaned, the F0 generation was fasted for 16 hours before sacrifice.

After weaning, the F1a pups (25/sex/group) were exposed to 0, 20, 100, or 500 ppm mecoprop (racemic form) via the diet. At least 98 days after formation of the F1 generation parental animals, the males and females were mated at a ratio of 1:1, avoiding mating of siblings. Females were allowed to litter (F2 pups) and at day 4 after parturition, culling to 8 pups/female was carried out. After the F2 pups had been weaned, the F1 generation was fasted for 16 hours before sacrifice.

The intake of racemic mecoprop (mg/kg bw/day) achieved in each generation is shown in Table 14.

Table 14: Test substance intake in the two generation study

	20 ppm	**100 ppm**	**500 ppm**
F0 males	2.0	9.8	49.0
F0 females (premating)	2.1	10.6	52.5
F0 females (F1a litter) - gestation period	1.7	8.7	42.8

- lactation period*	2.9	14.4	72.6
F0 females (F1b litter)			
- gestation period	1.6	8.0	40.0
- lactation period*	2.6	13.2	67.3
F1 males	1.8	9.3	47.3
F1 females (premating)	2.0	10.3	50.7
F1 females (F2 litter)			
- gestation period	1.6	8.5	41.6
- lactation period*	2.5	13.3	67.5

* days 0 - 14 post-partum only

Results

There were no treatment-related differences in mating and fertility indices for F1a and F1b and no treatment-related differences in F1a and F1b pup numbers and status at delivery.

The number of implantation sites and the number of corpora lutea were not determined in this study as this was not required in the 1983 version of the OECD 416 test guideline.

Bodyweight

At the top dose, small, inconsistent but statistically significant reductions in pup bodyweight gain were observed in the F1a group (6%, days 7-14) and in the F2 generation (8-11%, days 4-14).

Organ weights

At the top dose, increased relative kidney weights were observed in the F0 (12% /9% in males/females, respectively) and F1 parental animals (10%/8% in males/females respectively). No treatment-related histopathological findings were observed.

Effects on pups

There were no treatment-related differences in F1a and F1b pup numbers and status at delivery. The number of pups, which died or were cannibalized from day 1 to day 4 post-partum (before culling) was statistically increased in the F1a 500 ppm group ($p<0.01$). Also in the F2 pups, the number of dead pups on day 1 was significantly increased ($p<0.01$) in the 500 ppm group ($p<0.01$).

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

There are two available rat studies which inform on the potential of mecoprop-P to impair sexual function and fertility. The studies are summarised and compared in Table 15.

Table 15: Summary and comparison of reproductive toxicity studies

	Two-generation study	**Preliminary one-generation study**
Dose levels	0, 20, 100, or 500 ppm	0, 500, 800 or 1200 ppm
Age of rats at the start of study	5 weeks	7-9 weeks
Group sizes	35/sex/group	12/sex/group

Test substance	Mecoprop racemate	Mecoprop-P
Effects on fertility	None	↓ mean numbers of implantation sites compared to controls in all treated groups (dose-related, statistically significant) ↓ in number of pups born (statistically significant in the low and high dose groups). No dose-response relationship.
Parental toxicity	Effects on kidney weight	Effects on bodyweight gain (top dose)
Effects on pups	Delayed auditory canal opening in F2 only (top dose)	

In the one generation study (mecoprop-P), parental toxicity consisted of reduced body weight gain at the top dose. The effect was seen in both sexes, but the magnitude was greater in females; throughout the gestation period, body weight gain was reduced by up to 50%. No effect on body weight gain was observed in parental animals in the two generation study.

In the one-generation study, a statistically significant dose-related reduction in the mean numbers of implantation sites compared to controls was observed in all treated groups and there was a decrease in the mean number of pups born. In the two generation study, the number of implantation sites was not determined but in contrast to the one-generation study, the mean number of pups delivered per litter did not vary between each treatment group and generation providing no consistent pattern of response to indicate any association with treatment.

On one hand, the reduced number of implantation sites and mean number of pups born were statistically significant and may be indicative of a treatment-related effect of the test substance on fertility. However, these observations were made in a dose range-finding study with small group sizes. Parental toxicity (evidenced by reduced bodyweight gain) was observed in top dose animals in this study, particularly around the time of implantation. Ultimately, there was no dose-response relationship in the number of pups alive on day 4 and therefore the effects do not appear to be biologically relevant. The observed changes are within, or very close to, the historical control data (HCD) range. However, given that the concurrent control values lie outside the HCD, it is recognised that the HCD are somewhat limited. Reassuringly, there was no effect of treatment on the mean number of pups delivered per litter in the two generation study. Since the group sizes were larger in the two generation study, the probability to detect an effect is greater than in the one generation study, and therefore the absence of a statistical difference in litter size in any of the litters at 500ppm in the two generation study is reassuring.

In repeated dose studies, there were no effects that raised concerns for toxicity to the reproductive system, which adds to the weight of evidence suggesting that classification of mecoprop-P for sexual function and fertility is not warranted.

10.10.3 Comparison with the CLP criteria

In the one generation study, there were reductions in implantation sites and mean number of pups born. However, as discussed in sections 10.10.1 and 10.10.2, the two generation study is considered to be more robust because there was no reduction in litter size at 500ppm in any of the litters produced. When taking both reproduction studies into consideration, there is considered to be no clear evidence of a reproducible mecoprop-P-related adverse effect on sexual function and fertility in rats. Therefore no classification is proposed for this endpoint.

10.10.4 Adverse effects on development

The potential for mecoprop-P to induce developmental toxicity has been investigated in standard studies in rats and rabbits. An additional study, conducted with mecoprop-P in mice is available, which has a number of limitations, compared to a modern guideline compliant study. Additional studies, conducted in rabbits and mice with the mecoprop racemate, are also available. Again, the study in mice is very limited, compared to modern standards.

Table 16: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results and conclusions
Rat, Wistar, 25 females/group Oral (gavage) OECD 414 (1981), GLP The test substance was administered only during organogenesis, whereas the 2001 guideline stipulates administration should be from implantation to scheduled kill. This 1981 study protocol is considered sufficient to determine developmental toxicity. Anonymous (1993a) EU RAR B.6.6.2.1	Mecoprop-P, purity > 92.2%, Batch 91-1 given in a 0.5% carboxymethylcellulose suspension 0, 20, 50, or 100 mg mecoprop-P/kg/day from day 6 to 15 of gestation	**<u>50 mg/kg/d</u>** Food consumption was significantly reduced (by about 9%) from day 6-8 post coitus ($p<0.05$) **<u>100 mg/kg/d</u>** Significant reduction in food consumption from day 6-8 post coitus ($p<0.01$) (by about 22%) Impaired bodyweight of dams at day 8 ($p<0.05$), body weight gain during days 6-15 ($p<0.01$) ↓ 18%, and corrected body weight gain ($p<0.01$) ↓ 20%, Significant increase in the foetal and litter incidence of rudimentary cervical ribs ($p<0.01$) and in number of foetuses and litters with not ossified sternebrae ($p<0.01$). These are considered to be variations and not signs of developmental toxicity. No significant developmental toxicity in this study. NOAEL[a] (foetotoxicity) = 50 mg/kg bw/day NOAEL[a] (maternal toxicity) = 50 mg/kg bw/day
Developmental study Oral, gavage Rabbit, Dutch-Belted, 15-30/ group Anonymous	Mecoprop (racemate) 0, 12, 30 and 75 mg/kg bw/day from day 6 – 18 post insemination	No treatment related maternal effects at any dose level. No treatment-related clinical changes or deaths in the does. No increase in the incidence of foetuses showing major or minor external and visceral or skeletal defects. ↑ postimplantation loss in all treated groups in comparison to vehicle controls (1.1%, 9.2%, 5.2% and 2.6% at 0, 12, 30 and 75 mg/kg bw/day, respectively). ↓ mean number of implantations per doe in the mecoprop-treated groups (7.29,

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results and conclusions**
(1980)		7.00, 6.86 and 7.09 at 0, 12, 30 and 75 mg/kg bw/day, respectively). ↓ number of foetuses per dam (7.21, 6.36, 6.50 and 6.91 at 0, 12, 30 and 75 mg/kg bw/day, respectively) ↓ average litter weight in all treated groups (243.7, 220.7, 208.1 and 226.5g at 0, 12, 30 and 75 mg/kg bw/day, respectively). This reflects the reduced number of foetuses per dam. In the absence of clear dose-response relationships, none of the parameters listed above are considered to show a treatment-related effect indicative of developmental toxicity. NOAEL[a] (maternal) = 75 mg/kg bw/day NOAEL[a] (developmental) = 75 mg/kg bw/day
Preliminary dose range-finding study Rabbit, Himalayan 5/dose Dams were sacrificed on day 20 post insemination. Anonymous (1990b)	0, 40, 80, 120 mg/kg bw/day on days 7 – 19 post insemination Mecoprop-p	Mean late resorptions were 0.2, 2.4, 0.6, 2.5[a] per rabbit at doses of 0, 40, 80, 120 mg/kg bw/day, respectively. Mean live foetuses per dam – 5.8, 3.6, 5.0, 2.0[a] at 0, 40, 80, 120 mg/kg bw/day, respectively. **40 mg/kg bw/d** Marginally reduced food consumption and body weight loss **80 mg/kg bw/d** Overt signs of maternal toxicity (including increased kidney weight and increased creatinine, reduced food consumption and body weight) **120 mg/kg bw/d** 2/5 dams died (1on day 16 and 1 on day 20). These dams showed severe adverse clinical symptoms (like abdominal or lateral position, salivation, no defecation) on the days before death. Another dam did not get pregnant. Overt signs of maternal toxicity (including increased kidney weight and increased creatinine, reduced food consumption and body weight) [a]At the top dose, the 2 dams that died and the non- pregnant dam were not included in the calculations of the mean late resorptions per rabbit or the mean live fetuses per rabbit.
Study of the prenatal toxicity of mecoprop-P Rabbit, Himalayan, 15 females/group OECD 414 (1981) Oral (gavage)	Mecoprop- P (> 92.2% pure) 0, 5, 20, or 50 mg mecoprop-P/kg in 0.5% aqueous carboxymethylcellulose by gavage on	No treatment related maternal effects at any dose level. No dose-related increase in foetal malformations, variations and retardations. No substance-related differences in the number of implantation sites, number of live foetuses, foetal weight and sex ratio **5 mg/kg bw/d** No adverse effects reported. **20 mg/kg bw/d** No adverse effects reported.

<table>
<tr><th>Method, guideline, deviations if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results and conclusions</th></tr>
<tr><td>GLP
Anonymous (1993b)
EU RAR B.6.6.2.2</td><td>days 7-19 post insemination.</td><td><u>50 mg/kg bw/d</u>
Slight, statistically significant (p<0.05) increase in the mean number of late resorptions per rabbit (0.1, 0.0, 0.1, 0.4 at 0, 5, 20 and 50 mg/kg bw/day, respectively) considered not to be toxicologically significant

NOAEL[a] (maternal toxicity) > 50 mg/kg bw/day
NOAEL[a] (foetotoxicity) > 50 mg/kg bw/day</td></tr>
<tr><td>Mice, NMRI, 22-59/group
GLP status not stated
Guideline not stated

Published scientific article

Roll R & Matthiaschk G (1983).

This article was translated from German into English on 16/06/2017.

EU RAR B.6.6.2.3</td><td>0, 100, 200, 300, 400, 500, or 700 mg mecoprop racemate
or
0, 200, 300, 400, or 500 mg mecoprop-P/kg
in arachidis oil by gavage from day 6 to day 15 of gestation. (Quality of test substances not indicated)</td><td>Mecoprop-P
↓ foetal body weight in all treated groups
400mg/kg bw/day
↑ incidence of fused ribs and deformed thoracic vertebral nuclei
500mg/kg bw/day
↓ maternal bodyweight gain (16.7g vs 24.2g in controls)
↑ incidence of early resorptions and post implantation loss
↑ incidence of cleft palate, fused ribs and deformed thoracic vertebral nuclei
<table>
<tr><th>Dose (mg/kg bw)</th><th>0</th><th>200</th><th>300</th><th>400</th><th>500</th></tr>
<tr><td>No of dams</td><td>59</td><td>25</td><td>33</td><td>36</td><td>34</td></tr>
<tr><td>Full term foetuses</td><td>749</td><td>317</td><td>414</td><td>500</td><td>390</td></tr>
<tr><td>Full term foetuses per dam</td><td>12.7</td><td>12.7</td><td>12.5</td><td>13.9</td><td>11.5</td></tr>
<tr><td>Full term foetuses removed</td><td>670</td><td>278</td><td>365</td><td>447</td><td>323</td></tr>
<tr><td>Early resorptions (%)</td><td>8.4</td><td>11.4</td><td>9.4</td><td>7.6</td><td>13.8##</td></tr>
<tr><td>Post implantation loss (%)</td><td>10.6</td><td>12.3</td><td>11.8</td><td>10.6</td><td>17.1#</td></tr>
<tr><td>Foetal weight (g)</td><td>1.17</td><td>1.12</td><td>1.11#</td><td>1.04##</td><td>1.00##</td></tr>
<tr><td>Cleft palate
(number of foetuses)
(%)</td><td>
11
1.6</td><td>
3
1.1</td><td>
3
0.8</td><td>
11
2.5</td><td>
11
3.4#</td></tr>
<tr><td>Fused ribs
(number of foetuses)
(%)</td><td>
-
-</td><td>
-
-</td><td>
4
1.1</td><td>
20
4.5#</td><td>
28
8.7##</td></tr>
<tr><td>Deformed thoracic vertebral nuclei
(number of foetuses)
(%)</td><td>
2
0.3</td><td>
-
-</td><td>
3
0.8</td><td>
18
4.0#</td><td>
23
7.1##</td></tr>
</table>
significant p<0.009, ## significant p<0.0027

Mecoprop
↓ maternal bodyweight gain in all treated groups
↓ foetal body weight in all treated groups
500mg/kg bw/day
↑ incidence of cleft palate
700mg/kg bw/day</td></tr>
</table>

<table>
<tr><th>Method, guideline, deviations if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results and conclusions</th></tr>
<tr><td></td><td></td><td>↑ incidence of early resorptions and post implantation loss
↑ incidence of cleft palate and fused ribs
<table>
<tr><th>Dose (mg/kg bw)</th><th>0</th><th>100</th><th>200</th><th>300</th><th>400</th><th>500</th><th>700</th></tr>
<tr><td>No. of dams</td><td>24</td><td>37</td><td>34</td><td>30</td><td>27</td><td>34</td><td>22</td></tr>
<tr><td>Full term foetuses</td><td>300</td><td>432</td><td>411</td><td>319</td><td>293</td><td>371</td><td>252</td></tr>
<tr><td>Full term foetuses per dam</td><td>12.5</td><td>11.7</td><td>12.1</td><td>10.6</td><td>10.9</td><td>10.9</td><td>11.5</td></tr>
<tr><td>Full term foetuses removed</td><td>266</td><td>388</td><td>367</td><td>284</td><td>262</td><td>338</td><td>178</td></tr>
<tr><td>Early resorptions (%)</td><td>10.7</td><td>8.1</td><td>9.5</td><td>8.5</td><td>8.5</td><td>5.7</td><td>25.4##</td></tr>
<tr><td>Post implantation loss (%)</td><td>11.3</td><td>10.2</td><td>10.7</td><td>11.1</td><td>10.5</td><td>8.9</td><td>29.4##</td></tr>
<tr><td>Foetal weight (g)</td><td>1.17</td><td>1.16</td><td>1.12</td><td>1.09#</td><td>1.06#</td><td>1.03##</td><td>0.82##</td></tr>
<tr><td>Cleft palate
(number of foetuses)
(%)</td><td>
4
1.5</td><td>
8
2.1</td><td>
6
1.6</td><td>
3
1.1</td><td>
5
1.9</td><td>
13
3.8#</td><td>
35
19.7##</td></tr>
<tr><td>Fused ribs
(number of foetuses)
(%)</td><td>
-
-</td><td>
1
0.3</td><td>
-
-</td><td>
-
-</td><td>
3
1.1</td><td>
2
0.6</td><td>
26
14.6##</td></tr>
</table>
significant p<0.009, ## significant p<0.0027

NOAEL[a] (maternal) for both mecoprop and mecoprop-P = 500 mg/kg bw/day
NOAEL[a] (developmental) for both mecoprop and mecoprop-P = 200 mg/kg bw/day</td></tr>
</table>

[a] NOAEL and LOAEL values have been taken from the EU Risk Assessment Report

Rats

Female Wistar rats were exposed to 0, 20, 50 or 100 mg mecoprop-P/kg/day by gavage. Current guidelines (OECD 414, 2001) recommend dosing from implantation to scheduled kill. This study was conducted in accordance with OECD 414 (1981) and therefore animals were dosed on days 6-15 of gestation. However, the study is considered suitable for assessing potential developmental toxicity.

Dams were sacrificed on Gestation Day (GD) 20. At this time, pups were weighed, sexed and externally examined, before they were examined for skeletal or visceral anomalies.

Maternal toxicity

No deaths or clinical signs of toxicity were observed in dams. At the top dose, body weight gain over the dosing period was 18% lower than in control animals.

Findings

The weights of the uterus and placenta were not affected by treatment with mecoprop-P. Weight of the foetuses was slightly ($p<0.05$) reduced (by 2%) in the 100 mg/kg bw/day group. The study director considered this finding was secondary to the increased number of live foetuses in this dose group, but a treatment-related effect cannot be excluded. Dilated renal pelvis and/or hydroureter were reported in all groups without any statistical

significance. The incidences were reported to be within the range of biological variation in the original study report.

At the top dose, the incidence of rudimentary cervical ribs and the incidence of unossified sternebrae increased significantly, as shown in the table below.

Table 17: Results of the developmental toxicity study in rats

Dose (mg/kg bw/day)	**0**	**20**	**50**	**100**
No. of inseminated rats	25	25	25	25
No. of pregnant rats	24	20	23	20
No. of implantations/rat	13.8	14.9	13.8	14.9
No. of live foetuses/rat	12.8	13.8	13.1	13.9
Mean foetal weight (g)	4.0	4.0	4.0	3.9#
Rudimentary cervical ribs – foetal incidence	6 (3.8%)	5 (3.5%)	9 (5.8%)	26## (18%)
Rudimentary cervical ribs – litter incidence	6 (25%)	3 (15%)	6 (26%)	13# (65%)
Sternebrae not ossified – foetal incidence	6 (3.8%)	12 (8.5%)	8 (5.2%)	24## (17%)
Sternebrae not ossified – litter incidence	4 (17%)	9 (45%)	7 (30%)	12## (60%)

 # significant p<0.05, ## significant p<0.01

Relevant developmental effects from the two-generation study in rats

Pup deaths

F1 pups

A statistically significant increase in the number of pups which died or were cannibalized from day 1 to day 4 post-partum was observed at the top dose in the F1a generation, resulting in a significant reduction in the viability index of this group (93% vs 98% in controls). Pup deaths were observed in 11 out of 24 litters. A non-significant but dose-related increase in the sum of dead pups was observed in the F1b generation. Pup deaths were observed across the litters; at the top dose, pup deaths were seen in 11 out of 25 litters.

F2 pups

The number of dead pups on day 0 was statistically significantly increased at the top dose in the F2 generation. An increased number of F2 pups were cannibalised (16 pups) at 20ppm. However, 7 of those 16 pups were cannibalised by a single dam (no. 337). An F1 parental dam exposed to 100ppm racemic mecoprop (no. 358) gave birth to 13 live F2 pups. Notably, this dam did not nurse its pups properly and none of these 13 pups were alive on day 4 postpartum. This dam had particularly low body weight (297.5g on day 21 of lactation, compared to the mean body weight of 321.4g on this day), which suggests that the poor nursing behaviour was secondary to maternal toxicity.

The applicant considered the increased pup death to be caused by poor maternal care because of maternal toxicity. However, the only evidence of maternal toxicity is an increase in kidney weight and therefore this interpretation of the data is not supported. This effect was not observed in the preliminary one-generation study. Although the one-generation study had smaller group sizes, the dose levels were higher than in the two-generation study. Moreover, the two-generation study used the racemic form of mecoprop whereas rats were exposed to mecoprop-P in the one-generation study. Therefore, if increased pup deaths were a true substance-related adverse effect, one would have expected the effect to have been replicated in the one-generation study which evaluated higher doses. The absence of this effect in the one-generation study provides reassurance that the increase in pup deaths is not a specific effect of mecoprop-P. Also the inconsistent pattern of response over the 3 litters indicating normal variation. If the effect was real the pattern of response would not be sporadic.

Development and behaviour

Auditory canal opening was delayed at the top dose in F2 pups only, which could be secondary to reduced bodyweight. The lack of a similar delay in the F1a and F1b litters indicates that this finding is likely incidental to treatment.

Summary of findings in rats

No skeletal or visceral malformations were observed in the developmental study in rats. The only change observed was a significantly increased incidence of rudimentary cervical ribs and sternebrae not ossified at the top dose. These skeletal variations are considered to be treatment-related but such variations are of low concern. We note that such changes are also regarded of low concern by ECETOC (ECETOC Guidance on the Evaluation of Reproductive Toxicity).

The increased pup mortality in the two-generation study was not reproduced in the one-generation study and therefore does not present evidence of a clear reproducible adverse effect on development. The observations of delayed pinna unfolding and auditory canal opening are considered to be developmental delays rather than evidence of reproductive toxicity

Rabbits

Developmental toxicity study in rabbits

In a developmental study conducted in 1980, Dutch-Belted rabbits (15-30/group) were exposed to racemic mecoprop at 0, 12, 30 and 75 mg/kg bw/day from day 6 to 18 post insemination.

No treatment-related clinical changes or deaths were observed in the does.

As summarised in table 16, there was a an increase in postimplantation loss in all treated groups in comparison to vehicle controls. In addition, the mean number of implantations per doe and the number of foetuses per dam were lower than the corresponding values in vehicle controls. This was reflected in a decreased average litter weight in all treated groups. However, no dose-response relationship was evident for any of these observations. Therefore they are ot considered not to be treatment-related effects.

There was no increase in the incidence of external, visceral or skeletal variations and malformations.

This study is considered not to present any evidence of developmental toxicity.

Preliminary dose range-finding study in rabbits

In a preliminary dose range-finding study, 5 rabbits/group were exposed to 0, 40, 80 or 120mg mecoprop-P/kg bw/day on gestation days 7-19 post-insemination. The small group sizes in this study have been noted. Dams were sacrificed on day 20 post insemination, not the usual sacrifice time of 29 days.

Maternal toxicity was reported at all dose levels. 2/5 top dose females died. Slightly reduced food consumption and body weight loss were observed in low dose animals. At the mid and high doses, increased kidney weight, increased creatinine and reduced food consumption were observed.

Mean late resorptions per rabbit were 0.2, 2.4, 0.6 and 2.5 at 0, 40, 80 and 120mg/kg bw/day, respectively. Only two rabbits were included in the calculation at the top dose (of the three rabbits not included in the calculation, two died and the other did not get pregnant). The doses in this study were much higher than in the main rabbit study, yet no dose-response relationship in mean late resorptions was observed. It can be concluded that mean late resorptions in the rabbit were rather variable under the conditions of this study. Importantly, it is noted that this study provides limited information on embryonic/foetal toxicity because the dams were sacrificed on day 20 post insemination, which is much earlier than a standard sacrifice time of day 29.

Resorptions that were classified as 'early' after sacrifice on day 20 may have been classified as 'late' if the sacrifice had been carried out on day 29.

Pre-natal toxicity study of mecoprop-P in rabbits

A study of the prenatal toxicity of mecoprop-P was conducted in Himalayan rabbits (15 females/group) in an OECD TG 414 and GLP-compliant study. Doses of 0, 5, 20 or 50mg mecoprop-P/kg bw in 0.5% aqueous carboxymethylcellulose were administered to the rabbits by gavage on days 7-19 post insemination. Sacrifice was carried out on day 29 post insemination.

Maternal toxicity

Test substance-related effects on food consumption, body weight and bodyweight gain were not observed. At the low dose, one doe died on day 7 post insemination. At the top dose, minor skin lesions in the laryngeal area were observed in 2 dams. Both incidental to treatment.

Reproductive toxicity

No substance-related differences in number of implantation sites, number of live foetuses, foetal weight or sex ratio were observed. There were no dose-related increases in malformations, variations or retardations.

A higher mean percentage of pre-implantation loss was observed at the mid and high doses, although the effect was not statistically significant and incidental to treatment which commenced after implantation. There was a slight, but statistically significant increase in the number of late resorptions at the top dose only, as shown in the table below. The study author considered that the increase in the number of late resorptions at the top dose was not biologically relevant. No dose-dependent response in total numbers of resorptions per rabbit was observed.

In this study, there was a considerable amount of variability in the results. Taking mean post-implantation loss as an example, values ranged from 5.2 to 13.4%, without dose-dependence or statistical significance.

Table 18: Results of the Pre-natal toxicity study in rabbits

Dose (mg/kg bw/day)	**0**	**5**	**20**	**50**
No. of inseminated rabbits	15	15	15	15
No. of pregnant rabbits	15	15	15	14
No. of implantations/rabbit	7.3	7.1	6.8	6.9
Mean pre implantation loss (%)	8.2	9.5	14.7	13.7
Mean post implantation loss (%)	13.4	7.2	5.2	13.1
Mean No. of early resorptions/rabbit (total)	0.7 (11)	0.6 (8)	0.3 (5)	0.6 (9)
Mean No. of late resorptions/rabbit (total)	0.1 (1)	0.0 (0)	0.1 (1)	0.4# (5)
Mean No. of total resorptions/rabbit (total)	0.8 (12)	0.6 (8)	0.4 (6)	1.0 (14)
No. of live foetuses/rabbit	6.9	6.5	6.4	5.9
Mean foetal weight (g)	40.2	40.1	39.5	40.7
No. foetuses with incomplete ossification of sternebrae	28	30	23	30

 # significant p < 0.05

Summary of findings in rabbits

No skeletal or visceral malformations were observed in this study. Although the increased number of *late* resorptions in the rabbit at the top dose was statistically significant, the mean number of *total* resorptions per rabbit at the top dose (1.0) was close to the number in controls (0.8), indicating that the biological relevance

of the increased late resorptions may be questionable. Furthermore, since there was only a minor and non-statistically significant decrease in the number of live foetuses per rabbit at the top dose compared to controls, the increased number of late resorptions is probably a statistical anomaly rather than a toxicologically significant change. Given the large variability in the values of measured parameters in this study, none of the results are considered to present evidence of a significant adverse toxicological effect.

Mice

NMRI mice (22-59/group) were exposed to 0, 100, 200, 300, 400, 500, or 700 mg mecoprop or 0, 200, 300, 400, or 500 mg mecoprop-P/kg in arachidis oil by gavage from day 6 to day 15 of gestation and dams were sacrificed on day 18.

Since this was a published scientific article, GLP-compliance and test guideline were not stated and the findings were reported in little detail. Information on the management of the study animals is very limited. The mean values for a given dose level have been calculated as a foetal based mean (using group totals) and not as a litter based mean. The incidences within individual litters are not available. Therefore it is not possible to independently assess the results of this study.

Mecoprop-P

The extent to which the dams were monitored for clinical signs of toxicity is unclear but appears to be limited. Statistically significant decreased bodyweight gain was observed in dams at the top dose only (24.2, 22.8, 26.6, 27.1 and 16.7g at 0, 200, 300, 400 and 500mg/kg bw/day, respectively).

In mice exposed to mecoprop-P, there were statistically significant increases in the incidences of early resorptions and post implantation loss at the top dose only.

An increased incidence of cleft palate was observed from 400mg/kg bw/day and was significantly higher than controls at the top dose. Given the high incidence of this finding in concurrent controls and the presence of maternal toxicity, the observation of cleft palate does not raise sufficient concern to justify classification for developmental toxicity.

A statistically significant increased incidence of deformed thoracic vertebral nuclei was observed in mice exposed to mecoprop-P at the top two doses only (0.3, 0, 0.8, 4.0 and 7.1% at 0, 200, 300, 400 and 500 mg/kg bw/day, respectively).

A dose-related increased incidence in fused ribs was reported from 300mg mecoprop-P/kg bw/day and was statistically significant at 400 and 500 mg/kg bw/day. At these dose levels, foetal body weight was significantly lower than controls.

Mecoprop racemate

The results of this study show that the toxicity profiles of mecoprop-P and racemic mecoprop are comparable. In dams treated with the mecoprop racemate, there were statistically significant increases in the incidences of early resorptions and post implantation loss at the top dose only.

A significant reduction in foetal weight was observed at doses of 300mg/kg bw/day and above. Significantly increased incidences of cleft palate were observed from 500mg/kg bw/day. However, as described above, the weight of evidence suggests that this finding does not justify classification of mecoprop-P for adverse effects on development.

A significant increase in the incidence of fused ribs was reported at 700mg/kg bw day.

Summary of findings in mice

The effects observed after administration of mecoprop-P and racemic mecoprop were consistent. The majority of effects occurring after exposure of mice to mecoprop-P and racemic mecoprop were observed at the top dose level, at which there was a statistically significant decrease in foetal bodyweight and in maternal bodyweight gain. Due to significant limitations in the design and reporting of the study, the findings do not provide any useful information on the potential of mecoprop-P to adversely affect development. Therefore, this study is not considered further in this report, and is not used to support classification.

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

Developmental toxicity has been well investigated in rats and rabbits.

In rats, an increased incidence of a small number of skeletal variations was observed at the top dose in the developmental study. However, these skeletal variations are of low concern and do not warrant classification for developmental toxicity. These changes are not relevant for a discussion of developmental toxicity of mecoprop-P.

The increased pup mortality in the two-generation study was not reproduced in the one-generation study using higher dose levels and therefore does not present evidence of a clear reproducible adverse effect on development.

Delayed pinna unfolding and auditory canal opening were observed in the two-generation rat study. However, these were retarded development secondary to reduced pup weight, which is not considered to be indicative of developmental toxicity.

The only evidence of developmental toxicity in a standard rabbit study was an increased number of late resorptions at 50mg/kg/day, the highest dose tested. In a preliminary study, rabbits were administered higher doses of up to 120mg/kg/day mecoprop-P. No dose-related increase in late resorptions was observed in this very limited study. However, it is noted that the dams were sacrificed earlier in the preliminary study (day 20 post insemination) than in the standard study (day 29 post insemination). The increased incidence in late resorptions in the standard study is not considered to be biologically relevant and therefore does not justify classification for adverse effects on development.

10.10.6 Comparison with the CLP criteria

There is no information on the developmental toxicity potential of mecoprop-P in humans; therefore category 1A can be excluded.

Category 2 is reserved for substances for which there is some evidence from humans or experimental studies of an adverse effect on development and where the evidence is not sufficiently convincing to place the substance in category 1.

There is no evidence of an effect on development in rats following administration of mecoprop-P, in standard developmental toxicity studies in rats.

Possible evidence for developmental toxicity comes from a standard study in rabbits. In this study an increased number of late resorptions occurred in the absence of maternal toxicity at the top dose only. However, the number of live pups at the top dose was not significantly different from controls, which reduces the concern for developmental toxicity.

Concern is further reduced by the reproductive studies, conducted with mecoprop and mecoprop-P, which presented no reproducible evidence of an adverse effect on litter size.

In repeated dose toxicity studies, the only findings relevant to the discussion on reproductive toxicity are a slight increase in the incidence of benign uterine stromal polyps observed at 65mg/kg bw/day in a 2 year rat study and the observation of cystic corpora lutea in 3/5 dogs administered 19mg mecoprop-P/kg bw/day in a 1 year study. In isolation, these findings are considered not to support classification.

Therefore the available evidence is considered as conclusive but not sufficient for classification of mecoprop-P for adverse effects on development.

10.10.7 Adverse effects on or via lactation

There are no available studies specifically investigating the potential of mecoprop-P to exert effects on or via lactation. The only information available comes from studies in rats: a limited 1-generation study conducted with mecoprop-P and standard 2-generation study, conducted with mecoprop racemate.

Table 19: Summary table of animal studies on effects on or via lactation

<table>
<tr><th>Method, guideline, deviations if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results</th></tr>
<tr><td>2-generation reproduction study in rats
Wistar
25/sex/group
35 days old
OECD 416 (1983)
Anonymous (1992a)

EU RAR B.6.6.1.</td><td>Mecoprop racemate, purity 92.7%, TPH batch

0, 20, 100, or 500 ppm

Continuous dietary administration over 2 generations starting when the F0 generation were 35 days old</td><td>The study is described in detail in section 10.10.1
<table>
<tr><th>Litter type</th><th colspan="4">Total dead pups day 4 (dead day 0 + dead day 1-4)</th></tr>
<tr><td></td><td>0 ppm</td><td>20 ppm</td><td>100 ppm</td><td>500 ppm</td></tr>
<tr><td>F1a</td><td>8 (1+7)</td><td>6 (0+6)</td><td>15 (2+13)</td><td>23 (3+20##)</td></tr>
<tr><td>F1b</td><td>5 (1+4)</td><td>8 (1+7)</td><td>13 (4+9)</td><td>17 (6+11)</td></tr>
<tr><td>F2</td><td>17 (1+16)</td><td>22 (2+20)</td><td>22 (0+22)</td><td>32 (13##+19)</td></tr>
<tr><td></td><td colspan="4">Mean number of pups delivered per litter</td></tr>
<tr><td>F1a</td><td>14.5</td><td>13.1</td><td>14.6</td><td>14.9</td></tr>
<tr><td>F1b</td><td>15.8</td><td>15.0</td><td>15.3</td><td>15.7</td></tr>
<tr><td>F2</td><td>13.0</td><td>11.6</td><td>13.3</td><td>14.9</td></tr>
<tr><td></td><td colspan="4">Mean live pups/ litter Day 0</td></tr>
<tr><td>F1a</td><td>14.0</td><td>12.9</td><td>14.1</td><td>14.1</td></tr>
<tr><td>F1b</td><td>15.4</td><td>14.7</td><td>14.7</td><td>15.2</td></tr>
<tr><td>F2</td><td>12.9</td><td>11.4</td><td>12.9</td><td>14.4</td></tr>
<tr><td></td><td colspan="4">Mean live pups/ litter Day 4 (pre-culling)</td></tr>
<tr><td>F1a</td><td>13.6</td><td>12.6</td><td>13.5</td><td>13.2</td></tr>
<tr><td>F1b</td><td>15.2</td><td>14.3</td><td>14.1</td><td>14.5</td></tr>
<tr><td>F2</td><td>12.2</td><td>10.5</td><td>12.0</td><td>13.1</td></tr>
<tr><td></td><td colspan="4">Viability Index (%)</td></tr>
<tr><td>F1a</td><td>98</td><td>98</td><td>96</td><td>93</td></tr>
<tr><td>F1b</td><td>99</td><td>98</td><td>96</td><td>96</td></tr>
<tr><td>F2</td><td>95</td><td>92</td><td>93</td><td>91</td></tr>
</table>
significance level 0.05, ## significance level 0.01</td></tr>
<tr><td>Preliminary one-generation reproductive toxicity study in the rat
Rats, Han Wistar 12/sex/dose, 7-9 weeks old at the start of the study</td><td>Mecoprop-P, batch 91-1, purity 92.8%

0, 500, 800 or 1200 ppm mecoprop-P
Lactation period: the females were</td><td>The study is described in detail in section 10.10.1
<table>
<tr><th>Dose (ppm)</th><th>0</th><th>500</th><th>800</th><th>1200</th><th rowspan="2">HCD[a] Range</th></tr>
<tr><td>Mg/kg bw/day (females)</td><td>0</td><td>38.2</td><td>60.6</td><td>88.8</td></tr>
<tr><td>Mean pups born</td><td>12.7</td><td>11.2*</td><td>11.7</td><td>10.0**</td><td>9.3-11.1</td></tr>
<tr><td>% pups born compared with control</td><td>N/A</td><td>12%↓</td><td>8%↓</td><td>21%↓</td><td></td></tr>
<tr><td>Mean pups alive day 1</td><td>12.3</td><td>10.7</td><td>11.2</td><td>9.8</td><td></td></tr>
<tr><td>Mean pups alive day 4</td><td>11.1</td><td>9.7</td><td>11.0</td><td>9.0</td><td>9.1-10.8</td></tr>
</table></td></tr>
</table>

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results
Oral (diet) OECD 412 (1983) GLP Anonymous (2003) EU RAR B.6.6.1.2.	given diets containing nominal concentrations of 0, 300, 530 and 790 ppm mecoprop-P	

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

In the two-generation study, a statistically significant increase in the number of pups which died or were cannibalized from day 1 to day 4 post-partum was observed at the top dose in the F1a generation, resulting in a significant reduction in the viability index of this group. A non-significant but dose-related increase in the sum of dead pups was observed in the F1b and F2 generations. It is possible that the pup deaths resulted from effects on or via lactation but there is no clear evidence to support this assertion. With the exception of 2 F1 parental dams (one who cannibalised 7 pups and one who did not nurse her pups properly), there is no evidence indicative of poor maternal care or adverse effects on nursing. The pups may have been in poor health when they were born.

In the preliminary one-generation study, there was no evidence of effects on lactation.

10.10.9 Comparison with the CLP criteria

Classification for effects on or via lactation can be assigned on the basis of:

(a) human evidence indicating a hazard to babies during the lactation period; and/or

(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

No human evidence is available. The results of the one and two generation studies do not provide clear evidence of an adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk. The transfer of mecoprop-P in potentially toxic levels in breast milk is not known. Therefore no classification for effects on or via lactation is warranted.

10.10.10 Conclusion on classification and labelling for reproductive toxicity

No classification is appropriate for sexual function and fertility, development or effects on or via lactation.

No classification: Conclusive but insufficient for classification

10.11 Specific target organ toxicity-single exposure

This endpoint has not been evaluated.

10.12 Specific target organ toxicity-repeated exposure

Repeated dose oral toxicity studies in rats, mice and dogs on both mecoprop-P and racemic mecoprop are available. Studies with mecoprop-P and racemic mecoprop are presented in tables 20 and 26, respectively. One repeated dose dermal toxicity study is available and is summarised in table 20.

Table 20: Summary table of animal studies on STOT RE

Note, guidance values for classification are based on the values in ECHA's Guidance on the Application of the CLP Criteria (Version 5.0 – July 2017). Lifetime studies have been included because they provide information relevant to the assessment of specific target organ toxicity. Only the non-neoplastic findings are reported in this section.

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results**
Oral, Rats, Wistar (10/sex/group) OECD 407 (1981) - The 1981 guideline required the organ weights of the liver, kidney, adrenals and testes only. Deviation – the duration was extended from 28 days to 49 days. Non-GLP Quality Assurance Anonymous (1986a) EU RAR B.6.3.1. *Guidance values for classification* *Cat 1 ≤ 20mg/kg bw day* *20 < Cat 2 ≤ 200mg/kg bw/day*	49 days 0, 50, and 400 ppm mecoprop-P, batch 83/20, purity 99.4% equivalent to 0, 4.4/4.8, 35.2/38.0 mg/kg bw/day in males/females	↑ - increase; ↓ - decrease No observed adverse effects on food consumption, body weight or clinical signs. ***50ppm (4.4/4.8 mg/kg bw/day in males/females, respectively)*** ↑ absolute and relative kidney weight (males only, 5%) ***400ppm (35.2/38.0 mg/kg bw/day in males/females, respectively)*** ↓ cholesterol level (females, significant) in both blood samples (20% and 16% days 23 and 43 respectively) ↓ cholesterol level (males, significant) in the first blood sample (15% day 23) ↑ creatinine (females, significant, 15% day 23 only) ↑ urea (females, significant, 18% at day 23 only) ↑ absolute/relative kidney weight (↑8/10% in both sexes, statistically significant) NOAEL[a] = 50ppm

Rats, SD (15/sex/group) Oral, dietary Pre- GLP Similar to OECD 408 (1998) except relative organ weights were not recorded in the original study report. Deviations – no satellite group for follow-up observation was included, minor deviations with respect to the examination of clinical chemical parameters. No histopathological examination of the eyes due to technical problems. Anonymous (1979a) EU RAR B.6.3.2.1/01 *Cat 1 ≤ 10 mg/kg bw day* *10 < Cat 2 ≤ 100 mg/kg bw/day*	90 days 0, 200, 400, 800, 1600, and 3200 ppm mecoprop-P, batch GD 6720, 100% purity 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 males/females respectively	abs = absolute, rel = relative, m = male, f = female, ↑ - increase; ↓ - decrease No adverse symptoms or behavioural changes. No treatment-related increase in mortality or histopathological changes in any group. ***Doses relevant for classification*** ***200ppm (15.6/18.4 mg/kg bw/day in males/females, respectively)*** ↑ kidney weight (significant, males) (m – abs: ↑ 8%, rel: ↑ 7%; f – abs: ↑ 3%, rel: ↑ 12%) ***400ppm (31.9/37.8 mg/kg bw/day in males/females, respectively)*** ↓ body weight females 2.8% week 13, significant) ↑ kidney weight (significant, males) (m: abs: ↑14%, rel: ↑11%; f: abs: ↑5%, rel: ↑11%) ↑ blood urea nitrogen (15% males week 8; 17% females week 12) ↑ (frequency and degree) of serum alkaline phosphatase and alanine aminotransferase (both sexes) ***800ppm (67.6/75.8 mg/kg bw/day in males/females, respectively)*** ↓ body weight (females 4.4% week 13, significant) ↑ kidney weight (significant, males) (m – abs: ↑ 9%, rel: ↑ 9%; f – abs: ↑ 4%, rel: ↑ 12%) ↑ blood urea nitrogen (females 23% week 12) ↑ (frequency and degree) of serum alkaline phosphatase and alanine aminotransferase (both sexes) ***Doses above the guidance values for classification*** ***1600ppm (146.4/170.1 mg/kg bw/day in males/females, respectively)*** ↓ body weight (significant, ↓16 and 7% in females and males, respectively) ↑ liver weight (females, significant) ↑ relative kidney weight (m - ↑ 8%; f - ↑ 15%) ↑ haemoglobin (males 8% week 8, 3% week 12) ↑ blood urea nitrogen (23/29% m/f week 12) ↑ (frequency and degree) of serum alkaline phosphatase and alanine aminotransferase (both sexes) ↓ cholesterol ***3200ppm (403.2/403.5 mg/kg bw/day in males/females, respectively)*** ↓ body weights (significant, 30%/ 35% less than control animals in females/males, respectively) ↑ liver weight (females, significant) Significant ↓ kidney weight (both sexes, although ↑ *relative* kidney weight) (m – abs: ↓ 29%, rel: ↑ 12%; f – abs: ↓ 11%, rel: ↑ 20%) ↑ haemoglobin (males 8% week 8, 7% week 12) ↑ blood urea nitrogen (39/34% m/f week 12) ↑ (frequency and degree) of serum alkaline phosphatase and alanine aminotransferase (both sexes) ↓ cholesterol NOAEL[a] < 200 ppm

Supplementary 3-month oral toxicity study Rats, SD (10/sex/group) Anonymous (1979b) EU RAR B.6.3.2.1/02 *Cat 1 ≤ 10 mg/kg bw day* *10 < Cat 2 ≤ 100 mg/kg bw/day*	800, 1600, and 3200 ppm mecoprop-P, batch GD 6970, 99.9% purity equivalent to 84.1/117.8, 178.1/239.9, 429.5/539.0 mg/kg bw/day in males/females	↑ - increase; ↓ - decrease The following parameters were recorded: body weight (weekly), food consumption (weekly), clinical observations (daily), ophthalmoscopic examinations (week 0 and 13), and histopathological examinations of the eyes. No increased mortality, abnormal behaviour or ocular lesions. No decrease in food consumption No treatment-related histopathological effects on the eye ***Doses relevant for classification*** ***800ppm (84.1/117.8 mg/kg bw/day in males/females, respectively)*** ↓ 8% body weight in comparison to controls (females, significant) ***Doses above the guidance values for classification*** ***1600ppm (178.1/239.9 mg/kg bw/day) &*** ↓ body weight (significant), ↓ 9% and 7% and in comparison to controls in males and females, respectively. ***3200ppm (429.5/539.0 mg/kg bw/day in males/females, respectively)***) ↓ body weight (significant), ↓ 31% and 20% and in comparison to control in males and females, respectively.

Rat, Han Wistar (52/sex/dose) Oral, diet OECD 451 (1981) GLP Anonymous (2008) EU RAR B.6.5.1.1. *Cat 1 ≤ 1.25 mg/kg bw day* *1.25 < Cat 2 ≤ 12.5 mg/kg bw/day*	2 years 0, 100, 600 or 1200 ppm mecoprop-P (equivalent to 0, 5.3/6.6, 32.0/39.9, 64.6/81.7 mg/kg bw/day in males/females) 2% amorphous silica was added as an anti-caking agent added to all dose groups including control	↑ - increase; ↓ - decrease ***Doses relevant for classification*** ***100ppm (5.3/6.6 mg/kg bw/day in males/females, respectively)*** ↑ relative kidney weight (both sexes: m - ↑ 10%; f - ↑ 51%) with no supporting adverse histopathology ***Doses above the guidance values for classification*** ***600ppm (32.0/39.9 mg/kg bw/day in males/females, respectively)*** ↓ bodyweight (7%, females, most of the study) ↓ efficiency of food utilisation (females) ↑ relative kidney weight (females, ↑ 65%) ↓ incidence of fat recorded within the liver (both sexes) ↑ hepatic peroxisomal β-oxidation (significant in females) ↑ in pigment deposition (liver) in 12/52 females ***1200ppm (64.6/81.7 mg/kg bw/day in males/females, respectively)*** ↓ bodyweight (slight in males during year 1 &↓18% in females throughout study) ↓ food consumption (both sexes, ≤10%) ↓ efficiency of food utilisation (both sexes) ↑ relative weight of liver (f - ↑ 14%) & kidney (m - ↑ 21%; f - ↑ 73%) ↑ incidence of hyalinisation in the liver (37/52 females, 3/52 males; 0/52 controls) ↑ in pigment deposition (within macrophages and centri-lobular hepatocytes) in 42/52 females and 3/52 males (0/52 controls) ↓ incidence of fat within the liver (both sexes) ↑ incidence of hypertrophy of liver cells (14/52 females; 1/52 controls) ↑ hepatic peroxisomal β-oxidation (significant in both sexes) ↓ incidence of chronic progressive nephropathy in kidneys (males) ↑ (slight) in pelvic urolithiasis, mononuclear cell infiltration and vascular extasis of the pelvis (males, minimal severity) ↑ number of findings in female kidney compared to control (intratubular microlithiasis, tubular basophilia/dilatation and vascular ectasia of the renal pelvis) (minimal in extent) ↑ (slight) in mononuclear cell infiltration in the Harderian glands and increased pituitary cysts (both sexes, minimal in severity) ↑ (slight) in vascular extresia of the adrenal gland (graded minimal) in males ↑ (slight) haemosiderin in the spleen, increased dilation of the glandular stomach and increased glandular dilation in the uterus in females (minimal in severity) ↑ (slight) incidence of uterine stromal polyp (benign) in females NOAEL[a] (non-neoplastic findings, males) = 600ppm NOAEL[a] (non-neoplastic findings, females) < 100ppm

Mice, B6C3F1 (10/sex/group) Oral, diet OECD 408 (1981) GLP Anonymous (1993c) EU RAR B.6.3.2.2. *Cat 1 ≤ 10 mg/kg bw day* *10 < Cat 2 ≤ 100 mg/kg bw/day*	3 months 0, 100, 1000, and 2500 ppm mecoprop-P, batch 91-1, 96.5% (equivalent to 0, 20/30, 220/330, 740/930 mg/kg bw/day in males/females)	↑ - increase; ↓ - decrease ***Doses relevant for classification*** ***100ppm (20/30 mg/kg bw/day in males/females, respectively)*** ↑ urea (females only, ↑ 22%) ↓ triglycerides (females only, ↓ 44%) ***Doses above the guidance values for classification*** ***1000ppm (220/330 mg/kg bw/day in males/females, respectively)*** ↓ bodyweight (both sexes, significant, ↓ 8% in males, ↓ 9% in females) ↑ urea (both sexes, 15% in males and 23% in females) ↓ triglycerides (both sexes, 28% in males and 44% in females) ↑ creatinine (males only, 17%) ↓ lipid storage in the liver (both sexes) ***2500ppm (740/930 mg/kg bw/day in males/females, respectively)*** ↓ bodyweight (both sexes, significant, ↓ 10% in males, ↓ 9% in females) ↑ liver weight (both sexes, significant, ↑ 35% in males; ↑ 50% in females) ↓ kidney weight (males, significant, ↓18%) ↓ adrenal glands weight (females, significant, ↓ 20%) ↑ alkaline phosphatase, urea (20% in males, 37% in females), cholesterol and cyanide-insensitive palmitoyl-CoA-oxidation in liver homogenate (both sexes) ↓ triglycerides (both sexes, 34% in males and 59% in females) ↑ creatinine (21%) and glucose (males only) ↑ alanine aminotransferase (females only) ↓ haemoglobin (↓ 4%), mean corpuscular haemoglobin (↓ 2%) and globulins (↓ 12.7%) (males only) Dark-brown discoloration of the liver and decrease of lipid storage (both sexes) Eosinophilic cytoplasm of tubular epithelial cells in the kidney (both sexes) NOAEL[a] (males) = 100ppm NOAEL[a] for females could not be established

Mouse, B6C3F1 (50/sex/group) OECD 451 (1981) Deviation: Animals in the top dose group were sacrificed after 12 months due to severely reduced body weight gain. GLP Anonymous (1996) EU RAR B.6.5.2/01 *Cat 1 ≤ 1.67 mg/kg bw day* *1.67 < Cat 2 ≤ 16.7 mg/kg bw/day*	18 months Mecoprop-P, batch 91-1, purity 92.7% 0, 25, 250, and 2500 ppm Equivalent to 0/0, 4/4, 40/46 and 592/732 mg/kg bw/day in males/females, respectively.	↑ - increase; ↓ - decrease ***Doses relevant for classification*** ***25ppm (4/4 mg/kg bw/day in males/females, respectively)*** ↑ relative kidney weight compared to controls (↑ 10%/4% in males/ females, respectively) ↓ relative adrenal weight compared to controls (males, ↓ 21%) ***Doses above the guidance values for classification*** ***250ppm (40/46 mg/kg bw/day in males/females, respectively)*** ↑ relative kidney weight compared to controls (↑ 18%/20% in males/ females, respectively) ↓ relative adrenal weight compared to controls (males, ↓ 16%) ↑ incidence of chronic nephropathy in females (27 animals vs 13 in controls) ↑ incidence of small foci of amorphous basophilic or black foci in the kidney, diagnosed as calcification in females (26 animals vs 13 controls) ***2500ppm (592/732 mg/kg bw/day in males/females, respectively)*** Body weight gain was severely affected (statistically significant from day 7 in males and day 2 in females) ↓ bodyweight (both sexes) Animals were sacrificed after 12 months due to severely reduced bodyweight gain. NOAEL[a] (non-neoplastic findings, males) > 250ppm NOAEL[a] (non-neoplastic findings, females) = 25ppm
Supplementary study to the original mouse carcinogenicity study Mice, B6C3F1 (50/sex/group) Oral, GLP OECD 451 (1981) Deviation: Only one treated dose group Anonymous (1999) EU RAR B.6.5.2/02 *Cat 1 ≤ 1.67 mg/kg bw day* *1.67 < Cat 2 ≤ 16.7 mg/kg bw/day*	18 months, Mecoprop-P, batch 91-1, purity 92.7% 0 ppm or 700 ppm (males) or 800 ppm (females) Equivalent to 0 and 112mg/kg bw/ day in males and 0 and 188 mg/kg bw /day in females	↑ - increase; ↓ - decrease ***Doses above the guidance values for classification*** ***Males (112 mg/kg bw/day)/ Females (188 mg/kg bw/day)*** Impaired bodyweights (statistically significant) from 11 months in males and 7 months in females. Final bodyweight ↓ 4.9% in males and ↓ 10.2% in females compared to controls. ↑ (significant) relative weight of liver (m: ↑ 12%, f: ↑ 14%), kidney (↑ 5%, males) and brain (m: ↑ 5%, f: ↑ 10%). ↑ kidney weight (significant, females, ↑ 15% absolute and ↑ 26% relative) ↑ testis weight (significant, males, ↑ 5% absolute and 10% relative) In treated animals, there were ↑ incidences of: - macroscopically observable masses in the liver (15 males vs 8 controls, 9 females vs 0 controls) - chronic nephropathy (50 males vs 38 controls, 38 females vs 8 controls) - calcification in kidney (48 males vs 25 controls, 13 females vs 0 controls) - basophilic foci of cellular alteration in the liver (11 males vs 4 controls, 4 females vs 0 controls) ↓ incidence of lipid vacuoles in the kidney (0 males vs 48 in controls) NOAEL[a] (non-neoplastic findings, males) < 700 ppm NOAEL[a] (non-neoplastic findings, females) < 800 ppm

Dog, beagle (5/sex/dose) Oral, diet OECD 452 (1981), GLP The study meets the requirements of OECD 452 (2009) except that the spleen and heart were not weighed. Anonymous (1997b) EU RAR B.6.3.3.1. *Cat 1 ≤ 2.5 mg/kg bw day* *2.5 < Cat 2 ≤ 25 mg/kg bw/day*	1 year Mecoprop-P (89.9 % pure, technical grade) 0, 60, 180 and 600 ppm (corresponding to daily doses of 0, 2, 5, 19 mg mecoprop-P/kg body weight/day)	↑ - increase; ↓ - decrease ***Doses relevant for classification*** ***60ppm (2 mg/kg bw/day)*** ↓ absolute and relative liver weight (males only) Slight focal atrophy of the prostate gland in one male ***180ppm (5 mg/kg bw/day)*** ↓ absolute brain weight (females only) Slight focal atrophy of the prostate gland in one male ***600ppm (19 mg/kg bw/day)*** ↓ bodyweight and bodyweight gain (males only) ↓ inorganic phosphate and calcium on day 90 (females only) Slight focal tubular degeneration of the kidneys (unilateral) in one male Slight focal atrophy of the prostate gland in one male Cystic corpora lutea (3/5 females) Oedema in the interstitium of the mammary gland (1 female) NOAEL[a] = 5 mg/kg bw/day
Rabbit, New Zealand White (5/sex/group) Dermal, occlusive OCED 410 (1981) GLP Anonymous (1993d) EU RAR B.6.3.3. *Cat 1 ≤ 60 mg/kg bw day* *60 < Cat 2 ≤ 600 mg/kg bw/day*	21 days Mecoprop-P, purity 92.6%, Batch 91-1 0, 10, 100, or 1000 mg/kg bw/day Covered for 6 hours/day	↑ - increase; ↓ - decrease ***Doses relevant for classification*** ***10 mg/kg bw/day*** Slight erythema (days 3 – 20) in 7 animals ↓ blood level of urea (females, significant, ↓22%) ↓ cholesterol (females, non-significant, ↓27%) ***100 mg/kg bw/day*** ↓ spleen weights (females, significant) Well-defined erythema & slight or well defined oedema in 7 animals after day 8 Diffuse acanthosis in 2 animals ↓ blood level of urea (females, significant, ↓15%) ↓ cholesterol (females, significant, ↓46%) ***Doses above the guidance values for classification*** ***1000 mg/kg bw/day*** ↓ spleen weights (females, significant) Slight erythema at day 2 progressing to day 8 to well-defined erythema with slight or well defined oedema (8 animals) Well-defined erythema and moderate oedema in 1 animal. Desquamation (sloughing) of the stratum corneum in the majority of the rabbits Diffuse acanthosis in 6 animals. ↓ blood level of urea (females, significant, ↓22%) ↓ cholesterol (females, significant, ↓41%) NOAEL[a] (systemic effects) = 1000mg/kg bw/day NOAEL[a] for dermal irritation could not be established.

[a] NOAELs have been taken from the EU Risk Assessment Report

Oral

Studies in rats

49 days

Wistar rats (10/sex/group) were exposed to 0, 50, and 400 ppm mecoprop-P (99.4% purity) equivalent to 0, 4.4/4.8, 35.2/38.0 mg/kg bw/day in males/females in the diet. All dose levels in this study are relevant for classification.
The initial study duration (21 days) was extended to 49 days after an increased level of creatinine was observed at day 23 in animals exposed to 400ppm mecoprop-P. The study was conducted in accordance with OECD 407 and was subject to quality assurance.

No deaths were observed during the study period. There were no substance-related effects on food consumption, bodyweight or clinical signs in treated animals.

There was an increase in absolute kidney weight at 50 ppm (males only, 5%) and 400 ppm (8% in both sexes, statistically significant). Significant decreases in cholesterol levels were observed in both sexes at 400ppm. At the same dose, there was a significant increase in creatinine and urea values in females and in glutamic-pyruvic transaminase (alanine aminotransferase) in males.

The results indicate that the kidney is a target organ of mecoprop-P, although the observed changes were not accompanied by adverse histopathological effects and are therefore considered not to warrant classification.

90 days

One standard 90 day toxicity study and a supplementary study in rats are available.

In a 90 day study (similar to OECD 408 (1998)), SD rats (15/sex/group) were administered 0, 200, 400, 800, 1600, and 3200 ppm mecoprop-P, (100% purity) equivalent to 0, 15.6/18.4, 31.9/37.8, 67.6/75.8, 146/170, 403/404 mg/kg bw/day in males/females, respectively. In this study, dose levels up to and including 800ppm are relevant for classification.

Due to technical problems, histopathological examination of the eyes was not performed. This was addressed in the supplementary study.

In this study, no adverse clinical signs or behavioural changes were observed. There was no treatment-related increase in mortality and no treatment-related histopathological changes in any organ including the kidneys.

Bodyweight was significantly reduced in females from 400 ppm and in males from 1600 ppm.

A significant increase in kidney weight was observed in males at 200, 400, 800 ppm and 3200 ppm and in females at 3200 ppm. A significant increase in liver weight was observed in females only at 1600 and 3200 ppm.

Increases (with respect to frequency and degree) of blood urea nitrogen, serum alkaline phosphatase and alanine aminotransferase were observed in both sexes from 400ppm. Decreases in cholesterol were observed from 1600ppm. At high dose levels (1600 and 3200 ppm) small increases in haemoglobin were recorded.

Under the conditions of this study, the liver and kidneys were the target organs of mecoprop-P-induced toxicity in rats. It is noted that there were no supporting histopathological findings for the weight increases in these organs and therefore the evidence from this study is conclusive but not sufficient for classification.

Supplementary 3 month oral toxicity study

A supplementary study was conducted because there was no histopathological examination of the eyes in the original 3 month study described above. SD rats (10/sex/group) were exposed to up to 3200 ppm mecoprop-P (99.9% purity) equivalent to 430/539 mg/kg bw/day in males/females in the diet.

The only adverse effect in this study was a reduction in bodyweight of animals treated with mecoprop or mecoprop-P. No adverse effects on the eyes were observed. No other organs were investigated. The results from this study do not affect the conclusions of the main study.

2 years

One chronic toxicity study in rats is available.

Mecoprop-P was administered to Wistar rats (52/sex/dose) in the diet for 2 years at doses of 0, 100, 600 or 1200 ppm (equivalent to 0, 5.3/6.6, 32.0/39.9, 64.6/81.7 mg/kg bw/day in males/females) in accordance with OECD 451.

Reduced survival was reported in both sexes at the low dose only. Survival rate was at least 80% and 70% in males and females, respectively in the control, mid and high dose groups. At the low dose, survival rates were 69 and 58% in males and females, respectively.

There were more males at the top dose with dermal or subcutaneous masses than in the control or intermediate dose groups.

Reduced bodyweight was observed in females at the 600 ppm and in both sexes at 1200 ppm. A decrease in food consumption (up to 10%) and efficiency of food utilisation was also observed in both sexes at the top dose and a decrease in food utilisation was also observed in females at the mid dose.

An increase in relative kidney weight was observed in both sexes at 100 and 1200 ppm and in females only at the 600 ppm level. As shown in the table below, various adverse effects on the kidney were observed at the top dose, including a slight increase in pelvic urolithiasis, mononuclear cell infiltration and vascular extasis of the pelvis in males. In addition there was an increased number of minor findings in the female kidney compared to control (intratubular microlithiasis, tubular basophilia/dilatation and vascular ectasia of the renal pelvis). The decreased incidence of chronic progressive nephropathy in males is considered not to be an adverse effect.

Table 21: Kidney findings in a 2 year chronic toxicity study in rats

	Males				**Females**			
Dose (ppm)	**0**	**100**	**600**	**1200**	**0**	**100**	**600**	**1200**
Dose (mg/kg bw/day)	**0**	**5.3**	**32.0**	**64.6**	**0**	**6.6**	**39.9**	**81.7**
Chronic progressive nephropathy	10/52	4/18	1/11	1/52	5/52	3/23	1/13	4/52
Kidney pelvic urolithiasis	10/52	6/18	2/11	17/52	37/52	9/23	10/13	40/52
Kidney tubular basophilia	1/52	1/18	0/11	1/52	0/52	1/23	1/13	5/52
Kidney tubular dilation	1/52	0/18	0/11	1/52	0/52	1/23	1/13	6/52
Kidney interstitial mononuclear cell infiltration	11/52	1/18	2/11	19/52	8/52	3/23	0/13	5/52
Kidney pelvis vascular ectasia	0/52	0/18	0/11	1/52	1/52	0/23	0/13	13/52

A decreased incidence of fat within the liver was reported in both sexes at the mid and high doses. Significantly increased hepatic peroxisomal β-oxidation was observed in females at the mid dose and in both sexes at the top dose. Other adverse effects on the liver at the top dose were an increase in relative liver weight (females, 14%), hyalinization (predominantly in the centri-lobular regions), hypertrophy of liver cells and an increase in pigment deposition (within macrophages and centri-lobular hepatocytes), as shown in Table 22.

Table 22: Liver findings in a 2 year chronic toxicity study in rats

	Males				Females			
Dose (ppm)	**0**	**100**	**600**	**1200**	**0**	**100**	**600**	**1200**
Dose (mg/kg bw/day)	**0**	**5.3**	**32.0**	**64.6**	**0**	**6.6**	**39.9**	**81.7**
Liver centrilobular hepatocyte hyalinisation	0/52	0/52	0/52	3/52	0/52	0/52	0/52	37/52
Liver increased pigmentation	0/52	0/52	0/52	3/52	8/52	8/52	12/52	42/52
Hepatocyte fat vacuolation	23/52	26/52	11/52	5/52	22/52	23/52	11/52	13/52
Hepatocyte hypertrophy	0/52	0/52	0/52	0/52	1/52	3/52	3/52	14/52

At the top dose, there were also slight increases in mononuclear cell infiltration in the Harderian glands and increased pituitary cysts (both sexes), vascular extresia of the adrenal gland (graded minimal) in males, haemosiderin in the spleen, increased dilation of the glandular stomach, increased glandular dilation in the uterus in females and increased incidence of uterine stromal polyp (benign) in females, as shown below.

Table 23: Results of the 2 year chronic toxicity study in rats

	Males				Females			
Dose ppm	**0**	**100**	**600**	**1200**	**0**	**100**	**600**	**1200**
Dose Mg/kg bw/day	**0**	**5.3**	**32.0**	**64.6**	**0**	**6.6**	**39.9**	**81.7**
Adrenal gland vascular ectasia	2/34	5/19	4/13	9/52	35/52	17/24	12/17	26/52
Harderian gland mononuclear cell infiltration	8/52	2/15	1/10	14/52	9/52	5/23	2/10	14/52
Pituitary cysts	8/52	1/20	3/17	13/52	3/52	4/33	3/31	9/52
Spleen increased haemosiderin	2/52	1/20	0/10	2/52	4/52	5/23	6/14	9/52
Stomach glandular dilation	0/52	0/18	0/10	3/52	4/52	1/22	0/11	7/52
Thymus epithelial cysts	9/43	1/11	2/9	10/42	3/49	3/22	2/14	6/46
Uterus glandular dilation	-	-	-	-	12/52	9/24	4/15	19/52
Uterus stromal polyp (Benign)	-	-	-	-	1/52	0/24	2/15	4/52

In this study, the liver and kidneys were targets of mecoprop-P-induced toxicity. The extent of the findings in other organs was minimal and the incidences increased only slightly in comparison to controls and are therefore not considered to present a cause for concern.

In this study, the only dose level relevant for classification is 100ppm. At 100ppm, an increase in relative kidney weight was observed in both sexes. but there was no supporting histopathology and no evidence that this effect is adverse. Abnormally high white cell counts were also observed at this dose level. However, in isolation, they are not indicative of a specific target organ effect.

Studies in mice

90 days

B6C3F1 mice (10/sex/group) were exposed to 0, 100, 1000, and 2500 ppm mecoprop-P, 96.5% (equivalent to 0, 20/30, 220/330, 740/930 mg/kg bw/day in males/females) in the diet for 3 months in accordance with OECD 408. The only dose level relevant for classification is 100ppm.

A significant reduction in bodyweight was observed in both sexes at the mid and high doses.

A significant reduction in kidney weight was observed in males only at the top dose. An increase in urea was observed in females only at the low dose and in both sexes at the mid and high doses. Levels of creatinine increased in males only at the mid and top doses. Eosinophilic cytoplasm of tubular epithelial cells in the kidney was observed in both sexes at the top dose.

In both sexes at the top dose, there was dark brown discolouration of the liver and a significant increase in liver weight was observed in both sexes at the top dose. At the mid and top doses, lipid storage in the liver was reduced in both sexes.

A decrease in triglycerides was observed in females only at the low dose and in both sexes at the mid and high doses.
There were no haematological findings of toxicological significance in this study.

Like in rats, the liver and kidneys were the targets of mecoprop-P-induced toxicity in mice under the conditions of this study. However, at doses relevant for classification (100ppm), the only observations were changes in urea and triglyceride levels in females. Isolated changes in clinical chemistry parameters do not support classification for STOT-RE.

18 months

B6C3F1 mice (50/sex/dose) were exposed to 0, 25, 250, and 2500 ppm mecoprop-P of 92.7% purity in the diet for 18 months in accordance with OECD 451.

Bodyweight gain was severely affected at the top dose, becoming statistically significant from day 7 in males and from day 2 in females and bodyweight was decreased in both sexes at this dose level. On day 343, bodyweights of top dose males and females were 27 and 37% lower than controls and bodyweight gain was 58 and 71% lower in top dose males and females, respectively, in comparison to controls. Due to the severely reduced bodyweight gain, top dose animals were sacrificed after 12 months and there was no further examination of these animals. In animals that were treated for 18 months, the mortality rates were comparable to controls.

An increase in relative kidney weight compared to controls was observed in the low (10%/4% in males/ females, respectively) and mid (18%/20% in males/ females, respectively) dose groups. There was a reduction in relative adrenal gland weight compared to controls in males only at the low and mid dose groups (by 21% and 16%, respectively. In females in the mid dose group, there were also increased incidences of chronic nephropathy (27 vs 13 in controls) and small foci of amorphous basophilic or black foci, diagnosed as calcification (26 vs 13 in controls).

In this study, the kidney was the target organ of toxicity. However, the only dose level relevant for classification was 25ppm. At this dose level, the only observations were a small increase in relative kidney weight and a decrease in relative adrenal weight. In isolation, small changes in organ weight are insufficient for classification.

Supplementary study – Chronic toxicity in the mouse

Due to the loss of the top dose group in the original mouse carcinogenicity study, a supplementary study was conducted. All dose levels in this supplementary study were above the guidance values for classification.

B6C3F1 mice (50/sex/group) were exposed to 0 ppm or 700 ppm (males) or 800 ppm (females) mecoprop-P of 92.7% purity (equivalent to 0 mg/kg and 112 mg/kg bw/day (males) and 188 mg/kg bw/day (females) in the diet for 18 months in accordance with OCED 451.

There were 2 deaths in each of the following groups: male controls, female controls and treated males. Six treated females died. Therefore this study is considered acceptable to assess the chronic toxicity of mecoprop-P in mice.

Statistically significant reductions in bodyweight were observed in treated males from 11 months and in females from 7 months.

Statistically significant increase in relative weights of the liver, kidney and brain were observed in treated males and females as shown in Table 24.

Table 24: Organ weight changes in mice

	Male mice - organ weight as % of terminal body weight		Female mice - organ weight as % of terminal body weight	
	0ppm	700ppm	0ppm	800ppm
Absolute liver weight (g)	1.394	1.487	1.277	1.319
Relative liver weight (%)	3.768	4.228** (12%↑)	4.13	4.698** (14%↑)
Absolute kidney weight (g)	0.719	0.717	0.485	0.559** (15%↑)
Relative kidney weight (%)	1.941	2.032* (5%↑)	1.575	1.991** (26%↑)
Absolute brain weight (g)	0.490	0.490	0.507	0.507
Relative brain weight (%)	1.327	1.398* (5%↑)	1.659	1.818** (10%↑)

Increased incidences of chronic nephropathy and calcification in the kidney were observed in both sexes. Chronic nephropathy was characterised by areas of tubular atrophy, regeneration and dilatation, proteinaceous casts inside the tubules and/or interstitial fibrosis. Calcification in the kidney was graded as minimal or slight and was the term used to describe focal calcification of the renal tubules, the arterial wall, the interstitial tissue and/or along the tubular basement membranes. In treated males, there was a reduction in lipid vacuoles in the kidney in comparison to controls, as shown in the table below.

Table 25: Kidney findings in the kidney

	Males		Females	
	0ppm	700ppm	0ppm	800ppm
Chronic nephropathy	38	50	8	38
Calcification in kidney	25	48	0	13
Kidney: Lipid vacuoles	48	0	0	0

In the liver, there was an increased incidence of microscopically observable masses in both sexes. Some of these masses were identified as basophilic foci of cellular alteration in treated males (11 vs 4 in controls) and females (4 vs 0 in controls).

This chronic study in mice is consistent with the findings from the subchronic mouse study and with the findings in rats. Again, the liver and kidneys were target organs of toxicity. However, the dose levels in this study were above the guidance values for classification and are therefore not relevant to the discussion on classification.

Studies in dogs

One repeated dose toxicity study in dogs is available.

1 year

Beagle dogs (5/sex/dose) were exposed to mecoprop-P (89.9 % pure, technical grade), at dose levels of 0, 60, 180 and 600 ppm (equivalent to 0, 2, 5, 19 mg/kg body weight/day) for 1 year in accordance with OECD 452. All dose levels in this study are relevant for classification.

A few and incidentally occurring cases of diarrhoea and vomiting were reported in this study.

A decrease in bodyweight and bodyweight gain was observed in males at the top dose only. In males there was a decrease in absolute and relative liver weights at the low dose only. At the mid dose, a decrease in absolute brain weight was observed in females.

Slight unilateral focal tubular degeneration of the kidneys was observed in one high dose male.

There were no toxicologically significant haematological findings.

Slight focal atrophy of the prostate gland was observed in one male in each of the low, mid and high dose groups. In the absence of a dose-response relationship, this observation does not raise concern as a treatment-related effect. At the top dose, cystic corpora lutea were observed in 3 females and oedema in the interstitium

of the mammary gland was reported in 1 female.

None of the findings in this study are indicative of severe target organ toxicity and therefore the results of this study are considered to be conclusive but not sufficient for classification.

Dermal

One repeated dose dermal toxicity study in rabbits is available.

New Zealand White rabbits (5/sex/group) were dermally exposed to mecoprop–P for 21 days (males) or 22 days (females) at doses of 0, 10, 100, or 1000 mg/kg bw/day in accordance with OECD 410. The test site was covered with an occlusive dressing for 6 hours per day.

In this study, local effects were observed following dermal administration of mecoprop-P. There were no mortalities or effects on bodyweight The only potential systemic effects were a significant reduction in spleen weight in females at the mid and top dose levels, significant reductions in blood levels of urea in females at all dose levels and reductions in cholesterol levels in females at the mid and high doses.

Diffuse acanthosis was observed in 2 and 6 animals at the mid and top doses, respectively. At the low dose, slight erythema was observed from day 3-20 in 7 animals. At the mid dose, well-defined erythema and slight or well defined oedema was observed in 7 animals after day 8. At the top dose, slight erythema was observed at day 2 progressing to well-defined erythema with slight or well defined oedema in 8 animals on day 8. Well-defined erythema and moderate oedema was observed in 1 animal. Desquamination (sloughing) of the stratum corneum was observed in the majority of rabbits.

In this study, local effects were observed following dermal administration of mecoprop-P.

Inhalation

No repeated dose inhalation studies on mecoprop-P are available.

Human information

No human data are available.

Summary and discussion of repeated dose toxicity of mecoprop-P

Oral

The available repeated dose studies show that the liver and kidneys are target organs of toxicity following exposure to sufficiently high doses of mecoprop-P.

However, at dose levels relevant for classification, treatment-related effects were limited to small changes in bodyweight, small changes in clinical chemistry parameters and organ weight changes without supporting adverse histopathological effects. Therefore the repeated dose studies are not considered to present a cause for concern for specific target organ toxicity when test species are exposed to mecoprop-P at dose levels relevant for classification.

Dermal

One repeated dose dermal toxicity study is available. In this study, local effects were observed in animals following exposure to mecoprop-P. Since no systemic toxicity was observed, classification for specific target organ toxicity is not warranted.

Inhalation

No repeated dose inhalation studies are available.

Mecoprop (racemate)

Six additional oral repeated dose toxicity studies, in which rats and dogs were exposed to the mecoprop racemate, are also available and are summarised below. The studies on the racemate are included to illustrate that the repeated dose toxicity profiles of mecoprop-P and mecoprop racemate are comparable. This perspective was developed some time ago and underpins the assessment of reproductive toxicity, for which there is a 2 generation study on the racemate and a non-standard one-generation study on mecoprop-P.

Table 26: Summary of repeated dose toxicity studies on mecoprop (racemate)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results**
Oral, Rats, Wistar (10/sex/group) OECD 407 (1981) - The 1981 guideline required the organ weights of the liver, kidney, adrenals and testes only. Deviation – the duration was extended from 28 days to 49 days. Non-GLP Quality Assurance Anonymous (1986a) EU RAR B.6.3.1. *Guidance values for classification* *Cat 1 ≤ 20mg/kg bw day* *20 < Cat 2 ≤ 200mg/kg bw/day*	49 days 0, 50, and 400 ppm mecoprop racemate, batch 83/47, purity 92.7% equivalent to 0, 4.4/4.8, 35.1/37.5 mg/kg bw/day in males/females	↑ - increase; ↓ - decrease No observed adverse effects on food consumption, body weight or clinical signs. ***Doses relevant for classification*** ***50ppm (4.4/4.8 mg/kg bw/day in males/females, respectively)*** ↑ absolute kidney weight (males only, ↑6%) ***400ppm (35.1/37.5 mg/kg bw/day in males/females, respectively)*** ↓ cholesterol level (females, significant) in both blood samples (days 23 and 43) ↓ calcium concentration (females, significant) in blood sample from day 43 ↑ urea concentration (males, day 43 only). ↑ glutamic-pyruvic transaminase (alanine aminotransferase) (males, significant) ↑ absolute kidney weight (both sexes, ↑7% in males and ↑2% in females) NOAEL[a] = 50ppm
Rats, SD (15/sex/group) Oral, dietary Pre- GLP, Similar to OECD 408 (1998) except relative organ weights were not recorded in the original study report. Deviations – no satellite group for follow-up observation was included, minor deviations with respect to the examination of clinical chemical parameters. No histopathological examination of the eyes due to technical problems. Anonymous (1979a) EU RAR B.6.3.2.1/01 *Cat 1 ≤ 10 mg/kg bw day* *10 < Cat 2 ≤ 100 mg/kg bw/day*	90 days 0, 200, 800, and 3200 ppm mecoprop racemate, batch GD 6849, 93% purity equivalent to 0, 16.5/18.2, 67.9/75.9, 390.8/398.7 mg/kg bw/day in males/females respectively	abs = absolute, rel = relative, m = male, f = female, ↑ - increase; ↓ - decrease No adverse symptoms or behavioural changes. No treatment-related increase in mortality or histopathological changes in any group. ***Doses relevant for classification*** ***200ppm (16.5/18.2 mg/kg bw/day in males/females, respectively)*** ↑ kidney weights compared to control (m – abs: ↑9%, rel: ↑9%; f – abs: ↑9%, rel: ↑12%) ***800ppm (67.9/75.9 mg/kg bw/day in males/females, respectively)*** ↓ body weight (females, significant) ↑ kidney weight compared to control (m: abs: ↑11%, rel: ↑12%; f: abs: ↑4%, rel: ↑11%) ↑ (frequency and degree) of blood urea nitrogen, serum alkaline phosphatase and alanine aminotransferase (both sexes) ***Doses above the guidance values for classification*** ***3200ppm (390.8/398.7 mg/kg bw/day in males/females, respectively)*** ↓ body weights (significant, 30%/ 35% less than control animals in females/males, respectively) ↑ liver weight (females, significant) ↓ kidney weight (significant, although ↑ relative kidney weight) (m – abs: ↓ 29%, rel: ↑ 11%; f – abs: ↓ 16%, rel: ↑ 17%) ↑ (frequency and degree) of blood urea nitrogen, serum alkaline phosphatase and alanine aminotransferase (both sexes) NOAEL[a] < 200 ppm

Supplementary 3-month oral toxicity study Rats, SD (10/sex/group) Anonymous (1979b) EU RAR B.6.3.2.1/02 *Cat 1 ≤ 10 mg/kg bw day* *10 < Cat 2 ≤ 100 mg/kg bw/day*	0, 800, and 3200 ppm Mecoprop racemate (93% purity) equivalent to 0, 81.7/121.1 and 452.5/537.1 mg/kg bw/day in males/females, respectively.	↑ - increase; ↓ - decrease The following parameters were recorded: body weight (weekly), food consumption (weekly), clinical observations (daily), ophthalmoscopic examinations (week 0 and 13), and histopathological examinations of the eyes. No increased mortality, abnormal behaviour or ocular lesions. No decrease in food consumption No treatment-related histopathological effects on the eye ***Doses relevant for classification*** ***800ppm (84.1/117.8 mg/kg bw/day in males/females, respectively)*** ↓ body weight (females, ↓8.3%, significant) ***Doses above the guidance values for classification*** ***3200ppm (429.5/539.0 mg/kg bw/day in males/females, respectively)*** ↓ body weight (↓37.8% in males, ↓ 20.3% both sexes, significant)
Rats, Wistar (15/sex/group) Oral, dietary OECD 408 (1981) 3 months Non-GLP Quality Assurance Anonymous (1985) EU RAR B.6.3.2.1/03 *Cat 1 ≤ 10 mg/kg bw day* *10 < Cat 2 ≤ 100mg/kg bw/day*	0, 50, 150 or 450 ppm mecoprop racemate (purity, 92.7%) equivalent to 0, 3.8/4.4, 11.4/13.4, 34.0/39.3 mg/kg bw/day in males/females	↑ - increase; ↓ - decrease No treatment-related effects on mortality, clinical signs, food consumption or body weight In the RAR, significantly increased albumin levels and significantly reduced levels of platelets at all dose levels in female rats were explained to be due to incidental abnormal control values. ***Doses relevant for classification*** ***150ppm (11.4/13.4 mg/kg bw/day in males/females, respectively)*** ↑ relative kidney weight (14% males, 9% females) ***450ppm (34.0/39.3 mg/kg bw/day in males/females, respectively)*** ↑ creatine value (females) ↓ glucose concentration in plasma (males) ↑ relative kidney weight (↑17% males, ↑8% females) NOAEL[a] = 50ppm

Rat, Wistar (50/sex/dose) Oral, diet, 2 years GLP, OECD 453 (1981) Deficiencies: the spleen, epididymides, uterus, brain and thyroid were not weighed *satellite group I (10/sex/dose)* was dosed for 12 months *satellite group II (15/sex/dose)* was dosed for 24 months. Anonymous (1988) EU RAR B.6.5.1. *Cat 1 ≤ 1.25 mg/kg bw day* *1.25 < Cat 2 ≤ 12.5 mg/kg bw/day*	Mecoprop racemate, purity 92.7%, Batch TPH 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 males/females, respectively.	↑ - increase; ↓ - decrease No treatment-related mortality, clinical findings or histopathological changes. **Main groups** ***Doses relevant for classification*** ***20ppm (1.1/1.4 mg/kg bw/day in males/females, respectively)*** ↑ levels of triglycerides (males, significant) ↑ relative kidney weight (at 12 months only. Males, non-significant ↑ 10%) ***100ppm (5.5/6.9 mg/kg bw/day in males/females, respectively)*** ↑ levels of triglycerides (males, significant) ↑ relative kidney weight (males, significant, at 12 months only, ↑ 16%) ***Doses above the guidance values for classification*** ***400ppm (22.2/27.9 mg/kg bw/day in males/females, respectively)*** ↑ levels of triglycerides (males, significant) ↑ levels of urea after 18 and 24 months (significant) ↑ relative kidney weight (in both sexes but significant in males only at 12 months (↑ 18%) and 24 months (↑ 10%). **Satellite group I** ↓ bodyweight (males, significant) at 20 and 100ppm NOAEL[a] = 20ppm

Dog, beagle (4/sex/dose) Oral, diet 90 days Non-guideline Comparable to OECD 409 (1998) Deviation: for each dose group the results from each sex were combined Non-GLP Anonymous (1979c) EU RAR B.6.3.2.3. *Cat 1 ≤ 10 mg/kg bw day* *10 < Cat 2 ≤ 100 mg/kg bw/day*	mecoprop racemate purity 93.3% (calculated as 99.0% anhydrous dry material) 0, 4, 16 and 64 mg/kg bw/day	↑ - increase; ↓ - decrease Both sexes were analysed together. ***Doses relevant for classification*** ***16 mg/kg bw/day*** ↓ packed cell volume (↓ 7%) and red blood cell count (↓ 9%) (significant only after 6 weeks) ↓ bilirubin (↓ 25%, significant only after 6 weeks) ***64 mg/kg bw/day*** Transitory inflammatory response of the gingivae (2 dogs) Corneal ulcer in 1 male In 1 male, ulcera in the buccal mucosa resulted in withdrawal from mecoprop dosing and treatment with antibiotics. Brown discolouration of adipose tissue in the mesentery (3 dogs) ↓ weight gain (non-statistically significant) ↑ relative weight of kidney (20%), liver (25%), heart (18%), lungs (16%) and brain (26%) (significant, both sexes combined) ↓ weight of thymus (absolute ↓ 47% and relative ↓ 33%) ↓ (significant) haemoglobin (↓ 23% at week 6 and 16% at week 13), packed cell volume (↓ 24% at week 6 and 19% at week 13) and red blood cell count (↓ 25% at week 6 and 18% at week 13) ↓ lymphocytes (↓ 32%, significant only after 6 weeks) ↑ neutrophils (↑ 25%, significant only after 6 weeks) ↑ urea (significant, ↑ 59% after 6 weeks and 24% after 13 weeks) ↓ total protein (↓ 9%), albumin (↓ 21%) and alkaline phosphatase (↓ 28%) (all significant after 6 weeks only) ↑ retention of phenol red and Bromosulphophthalein NOAEL[a] = 4 mg/kg bw/day

[a] NOAELs have been taken from the EU Risk Assessment Report

Immunotoxicity studies

Table 27: Summary of immunotoxicity studies

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results**
Acute, 14 day and 90 day immune-toxicity studies Wistar rats Gavage Dosing volume = 5ml/kg bw No statement in relation to guideline or GLP status <u>Acute</u> 12 males/group <u>14 days</u> 12 males/group with only 5 males per group at 800 mg/kg bw/day <u>90 days</u> 20/sex/group Anonymous (1989a) EU RAR B.6.8.2.3/01	Mecoprop racemate (potassium salt, 97% purity, dissolved in water) <u>Acute</u> 0, 320, 800 and 1300 mg/kg bw/day (12 males/group) 1 dose <u>14 days</u> 0, 100, 320 and 800mg/kg bw/day 10 doses in total <u>90 days</u> 0, 0.8, 8, 80 and 320 mg/kg bw/day 95 doses in total	***Thymus*** Significant ↓ thymus weight at 1300 mg/kg bw in the acute study, at ≥ 320 mg/kg bw in the 14 day study, at ≥ 8mg/kg bw and 320mg/kg bw in males and females, respectively in the 90 day study. Degenerative processes consisting of ↓ density of lymphocytes and ↑ decay of leucocytes in the cortex at ≥ 320 mg/kg bw ***Spleen*** Significant ↓ spleen weight at 1300 mg/kg bw in the acute study and at 800 mg/kg bw in the 14 day study ↓ white pulp tissue in all of the studies Enlargement of the haematopoietic tissue of the spleen in the 14 and 90 day studies at 320 mg/kg bw/day ***Mesenteric lymph nodes*** No histological changes The number of total leucocytes was not affected. Significant dose-related changes in differential leucocyte counts in the 14 and 90 days studies (↓lymphocytes and ↑ neutrophilic granulocytes)

<table>
<tr>
<td>Immuno-toxicity study

Wistar rats

Gavage

Non-guideline

GLP status were not stated

Anonymous (1990c)

EU RAR B.6.8.2.3/02</td>
<td>Mecoprop racemate (97% purity) suspended in water

Dosing volume: 5ml/kg bw.

<table>
<tr><th>Study</th><th>Dose (mg/ kg bw/ day)</th><th>Number of doses</th><th>Number of animals in humoral immunity testing</th><th>Number of animals in cellular immunity testing</th></tr>
<tr><td>1</td><td>0
150
500</td><td>3*
3*
3*</td><td>12
12
12</td><td>9
-
9</td></tr>
<tr><td>2</td><td>0
320</td><td>15
15</td><td>12
12</td><td>9
9</td></tr>
<tr><td>3</td><td>0
320
0
80
320</td><td>10
10
10
10
10</td><td colspan="2">Adrenalectomised animals (n=?)
Adrenalectomised animals (n=?)
Controls (n=?)
Controls (n=?)
Controls (n=?)</td></tr>
</table>
* the animals were dosed every second day</td>
<td>Study 1

500mg/kg bw/day
↓ serum Immunoglobulin G (IgG) compared to controls (significant)
↓ reaction with respect to delayed sensitivity reactions in the ear test (significant)

Study 2

15 x 320mg/kg bw
↓ IgG (significant)
↓ response in the ear test (significant)

Study 3

320 mg/kg bw in the control group
↓ spleen weight, IgG concentration and lymphocyte count compared to 0mg/kg bw controls (significant). None of these findings were noted in the adrenalectomised animals at 80 and 320 mg/kg bw.</td>
</tr>
</table>

Haematology study

Table 28: Summary of haematology study

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results**
Inhibition of human and rabbit platelet aggregation by chlorophenoxyacid herbicides *In vitro* Non-guideline. Platelet aggregation in platelet-rich plasma was induced by adding different amounts of either adenosine diphosphate, adrenaline or collagen to a sample of mecoprop at 37 °C. No statement in relation to GLP Elo HA, Luoma T, & Ylitalo P (1991) EU RAR B.6.8.2.2	Mecoprop racemate (purity >99%) Concentration levels not stated	Between 0.1 and 2 mg/ml, mecoprop caused a clear dose-dependent inhibition of human platelet aggregation in all the three aggregation-inducing systems. No inhibition was seen at 0.05 mg/ml.

Oral

Studies in rats

49 days

Wistar rats (10/sex/group) were exposed to 0, 50, and 400 ppm mecoprop (racemic form; 92.7% purity) equivalent to 0, 4.4/4.8, 35.1/37.5 mg/kg bw/day in males/females via the diet for 49 days.

No deaths were observed during the study period. There were no substance-related effects on food consumption, bodyweight or clinical signs.

There was an increase in absolute kidney weight at 50ppm (males only, 6%) and 400ppm (7% in males and 2% in females). At 400ppm, there was also a significant decrease in levels of cholesterol and calcium in females and in increase in urea concentration in males only. A significant increase in glutamic-pyruvic transaminase (alanine aminotransferase) was also observed in males.

Therefore, the results are consistent with those of mecoprop-P. The kidney is a target organ, although the observed changes were not accompanied by adverse histopathological effects in the kidney.

In the EU Risk Assessment Report, it was concluded that the overall NOAEL in this study is 50ppm.

90 days

Two standard 90 day toxicity studies and a supplementary study in rats are available.

1) In a 90 day study (similar to OECD 408 (1998)), SD rats (15/sex/group) were administered 0, 200, 800, and 3200 ppm mecoprop racemate (93% purity), equivalent to 0, 16.5/18.2, 67.9/75.9, 391/399 mg/kg bw/day in males/females respectively. Due to technical problems, histopathological examination of the eyes was not performed.

In this study, no adverse clinical signs or behavioural changes were observed. There was no treatment-related increase in mortality or histopathological changes, including the kidneys.

Bodyweights of females were significantly reduced at the mid dose in comparison to controls. At the top dose, body weights were significantly reduced (30% and 35% less than control animals in females and males, respectively).

Increased kidney weights compared to controls were observed in both sexes at the low and mid doses. At the top dose, there was a significant decrease in kidney weight, although relative kidney weight increased. A significant increase in liver weight was observed in females at the top dose only.

Increases (with respect to frequency and degree) of blood urea nitrogen, serum alkaline phosphatase and alanine aminotransferase were observed in both sexes at the mid and high dose levels.

Under the conditions of this study, the liver and kidneys were the target organs of mecoprop induced toxicity in rats.

In the EU Risk Assessment Report, it was concluded that the overall NOAEL in this study is < 200ppm.

Supplementary 3 month oral toxicity study

A supplementary study was conducted because there was no histopathological examination of the eyes in the original 3 month study described above. SD rats (10/sex/group) were exposed to up to 3200 ppm racemic mecoprop (93% purity) equivalent to 453/537 mg/kg bw/day in males/females.

The only adverse effect in this study was a reduction in bodyweight of treated animals. No adverse effects the eyes were observed. No other organs were investigated.

2) Wistar rats (15/sex/group) were exposed to mecoprop (racemic form, 92.7%) for 90 days at doses of 0, 50, 150 or 450 ppm equivalent to 0, 3.8/4.4, 11.4/13.4, 34.0/39.3 mg/kg bw/day in males/females, respectively in accordance with OECD 408.

An increased relative kidney weight was observed at the mid dose (↑14%/9% in males/females) and high dose (↑17%/8% in males/females).

At the top dose, an increased level of creatine was observed in females and a decreased concentration of glucose in the plasma was observed in males.

Although significantly increased albumin levels and significantly reduced levels of platelets were observed in females at all dose levels, these were explained in the EU Risk Assessment Report to be due to incidental abnormal control values.

Consistent with the other repeated dose studies in rats, the kidney can be identified as a target organ of racemic mecoprop toxicity in this study.

In the EU Risk Assessment Report, it was concluded that the overall NOAEL in this study is 50ppm.

2 years

One chronic toxicity study in rats is available.

Mecoprop (racemate, 92.7% purity) was administered to Wistar rats (50/sex/group) at doses of 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 males/females, respectively, for 24 months in accordance with OCED 453. Satellite groups were also included in this study. Satellite group I (10 rats/sex/dose) was dosed for 12 months, whereas satellite group II (15 rats/sex/dose) was dosed for 24 months.

A non-statistically significant increase in relative kidney weight was observed in males at 20 and 100ppm at 12 months only. The increase in relative kidney weight was statistically significant in both sexes at the top dose after 12 months, but only in males at 24 months. The changes in kidney weights were not accompanied by histopathological changes.

Significantly increased levels of triglycerides were observed in males only at all doses. At the top dose, there was also a significant increase in levels of urea after 18 and 24 months.

In the EU Risk Assessment Report, it was concluded that the overall NOAEL in this study is 20ppm.

Immunotoxicity studies

Two immunotoxicity studies in the rat are available.

Anonymous (1989a)

Potential immunotoxic effects of mecoprop (racemate, potassium salt) were investigated in Wistar rats in 3 studies (acute, 14 days and 90 days in duration). The test substance was dissolved in water and administered to the animals by gavage. Details of the dosing regime are tabulated below.

Table 29: Dosing regime in the immunotoxicity study, Anonymous (1989)

Study	Dose levels, mg/kg bw/day					total no. of doses	no. of rats in each dose group, m/f
acute	0	320	800	1300	-	1	12/-
14-day	0	100	320	800	-	10*	12/-
90-day	0	0.8	8	80	320	95	20/20

* At 800 mg/kg only 5 rats were used.

The scope and reporting of this study are limited. Investigations were limited to organs weights of the thymus and spleen, histopathology of the thymus, spleen and mesenteric lymph nodes, morphometry of the spleen and total and differential leucocyte counts.

Thymus
A significant decrease in thymus weight was observed at 1300 mg/kg bw in the acute study, at ≥ 320 mg/kg bw in the 14 day study, at ≥ 8mg/kg bw and 320mg/kg bw in males and females, respectively in the 90 day study. At ≥ 320 mg/kg bw, degenerative processes consisting of decreased density of lymphocytes and increased decay of leucocytes were observed in the cortex.

Spleen
A significant decrease in spleen weight was observed at 1300 mg/kg bw in the acute study and at 800 mg/kg bw in the 14 day study. In all 3 studies reported here, a reduction in white pulp tissue was observed. Additionally, enlargement of the haematopoietic tissue of the spleen was noted in the 14 and 90 day studies at 320 mg/kg bw/day.

No histological changes were observed in the mesenteric lymph nodes.

The number of total leucocytes was not affected. However, there were significant dose-related changes in differential leucocyte counts in the 14 and 90 day studies (decrease in lymphocytes and increase in neutrophilic granulocytes).

Anonymous (1990c)

Immunotoxicity has been investigated further in Wistar rats. Potential effects of racemic mecoprop on humoral and cell immunity in adrenalectomised animals were investigated in 3 sub studies. Details of the dosing regime are tabulated below.

Table 30: Dosing regime in the immunotoxicity study (Anonymous, 1990c)

Study	Dose (mg/kg bw/ day)	Number of doses	Number of animals in humoral immunity testing	Number of animals in cellular immunity testing
1	0 150 500	3* 3* 3*	12 12 12	9 - 9
2	0 320	15 15	12 12	9 9
3	0 320 0 80 320	10 10 10 10 10	Adrenalectomised animals (n=?) Adrenalectomised animals (n=?) Controls (n=?) Controls (n=?) Controls (n=?)	

* the animals were dosed every second day

At 500mg/kg bw in sub study 1, there was a significant reduction in serum immunoglobulin G (IgG) and also a significantly decreased reaction with respect to delayed sensitivity reactions in the ear test in comparison to controls.

At a dose level of 15 x 320mg/kg bw in the second sub-study, significant reductions in IgG and response in the ear test were observed.

At 320 mg/kg bw in the control group in sub study 3, there were significantly reductions in spleen weight, IgG concentration and lymphocyte count compared to 0mg/kg bw controls. None of these findings were noted in the adrenalectomised animals at 80 and 320 mg/kg bw.

Summary of immunotoxicity studies

Two immunotoxicity studies in Wistar rats are available. Racemic mecoprop was administered to rats in both studies. The findings observed are considered to have arisen due to a stress-induced release of steroid hormones, which was secondary to general toxicity and insufficient to warrant classification for a specific effect on the immune system.

Studies in mice

No studies in mice are available.

Studies in dogs

One repeated dose toxicity studies in dogs is available.

90 days

Beagle dogs (4/sex/group) were exposed to 0, 4, 16 or 64 mg mecoprop (racemic) /kg bw/day (purity 93.3%) in the diet for 90 days. The method used in this study is comparable to OECD 409 (1998). For each dose group, the results from each sex were combined.

At the top dose level, there were significant increases in the relative weights of the kidney (20%), liver (25%), heart (17.5%), lungs (16%) and brain (26%). A non-significant dose-dependent reduction in absolute and relative thymus weight was observed.

At the top dose, there were decreases in total protein, albumin and alkaline phosphatase, which were significant only after 6 weeks, and an increase in levels of urea. A decrease in bilirubin was observed at the mid dose only and was significant only after 6 weeks. Transient changes are not considered sufficient to warrant classification.

In this study, organ function tests were performed on the liver and kidneys using the Bromosulphophthalein (BSP) method and the phenolsulphophthaleine (PSP) method, respectively.

The kidney function test was carried out on all animals. At week 13, the dogs fasted for 16 hours before receiving 1mg PSP/kg bw by intravenous injection. A blood sample was taken sixty minutes later. Phenol red retention was higher than controls in top dose dogs (41.0, 38.3, 43.7 and 74.4 µg/100ml at 0, 4, 16 and 64 mg/kg bw/day, respectively), which may be indicative of an adverse effect on kidney function. In the absence of supporting histopathological evidence, this observation is not considered to show conclusively that kidney function was impaired.

The liver function test was carried out on animals in the control and top dose groups only at week 13. The animals in these dose groups were intravenously injected with 12.5 mg BSP/kg bw. Blood samples were taken one and thirty minutes later in order to measure BSP retention. BSP retention was statistically significantly higher in the top dose group (6.2%) than controls (3.0%).

Table 31: Individual animal data for the liver function test in dogs

		BSP retention (%)	
Dose (mg/kg bw/day)		Males	Females
0		2.2	2.0
		2.3	3.6
		3.4	Not measured
		5.0	2.7
	Mean	Males – 3.2, Females – 2.8, Combined – 3.0	

64		18.8	4.0
		3.8	4.5
		3.3	5.7
		3.6	6.1
	Mean	Males – 7.4, Females – 5.1, Combined - 6.2	

As shown in the table above, the increase in BSP retention was mainly attributable to a particularly high value in one top dose male, and therefore this result is not considered to show an adverse treatment-related effect on liver function.

Decreased packed cell volume and red blood cell count was observed at the mid and high dose levels. At the top dose, this was also accompanied by decreased haemoglobin and lymphocytes and an increase in neutrophils.

At the top dose, brown discolouration of adipose tissue in the mesentery was observed in 3 dogs. Additionally, transitory inflammatory response of the gingivae was observed in 2 dogs and 1 male had a corneal ulcer. In another male, ulcera in the buccal mucosa resulted in withdrawal from racemic mecoprop dosing and treatment with antibiotics.

In the dog, target organs of toxicity appear to be the liver and kidneys.

In the EU Risk Assessment Report, it was concluded that the overall NOAEL in this study is 4 mg/kg bw/day.

Dermal

No repeated dose dermal studies on racemic mecoprop are available.

Inhalation

No repeated dose inhalation studies on racemic mecoprop are available.

Human information

No human data are available.

Additional information

Haematology Study

In a non-guideline *in vitro* study *(*Anonymous, 1991), inhibition of human and rabbit platelet aggregation by racemic mecoprop and other chlorophenoxyacid herbicides was investigated. In order to study platelet aggregation, adenosine diphosphate, adrenaline or collagen were added to a sample of platelet-rich plasma and mecoprop. The concentrations of each substance used in this study were not stated. Details on the conduct of this report are limited.

A clear dose-dependent inhibition of human platelet aggregation was observed in all three aggregation-inducing systems with racemic mecoprop at concentrations of between 0.1 and 2 mg/ml. At 0.5mg/ml mecoprop, no inhibition was observed.

This study shows that racemic mecoprop has the potential to inhibit platelet aggregation *in vitro*. However, in isolation, this finding is not considered to be relevant to the discussion on classification.

10.12.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

Oral

The available repeated dose studies show that the liver and kidneys are target organs of toxicity following exposure to sufficiently high doses of mecoprop-P. However, there is no evidence of impaired organ function at dose levels relevant for classification. The results from studies of racemic mecoprop were consistent with those from mecoprop-P.

Dermal

In rabbits exposed to mecoprop-P by the dermal route, no severe systemic effects were reported. Dermal reactions were observed at dose levels below the guidance values for classification, and consisted ofwell-defined erythema, slight or well-defined oedema and diffuse acanthosis. These effects are not considered to represent significant or severe toxicity.

Inhalation

No repeated dose studies by the inhalation route are available.

10.12.2 Comparison with the CLP criteria

Oral

The available studies identified the liver and kidneys as target organs of toxicity in animals exposed to mecoprop-P by the oral route. However, at dose levels below the guidance values for classification, the effects were limited to small changes in bodyweight, organ weight and clinical chemistry.
In section 3.9.2.8 of Annex I of the CLP Regulation, it is recognised that effects may be seen in humans and/or animals that do not justify classification. Such effects include, but are not limited to:

(a) clinical observations or small changes in bodyweight gain, food consumption or water intake that have toxicological importance but that do not, by themselves, indicate ‘significant’ toxicity;

(b) small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;

(c) changes in organ weights with no evidence of organ dysfunction;

(d) adaptive responses that are not considered toxicologically relevant;

(e) substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification.

The effects observed at dose levels relevant for classification were not accompanied by supporting adverse histopathological effects. There is no evidence of impaired organ function at dose levels relevant for classification and therefore it is concluded that no classification for STOT-RE via the oral route is warranted.

Dermal

No significant or severe effects were observed in the available dermal study. Therefore, classification is not considered to be warranted.

Inhalation

No conclusions can be drawn on the repeated dose toxicity of mecoprop-P following exposure by inhalation because no relevant studies are available.

10.12.3 Conclusion on classification and labelling for STOT RE

No classification; data conclusive but not sufficient for classification

10.13 Aspiration hazard

This hazard was not assessed in this proposal.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Mecoprop-P (mecoprop-P acid referred to as MCPP-P in this section) CAS: 16484-77-8 is a phenoxy herbicide intended for use against broadleaf weeds. MCPP-P is the pure R enantiomer which is included in the racemic mixture (S:R enantiomers) that is mecoprop (MCPP, CAS: 93-65-2). The R enantiomer possess the herbicidal activity. The S enantiomer is considered herbicidally inactive.

Available environmental fate and hazard studies have been considered under Directive 91/414/EEC and Regulation (EC) No 1107/2009 and summarised in the Renewal Assessment Report (RAR) 2017.

The key information pertinent to determining a classification is presented below. Some fate studies were conducted with the racemic mixture MCPP whilst some ecotoxicity studies were conducted with MCPP-P dimethylamine (DMA) salt and MCPP-P formulations. Where relevant these are presented and discussed in relation to MCPP-P.

The water solubility of MCPP-P in pure water at 20 °C has been experimentally determined (EC Test Guideline A.6) to be 6.65 g/l at pH4 and >250 g/l at pH 7 and 9 (Comb, 2000a).

Following OECD Test Guideline 112, the dissociation constant for MCPP-P is 3.7 (Comb, 2000a). It is likely the substance will be largely ionised within an environmentally relevant pH range.

MCPP-P is surface active with a surface tension value of 50.0 mN/m (90% saturated solution) at 20 °C (Comb, 2000a).

A summary of reliable valid information considering the aquatic fate of MCPP-P is presented in Table 32 below. Soil data have not been presented as suitable aquatic data are available.

11.1 Rapid degradability of organic substances

Table 32: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
Aquatic hydrolysis BBA Merkblatt 55, not GLP, MCPP (>99.5%)	Hydrolytically stable at pH 5, 7 and 9 at 70 °C DT_{50} considered >16 days at study temperature and environmentally relevant pH	MCPP racemic mixture Valid (As DT_{50} values were >16 days at 70 °C, they were not converted to 12 °C as it is assumed they would be >16 days)	Anonymous, 1998
Aquatic hydrolysis US-EPA Subdivision N161-1, 161-2, GLP, MCPP (96.9%)	Hydrolytically stable at pH 5, 7 and 9 at 25 °C DT_{50} considered >16 days at environmentally relevant pH	MCPP racemic mixture Valid (As DT50 values were >16 days at 25 oC, they were not converted to 12 oC as it is assumed they would be >16 days)	Obrist, 1986, 1988, 1990
Ready biodegradation OECD Guideline 301F, GLP, MCPP-P (91.7%)	84-86% mineralisation day 28 Readily biodegradable meeting 10 day window	MCPP-P Valid	Feil, 2010
Aquatic photolysis, FIFRA Subdivision N: 161-2, GLP,	DT_{50} = 5.13 to 7.04 days artificial sunlight DT_{50} = 3.39 to 4.65 days at 42°N Main degradant *o*-cresol with	MCPP-P Valid	Connor, 1996b and Hazlerigg, 2015

Method	Results	Remarks	Reference
MCPP-P (99.2-99.3%)	max. 30.4% AR day 30. ~10% mineralisation at study termination day 30. *o*-cresol DT_{50} = 63.5 days artificial sunlight *o*-cresol DT_{50} = 41.91 days at 42°N		
Freshwater aerobic mineralisation in surface water OECD Guideline 309, GLP, MCPP-P (99.71%)	DT_{50} values not able to be reliably calculated due to negligible mineralisation. <2% AR mineralisation as CO_2 by day 58. No degradants observed.	MCPP-P Valid	Traub, 2014
Freshwater-sediment mineralisation simulation, BBA, Part IV, s. 5.1, GLP, MCPP-P (98.9%)	55.29 to 57.94% mineralisation day 100	MCPP-P Valid [DT_{50} values determined by Hazlerigg and Garratt, 2014 and RMS update – see row below]	Cooper and Unsworth, 1996
Re-analysis of data from Cooper and Unsworth using FOCUS kinetic	DT_{50} whole system considered 23.4 to 58.9 days at 20 °C Converted to 12 °C: 44.4 to 111.7 days	MCPP-P Valid	Hazlerigg and Garratt, 2014
Freshwater-sediment mineralisation simulation, OECD 308, MCPP-P (99.64%)	DT_{50} whole system: 83.2 to 244 days at 20 °C Converted to 12 °C: 157.8 to 462.7 days	MCPP-P Valid	Roohi, 2015

11.1.1 Ready biodegradability

Study 1 – Feil (2010)

A GLP ready biodegradation study following OECD Test Guideline 310F (manometric respiration) is available using MCPP-P at 83 mg/l (direct addition with no use of solvents). The study used aerobic activated sludge from a wastewater treatment plant treating predominantly domestic wastewater. Two test item replicates were included along with a sodium benzoate as a reference control which was considered valid. A toxicity control was also included indicating the test item was not inhibitory to the microbial inoculum. The study was run in the dark at 22 ±1°C and pH 7.5-7.6 for 28 days with constant stirring of the airtight vessels. Study validation criteria were met.

On day 7, 7-11% (mean 9%) mineralisation was observed. On day 8 this was 19-22% (mean 20.5%) meaning 10% mineralisation was observed around day 7. By day 17, 80-82% (mean 81%) mineralisation was determined. This exceeds the ≥60% (based on ThOD) required to be considered readily biodegradable within the 10-day window timeframe. By day 28, 84-86% (mean 85%) mineralisation was observed.

On this basis, MCPP-P is considered readily biodegradable meeting the 10-day window.

11.1.2 BOD_5/COD

No data.

11.1.3 Hydrolysis

Study 1 – Anonymous, (1982)

A non-GLP hydrolysis test following BBA Merkblatt 55 test guideline at 70 °C over 8 days at pH 5, 7 and 9 is available using MCPP. Recoveries were 100% at study termination. No hydrolysis was observed and the test substance was found to be stable in aqueous solution under sterile conditions.

Study 2 – Obrist, (1986, 1988 amendment and 1990 supplement)

A GLP hydrolysis test following US-EPA Subdivision N161-1 and 161-2 test guidelines at 25 °C over 31 days at pH 5, 7 and 9 is available using ^{14}C-MCPP. Recoveries were 100% at study termination. No hydrolysis was observed and the test substance was found to be stable in aqueous solution under sterile conditions.

Summary

Overall, MCPP is considered hydrolytically stable at an environmentally relevant pH and study temperatures between 25 and 70 °C. On this basis MCPP is considered hydrolytically stable at an environmentally relevant temperature with a half-life greater than 16 days. While the hydrolysis studies were conducted on the racemic mixture MCPP, differences in hydrolysis between MCPP and MCPP-P are not expected. On this basis, the data are read-across and MCPP-P is considered hydrolytically stable.

11.1.4 Other convincing scientific evidence

11.1.4.1 Field investigations and monitoring data (if relevant for C&L)

Literature data relating to the environmental fate of MCPP-P was identified under review for Regulation 1107/2009 and included in the RAR (2017). As standardised experimental data are available for classification, the literature data are not discussed further.

11.1.4.2 Inherent and enhanced ready biodegradability tests

No data.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

Study 1 – Traub (2014)

A freshwater aquatic biodegradation in surface water simulation study is available following OECD Guideline 309 and GLP. The study used ^{14}C-MCPP-P and surface water (top 6 cm) from Rhineland-Palatinate aerobic aquatic system.

Test vessels were prepared with water which had the particles removed by sedimentation prior to use. The surface water dissolved organic carbon content was 8.6 mg/l and BOD5 was <3 mg/l. The item was applied at two concentrations (10 µg/l and 100 µg/l in acetonitrile) on to the water layer. The study ran for 58 days in the dark at 20 ±2 °C. Sodium benzoate was used as a reference substance with 82-87% mineralisation by day 13 indicating the surface water contained active microbial populations.

Radioactivity was determined by liquid scintillation counting (LSC) and thin layer chromatography (TLC). Mean recoveries for both test concentrations were 97-102% of Applied Radioactivity (AR).

Mineralisation was negligible for both test concentrations with <2% AR detected as CO_2. Organic volatiles were detected at <1% AR and no degradants were observed.

Given the lack of degradation, DT_{50} values could not reliably be calculated.

Study 2 – Cooper and Unsworth (1996)

A freshwater aquatic biodegradation in surface water simulation study is available following BBA guideline Part IV, section 5.1 and GLP. The study used ^{14}C-MCPP-P and two natural aquatic systems: Manningtree stream, UK and River Roding, Ongar, UK. Table 33 presents the characteristics of each aquatic system.

Table 33: Physiochemical parameters of the water/sediment systems in Cooper and Unsworth, 1996.

Sediment Parameter	Manningtree stream	Ongar river
Texture Class	Sandy silt loam	Clay loam
% Sand	40.09	33.9
% Silt	44.72	34.01
% Clay	15.18	32.08
pH	6.7	8.6
% Organic Carbon (%)	5.3	3.1
CEC (meq/100 g)	11.9	63.2
Water Parameter	**Manningtree stream**	**Ongar river**
Oxygen (%)	63	82
pH	5.57	6.94
Hardness mg equivalent $CaCO_3$/l (ppm)	319	413
Organic Carbon (mg/l)	18.59	59.46
Redox potential (mV)	248	225

Test systems were prepared with filtered water and sieved sediment with depths of approximately 5 and 7.5 cm respectively. The test item was applied to the water layer at a rate of 0.449 mg/l. The study ran for 100 days in the dark at 20 ±2 °C.

For analysis, water and sediment layers were separated by centrifugation with subsequent decanting of the water layer. The radioactivity was quantified by LSC and then analysed by HPLC. Overall recoveries were 114 to 103.7% AR for the Manningtree system and 112.6 to 87.4% AR for the Ongar system.

The distribution of radioactivity was transferred to sediment over the study period with MCPP-P the main fraction in sediment. In addition, three minor fractions of unknown degradants were observed in sediment.

The study did not calculate mineralisation half-lives. Based on observed mineralisation measurements it is noted that 56.45% mineralisation was observed on day 30 in the Ongar system and 55.29% mineralisation was observed on day 100 (termination) in the Manningtree system. The maximum level of mineralisation was 57.94% on day 100 in the Ongar system.

Study 3 – Hazlerigg and Garrat (2014)

Re-analysis of the data from Cooper and Unsworth (1996) was undertaken following FOCUS guidance using Kingui v2 to calculate DT_{50} values.

Following Single First Order (SFO) kinetics, the study reported whole system DT_{50} values of 59 days for Manningtree and 35 days for Ongar

It was noted that confidence in sediment data was lower than water data due the absences of a clear decline phase. Under Reg. 1107/2009 review, it was considered that the applied kinetics were not reliable and further analysis was undertaken by the Rapporteur Member State (RMS). The RMS repeated the kinetic modelling using the software CAKE v2.0 and various kinetic models: SFO, First Order Multi-Compartment (FOMC), and Hockey Stick (HS) models optimised using Ordinary Least Squares (OLS) and Iteratively Reweighted Least Squares (IRLS).

For the Manningtree system, the SFO model with OLS was considered the most appropriate fit resulting in whole system DT_{50} of 58.9 days at study temperature.

For the Ongar system, the HS model with OLS was considered the most appropriate fit resulting in whole system DT_{50} of 23.4 days at study temperature.

For the purpose of classification these values have been converted to 12 °C, in line with ECHA guidance and Member State Committee testing protocols, to reflect a more environmentally relevant temperature.

- Manningtree: 111.7 days
- Ongar: 44.4 days

Study 4 – Roohi (2015)

A freshwater aquatic biodegradation simulation study is available following OECD Guideline 308 and GLP. The study used ^{14}C-MCPP-P and two natural aquatic systems: Calwich Abbey Lake, England and Swiss Lake, England. Table 34 presents the characteristics of each aquatic system.

Table 34: Physiochemical parameters of the MCPP-P water/sediment systems in Roohi, 2015.

Sediment Parameter	Calwich Abbey Lake	Swiss Lake
Geographic Location	Calwich Abbey Lake, Calwich, Ashbourne, Derbyshire, England	Swiss Lake, Chatsworth, Derbyshire, England
Texture Class	Silt Loam to sandy silt loam	Loamy sand
% Sand	38	85
% Silt	53	10
% Clay	9	6.5
pH	7.2	6.6
% Organic Carbon (%)	5.0	0.71
CEC (meq/100 g)	10.7	3.1
Water Parameter	**Calwich Abbey Lake**	**Swiss Lake**
pH	8.2	7.1
Hardness mg equivalent $CaCO_3$/l (ppm)	257	35
Organic Carbon (mg/l)	2.6	17.7

Test systems were prepared with filtered water and sieved sediment at a ratio of 4:1 water:sediment (w:w). The test item was applied to the water layer at a rate of 0.138 mg/l. The study ran for 98 days in the dark at 20 ±2 °C.

For analysis, water and sediment layers were separated by centrifugation with subsequent decanting of the water layer. The radioactivity was quantified by LSC and then analysed by HPLC. Overall recoveries were acceptable as follows:

- Calwich Abbey: 92.7-102% AR (mean 96.9% AR)
- Swiss Lake: 95.3-101.7% AR (mean 99.7% AR)

MCPP-P was observed to decline in the each test system with significant mineralisation and partitioning to sediment.

After an initial lag phase (4.9% AR CO_2 by day 56) mineralisation in the Calwich Abbey system reached 50% AR $CO_2$by day 98. Dissipation and mineralisation was slower in the Swiss Lake system with 13.45% AR CO_2 by day 98.

Several degradants were detected over the study period. None were >5% AR at any time point in the total system and were not identified.

Following FOCUS guidance and using the software CAKEv2.0 degradation kinetics and whole systems DT_{50} values were calculated using various kinetic models. The following were considered best fit models and DT_{50} total system values at study temperature:

- Calwich Abbey: DT_{50} 83.2 days (HS-IRLS)
- Swiss Lake: DT_{50} 244 days (SFO-IRLS)

For the purpose of classification these values have been converted to 12 °C, in line with ECHA guidance and Member State Committee testing protocols, to reflect a more environmentally relevant temperature.

- Calwich Abbey: DT_{50} 157.8 days at 12 °C
- Swiss Lake: DT_{50} 462.7 days at 12 °C

11.1.4.4 Photochemical degradation

Study 1 – Connor (1996b) and Hazlerigg (2015)

A GLP aquatic photolysis study is available following FIFRA Subdivision N 161-2 test guideline and using MCPP-P. The test used radiolabelled test item at approximately 10 mg/l nominal in sterile test solutions at pH 5, 7 and 9. Samples were irradiated at 25 ± 2 °C, with stirring for 30 days using a xenon arc light source (wavelengths <300 nm removed) with a 12 hour light/dark cycle. Samples were analysed by Liquid Scintillation Counting (LSC) and High Performance Liquid Chromatography (HPLC) with radio detection. The study also included control non-irradiated samples.

Recoveries were 73.6 to 103% for irradiated samples and 94.3 to 104% for dark controls. CO_2 accounted for ~10% radioactivity and the degradant *o*-cresol was detected at up to 30.4% AR. No degradation was observed in dark controls.

Following Single First Order kinetics, DT_{50} values for MCPP-P at study temperature and pH 5,7 and 9 were calculated as follows
- Artificial light = 5.13 to 7.04 days
- Sunlight at 42°N (southern Europe) = 3.39 to 4.65 days

In addition, Single First Order kinetics, DT_{50} values were calculated at study temperature and pH 7 for the main degradant *o*-cresol as follows:
- Artificial light = 63.5 days
- Sunlight at 42°N (southern Europe) = 41.91days

11.1.4.5. Rapid degradability summary

MCPP-P is considered hydrolytically stable.

MCPP-P is susceptible to photodegradation. Study experimental DT_{50} values were 3.39 to 4.65 days based on southern Europe sunshine. In addition, the calculated DT_{50} for the principle degradant *o*-cresol was determined to be 41.91 days based on southern Europe sunshine. It is noted that the actual degree of photodegradation in the aquatic environment depends on local conditions and seasons and is difficult to quantify. Given the available data, there is insufficient information to evaluate photodegradation in the European environment in terms of mineralisation or transformation to non-classifiable substances.

In an OECD Test Guideline 301F study, MCPP-P was considered readily biodegradable meeting the 10 day window.

Limited mineralisation was observed in a surface water simulation study and water/sediment simulation studies using MCPP-P although this significantly less than 70% by day 28. Whole system DT_{50} values at 12 °C range from 44.4 to 463 days. several aquatic degradants were observed although none at >5% AR.

While MCPP-P is considered readily biodegradable following a valid OECD 301F study with non-adapted inoculum, it is noted that limited mineralisation was observed in various simulations tests. Degradation half lives can be influenced and vary based on the test system media which may explain the observed difference. In general, chemicals that pass the OECD 301 ready biodegradation criteria under stringent test conditions are likely to undergo rapid degradation in the aquatic environment under most conditions.

Overall, on the basis of the ready biodegradation study, MCPP-P is considered to be rapidly degradable for the purpose of classification.

11.2 Environmental transformation of metals or inorganic metals compounds

Not relevant.

11.3 Environmental fate and other relevant information

Two adsorption in soil studies are available following OECD 106 and GLP.

Study 1 – Matla and Vonk (1993)

Using 4 soils with low pH (4.3-4.4) and organic matter in the range 3.6-5.6%, the Kfoc values were 135 to 169.

Study 2 – Simmonds (2010)

Using 4 soils (pH 5.7-7.3 and 5-6.4% organic matter), the Koc values were 12 to 34 with a mean of 21.

Overall, MCPP-P is considered to be mobile in soil.

Henry's Law Constant

The calculated Henry's Law Constant of 1.7 x 10^{-4} Pa.m^3.mol (Comb, 2000a) indicates MCPP-P is unlikely to partition from water. Bioaccumulation

11.4 Bioaccumulation

Table 35: Summary of relevant information on bioaccumulation

Method	Results	Remarks	Reference
Partition coefficient, EC A.8, OECD 107 (shake flask) purity 99.8%	logPow at 20 °C: 2.19 at pH 4 -0.19 at pH 7 -0.64 at pH 10	MCPP-P Unclear if reliable as substance is surface active	Comb, 2000a
Log Kow prediction, KOWWIN	2.94		RAR, 2017

Method	Results	Remarks	Reference
Experimental aquatic BCF test in fish to US EPA Subdivision E 71-6, GLP, purity 96.3%	Whole fish BCF: 3 l/kg (not lipid normalised) Depuration half-life DT_{50}: 27.4 hours	MCPP racemic mixture Flow through, 28 days exposure, 14 days depuration. One test concentration, 1 mg/l mecoprop. Valid	Anonymous, 1986b

11.4.1 Estimated bioaccumulation

Using KOWWIN a logKow value of 2.94 was included in the RAR.

11.4.2 Measured partition coefficient and bioaccumulation test data

Study 1 – Comb (2000a)

The octanol:water partition coefficient of MCPP-P was determined following EC Test Guideline A.8.v OECD 107 (shake flask method). The study was conducted using pure water at pH 4, 7 and 9 at 20 °C. The quoted logPow values were:

2.19 at pH 4
-0.19 at pH 7
-0.64 at pH 10

Given MCPP-P is surface active (50 mN/m, 90% saturated solution), the reliability of the value is unclear.

Study 2 – Anonymous 1986b

While an experimental BCF is not available for MCPP-P, a bioconcentration in fish study is available using radiolabelled MCPP (96.3%). Given MCPP is a racemic mixture including MCPP-P (R enantiomer), the study is considered relevant.

The study followed GLP and US EPA test guideline Subdivision E 71-6. The study was considered to meet validation criteria for OECD test guideline 305.

It used a flow-through system with Bluegill sunfish (*Lepomis macrochirus*) and only one exposure concentration nominally 1 mg/l as two replicates. The exposure period ran for 28 days followed by a 14 day depuration period.

The whole fish bioconcentration factor (BCF) was determined to be 3 l/kg based on ^{14}C-mecoprop equivalents.

The lipid content of the fish is not known and the endpoint was not corrected for this.

Analysis of extractable radioactivity in edible tissues at day 21 and 28 identified 3 metabolites.

The whole fish DT_{50} was calculated to be 27.4 hours based on radioactivity.

11.4.2.1 Bioaccumulation summary

MCPP-P is considered to have a Log Kow below the CLP threshold of 4. An experimental BCF for MCPP is below the CLP threshold of 500. Overall, MCPP-P is considered to have a low potential for bioaccumulation.

11.5 Acute aquatic hazard

In addition to studies using MCPP-P, studies using MCPP racemic mixture, MCPP-P dimethylamine (DMA) salt and a MCPP-P formulation (liquid soluble concentrate containing 600 mg mecoprop-P acid with confidential co-formulates at unknown levels) are presented in the RAR.

Valid studies relevant for the classification of MCPP-P are presented in Table 36. This includes studies using MCPP dimethylamine (DMA) salt if there is not an equivalent study using MCPP-P or if the endpoint reflects the most sensitive trophic level. Where this is the case, endpoints are presented as MCPP-P equivalents.

Endpoints for *Myriophyllum spicatum* with studies using the formulation Mecoprop-P K 600 g/l are presented as additional information. While MCPP-P is a herbicide and *Myriophyllum spicatum* appears to be more sensitive than other aquatic plants, the formulation includes co-formulants (details in Confidential Annex II) in addition to water and the impact of these substances in the studies is not clear. For example it is unknown if the co-formulant properties could have enhanced ecotoxicity. In addition, although one co-formulant accounts for around 0.004 % w/w, it has an environmental self-classification (Aquatic Chronic 2 and 4). Also, the ecotoxicity to *Myriophyllum spicatum* for co-formulants unknown.

The RAR noted a single aquatic degradant of potential relevance: *o*-cresol (CAS: 95-48-7) max. 30.4% by day 30 in an artificial sunlight photolysis study. The substance has a harmonised classification (Index number: 604-004-00-9) which does not include an environmental classification. It is noted that the substance has a self-classification of Aquatic Chronic 3[1] based on publically available data on the ECHA website. While some ecotoxicity data is available (https://echa.europa.eu/registration-dossier/-/registered-dossier/14924/1), these are not discussed further as their validity has not been clarified.

No other environmentally significant degradants were identified.

Overall, degradants are not considered further in relation to the classification of MCPP-P.

Table 36: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results	Remarks	Reference
Acute toxicity to fish, OECD 203, GLP	Rainbow trout (*Oncorhynchus mykiss*)	MCPP-P (98.6%)	96-h LC_{50} 171 mg/l MCPP-P (mm)	Valid Limited reliability	Anonymous , 1984
Acute toxicity to fish, US EPA E 72-1, GLP	Bluegill sunfish (*Lepomis macrochirus*)	MCPP-P (91.4%)	96-h LC_{50} >100 mg/l MCPP-P (n verified)	Valid	Anonymous, 1989b
Daphnia sp. Acute Immobilisation OECD 202, GLP	*Daphnia magna*	MCPP-P (89.7%)	48-h EC_{50} >91 mg/l MCPP-P (mm)	Valid	Bell, 1994
Daphnia sp. Acute Immobilisation EEC Dir 79/831, Annex V, Part C, GLP	*Daphnia magna*	MCPP-P (>90%)	48-h EC_{50} >100mg/l MCPP-P (n verified)	Valid	Elendt-Schneider, 1991
Freshwater	*Pseudokirchneriella*	MCPP-P	72-h E_rC_{50}	Valid	Dohmen, 1993b

[1] https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/126794

Algal Growth Inhibition OECD 201, GLP	*subcapitata*	(92.2%)	>729 mg/l MCPP-P (n verified)		
Freshwater Algal Growth Inhibition OECD 201, GLP	*Anabaena flos-aquae*	MCPP-P DMA salt (92.2%)	72-h E_rC_{50} 23.9 mg/l MCPP-P (mm)	Valid	Armstrong, 2000
Freshwater Algal Growth Inhibition OECD 201, GLP	*Navicula pelliculosa*	MCPP-P DMA salt (601.4 g MCCP-P/l)	72-h E_rC_{50} 105 mg/l MCPP-P (mm)	Valid	Jenkins, 2007
Freshwater Algal Growth Inhibition OECD 201, GLP	*Skeletonema costatum*	MCPP-P DMA salt (601.4 g MCCP-P/l)	72-h E_rC_{50} 102 mg/l MCPP-P (mm)	Valid	Burke, 2007
Lemna sp. Growth Inhibition Test OECD Guideline 221, GLP	*Lemna minor*	MCPP-P DMA salt (765.7 g MCCP-P/l)	7 day E_rC_{50} >56 mg/l MCPP-P (n verified)	Valid	Caley and Kelly, 1999
Lemna sp. Growth Inhibition Test FIFRA 122-2 and 122-3, GLP	*Lemna gibba*	MCPP-P DMA salt (65.62 % active salt)	9 day E_rC_{50} 4.86 mg/l MCPP-P (mm) 6 day E_rC_{50} 5.92 mg/l MCPP-P (mm)	Valid 7 day value not available	Hoberg and Witting, 1992
Myriophyllum spicatum Growth Inhibition Test OECD Guideline draft, GLP	*Myriophyllum spicatum*	Mecoprop-P K 600 formulation (601.4 g/l active ingredient)	14 day E_rC_{50} 0.0269 mg/l (shoot length) MCPP-P (n verified)	Valid Additional information	Gonsior, 2015
Myriophyllum spicatum Growth Inhibition Test OECD Guideline draft, GLP	*Myriophyllum spicatum*	Mecoprop-P K 600 g/l (582.9 g/l active ingredient)	14 day E_rC_{50} 0.0329 mg/l MCPP-P (n verified)	Valid Additional information	Seeland-Fremer and Mosch, 2015

Notes:
mm refers to mean measured concentrations
n refers to nominal concentrations

11.5.1 Acute (short-term) toxicity to fish

Study 1 – Anonymous, 1984

The study used MCPP-P and followed OECD Test Guideline 203 with Rainbow trout (*Oncorhynchus mykiss*). A nominal exposure range 31.6, 46.4, 68.1, 100, 147, 215 and 316 mg/l was employed in a static system. Undissolved test material was observed at all concentrations and increased with increasing exposure concentration. At 72 hours no undissolved material was visible and at termination the study was considered to meet test guideline criteria. Measured concentrations were not within 20% nominal and the 96-h LC_{50} was recalculated for review under Regulation (EC) No 1107/2009 as 171 mg a.s./l (MCPP-P). This is based on 0% mortality at nominal treatment 147 mg/l (mean measured 135 mg/l) and 100% mortality at nominal treatment 215 mg/l (mean measured 207 mg/l).

It is noted that due to the undissolved material, the reliability of the test is reduced.

Study 2 – Anonymous, 1989b

The study used MCPP-P and followed US EPA Test Guideline Subdivision E 72-1 with Bluegill sunfish (*Lepomis macrochirus*). Two nominal exposure concentrations of 50 and 100 mg/l were employed in a static system. The study was considered to meet test guideline criteria. Measured concentrations were within 20% nominal. No mortality was observed at 50 mg/l and 13% mortality was observed at the highest exposure concentration of 100 mg/l. On that basis the 96-h LC_{50} was considered to be >100 mg a.s./l (MCPP-P).

The RAR references 5 further acute toxicity to fish studies using MCPP racemic and MCPP-P DMA salt. As the studies are not more sensitive than endpoints from studies using MCPP-P, details are not included in this CLH report.

Additional information

A prolonged toxicity to fish study (Anonymous 1993e) following OECD Test Guideline 204 is available using MCPP-P. The study used Rainbow trout (*Salmo gairdneri*) and ran for 28 days using a flow through system. The nominal exposure range was 1, 10, 50 and 100 mg/l. No mortality was observed. Based on mean body weight, the study NOEC was 50 mg/l. As analytical measurements were within 20% nominal, the endpoint is based on nominal concentrations.

This study is included as supporting information as in April 2014 the test guideline was removed by OECD.

A second prolonged toxicity to fish study (Anonymous, 1990d) is also referenced in the RAR using MCPP as DMA salt. It is not considered reliable as test concentrations could not be verified.

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

Study 1 – Bell (1994)

A static acute toxicity to *Daphnia magna* study is available following OECD Test Guideline 202 and MCPP-P. Study conditions were acceptable and validity criteria were met. The exposure range was nominally 1, 2.2, 4.6, 10, 22, 46 and 100 mg/l. Analytical measurements were 81-92% of nominal. Based on mean measured concentrations, the 48-h EC_{50} was >91 mg/l as MCPP-P.

Study 2 – Elendt-Schneider (1991)

A static acute toxicity to *Daphnia magna* study using MCPP-P is available following EEC Dir 79/831, Annex V Part C which was considered to closely follow OECD Test Guideline 202. Study conditions were acceptable and validity criteria were met. The exposure range was nominally 12.5, 25, 59 and 100 mg/l. Analytical measurements were 97.6-103.5% of nominal. The 48-h EC_{50} was >100 mg/l (nominal concentration) as MCPP-P.

11.5.3 Acute (short-term) toxicity to algae or other aquatic plants

One toxicity to algae study is available using MCPP-P, the study details are presented below.

Three further toxicity to algae studies with different species are available using MCPP-P DMA salt. These are also presented below as MCPP-P is herbicide so algae and aquatic plants are considered the key trophic level.

A 7-day toxicity to *Lemna* sp. study is also available using MCPP-P DMA salt. Details are included below as a study with pure MCPP-P is not available and the endpoints are relevant for classification.

Two studies assessing growth inhibition to the aquatic plant *Myriophyllum spicatum* are available using the product Mecoprop-P K 600. Mecoprop-P K 600 g/l is a liquid soluble concentrate containing 600 g mecoprop-P acid/l, formulated as the potassium salt. The studies are considered valid and reliable. Given this test species is considerably more sensitive than standard test species, the endpoints are discussed below for hazard classification with values presented as MCPP-P.

Study 1 – Dohmen, (1993b)

A 72-hour static algal growth inhibition test using MCPP-P and the freshwater algae *Pseudokirchneriella subcapitata* is available following GLP and OECD Test Guideline 201. Study conditions were acceptable and validity criteria were met – including those in the current OECD 201 test guideline. The nominal exposure range was 3, 9, 27, 81, 243 and 729 mg/l. Analytical measurement by HPLC-UV were 97.4 to 105.2% of nominal.

The 72-h E_rC_{50} was calculated to be >729 mg/l MCPP-P based on nominal concentrations.

Study 2 – Armstrong, (2000)

A 72-hour static algal growth inhibition test using the freshwater algae *Anabaena flos-aquae* and MCPP-P DMA salt is available following GLP and OECD Test Guideline 201. Study conditions were acceptable and validity criteria were met. The 72-h E_rC_{50} was calculated to be 23.9 mg/l MCPP-P based on mean measured concentrations.

Study 3 – Jenkins (2007)

A 72-hour static algal growth inhibition test using the freshwater algae *Navicula pelliculosa* and MCPP-P DMA salt is available following GLP and OECD Test Guideline 201. Study conditions were acceptable and validity criteria were met. The 72-h E_rC_{50} was calculated to be 105 mg/l MCPP-P based on mean measured concentrations.

Study 4 – Burke (2007)

A 96-hour static algal growth inhibition test using the marine algae *Skeletonema costatum* and MCPP-P DMA salt is available following GLP and OECD Test Guideline 201. Study conditions were acceptable and validity criteria were met. The 72-h E_rC_{50} was calculated to be 102 mg/l MCPP-P based on mean measured concentrations.

Study 5 – Caley and Kelly (1999)

A semi-static 7-day toxicity to *Lemna minor* study using MCPP-P DMA salt is available following GLP and OECD Test Guideline 221. The nominal exposure range was 0.1, 0.32, 1.0, 3.2, 10, 32 and 100 mg MCPP-P DMA salt/l. Measured concentrations were within 20% of nominal. The pH of exposure solutions increased by >1.5 units over the study period although this is not considered to have impacted test results. Validity criteria were met and the test is considered reliable.

The study 7-d E_rC_{50} was above the highest exposure concentration and considered to be >56 mg MCPP-P/l based on nominal concentrations.

Study 6 - Hoberg & Wittering (1992)

A semi-static 14-day toxicity to *Lemna gibba* study using MCPP-P DMA salt is available following GLP and FIFRA Test Guideline 122-2 and 122-3. Observations were undertaken on days 3, 6, 9, 12 and 14. Analytical measurement was included and results were calculated based on mean measured MCPP-P DMA salt with equivalent concentrations as MCPP-P acid. The study reported the 14-day $EC_{50(\text{frond number})}$ as 1.6 mg MCPP-P/l based on mean measured concentrations.

As endpoints based on a 7 day study duration are preferred for classification, the study data have been reanalysed (Exponent, 2017) using non-linear regression analysis for ECx values. The analysis determined the below endpoints which are based on growth rate (frond number) and mean measured concentrations of MCPP-P DMA salt, presented as MCPP-P acid.

Table 37: *Lemna gibba* EC_{50} (95% confidence limits) values over study duration as mg/l MCPP-P acid (Hoberg & Wittering, 1992 and Exponent, 2017)

Endpoint	0 – 3 days	0 – 6 days	0 – 9 days	0 – 12 days	0 – 14 days
E_rC_{50}	3.30 (0.01 – 862)	5.92 (0.96 – 33)	4.86 (1.5 – 15)	3.54 (1.6 – 7.5)	3.09 (1.5 – 6.5)

Study 7 - Gonsior (2015) – Additional information

This study used the formulation Mecoprop-P K 600 with 601.4 g/l active ingredient. The 14 day, semi-static, GLP study followed OECD Draft Guideline: Water-Sediment *Myriophyllum* sp. Toxicity Test based on Draft AMRAP Method: Growth Inhibition Test for the Rooted Aquatic Macrophyte, *Myriophyllum* sp. Submitted to OECD for Evaluation, 22 July 2013. A water-sediment system was employed with a single shoot of uniform size (± 10%) rooted in artificial sediment according to OECD Test Guideline 219 (350 g wet weight per vessel) and overlaid with 1.5 litre of aqueous media.

The test item was applied to the water phase with the following nominal concentrations range: 1.91, 6.10, 19.5, 62.5 and 200 µg/l. This was equivalent to 0.917, 2.93, 9.37, 30.0 and 96.1 µg/l active ingredient MCPP-P. Two days after the preparation of test systems the shoot was planted and the test item applied to the water phase with gentle stirring.

Observations included shoot length, plant fresh weight, plant dry weight and number and length of side shoots.

Measured MCPP-P (refer to Table 38) at the start was 102 and 111 % of nominal in the overlaying water. After 14 days mean MCPP-P concentrations in the overlaying water were 87-107% of nominal. As this is between 80 and 120 % of nominal endpoints were based on nominal concentrations. Test validity criteria were met.

Table 38: Measured concentrations of MCPP-P in overlying water (Gonsior, 2015)

Time	Nominal concentration		Overlaying water (measured concentrations)	
	Test item	Mecoprop-p acid	Mecoprop-p acid	
[d]	[µg/L]	[µg/L]	[µg/L]	[% of nominal]
0	control	0.00	n.d.	-
14			n.d.	-
0	1.91	0.917	1.02	111
14			0.808	88
0	6.10	2.93	3.00	102
14			2.56	87
0	19.5	9.37	10.0	107
14			8.88	95
0	62.5	30.0	33.2	111
14			29.6	99
0	200	96.1	101	105
14			103	107
Mean test start (0d)				107
Mean test end (14d)				95

LOQ = 0.0961 mg/L Mecoprop-p for water; n.d. = not detectable

Table 39: Measured concentrations of MCPP-P in sediment (Gonsior, 2015)

Time	Nominal concentration		Sediment (measured concentrations)	
	Test item	Mecoprop-p acid	Mecoprop-p acid	Mecoprop-p acid[1)]
[d]	[µg/L]	[µg/L]	[mg/kg]	[% of nominal]
14	control	0.00	n.d.	-
	1.91	0.917	n.d.	-
	6.10	2.93	n.d.	-
	19.5	9.37	< LOQ	-
	62.5	30.0	0.00899	7
	200	96.1	0.0277	7

LOQ = 0.005 mg/kg Mecoprop-p for sediment; n.d. = not detectable; [1)]based on 1.5 L test medium and 350 g wet sediment

The following endpoints were calculated based on the active ingredient MCPP-P:

14-d $E_rC_{50\ shoot\ length}$ 26.9 µg/l (0.0269 mg/l)

14-d $E_rC_{50\ wet\ weight}$ 53.3 µg/l (0.0533 mg/l)

14-d $E_rC_{50\ dry\ weight}$ >200 µg/l (0.2 mg/l)

Measured concentrations of MCPP-P in the water and sediment phases are presented above (Table 38 and 39). MCPP-P concentrations in the overlying water remained within 20% of nominal application rates. While sediment analysis was only conducted at the end of the study, MCPP-P was only detected in highest exposure treatments sediment which were 7% of nominal or less. On this basis, it is considered that the active ingredient remained in the water phases sufficiently for the quoted endpoint to be reliable.

Study 8 – Seeland-Fremer and Mosch (2015) Additional information

The study used the formulation Mecoprop-P K 600 with 582.9 g/l active ingredient. The 14 day, static, GLP study followed OECD Guideline: New Test Guideline 239: Water-Sediment *Myriophyllum spicatum* Toxicity Test (20-May-2014).

A water-sediment system was employed with a single shoot of uniform size (± 10%) rooted in artificial sediment according to OECD Test Guideline 219 and overlaid with aqueous media.

The test item was applied to the water phase with the following nominal concentrations range: 10, 31.7, 100, 316 and 1000 µg/l. This was equivalent to 4.74, 15, 47.4, 150 and 474 µg/l active ingredient MCPP-P. The test item applied to the water phase with gentle stirring.

Observations included shoot length, plant fresh weight and plant dry weight. Analytical measurement of fresh aqueous media was 103 to 113% of nominal with expired solutions on day 14 being 89-100% of nominal. There was no analytical measurement of sediment. However, given the low losses observed in the aqueous phase in the study and analytical verification in the Gonsior, 2015 study, it is likely sediment concentrations were minimal indicating the quoted endpoint to be reliable. Given aqueous phase mean measured concentrations were within 20% of nominal, endpoints were based on nominal and calculated for active ingredient MCPP-P. The following endpoints were determined for the study.

Table 40: *Myriophyllum spicatum* endpoints based on MCPP-P (Seeland-Fremer and Mosch, 2015)

Endpoint	Shoot length	Biomass (fresh weight)	Biomass (dry weight)
E_rC_{10}	< 4.74 µg/l (<0.00474 mg/l)	< 4.74 µg/l (<0.00474 mg/l)	< 4.74 µg/l (<0.00474 mg/l)
E_rC_{50}	133 µg/l (0.133 mg/l)	38.9 µg/l (0.0389 mg/l)	32.9 µg/l (0.0329 mg/l)
NOE_rC	4.74 µg/l (0.00474 mg/l)	< 4.74 µg/l (<0.00474 mg/l)	15 µg/l (0.015 mg/l)

11.5.4 Acute (short-term) toxicity to other aquatic organisms

No data.

11.6 Long-term aquatic hazard

In addition to studies using MCPP-P, studies using MCPP racemic mixture, MCPP-P dimethylamine (DMA) salt and a MCPP-P formulation (liquid soluble concentrate containing 600 mg mecoprop-P acid with confidential co-formulates at unknown levels) are presented in the RAR.

Valid studies relevant for the classification of MCPP-P are presented in Table 41. This includes studies using MCPP dimethylamine (DMA) salt if there is not an equivalent study using MCPP-P or if the endpoint reflects the most sensitive trophic level endpoint. Where this is the case, endpoints are presented as MCPP-P.

Endpoints for Myriophyllum spicatum with studies using the formulation Mecoprop-P K 600 g/l are presented as additional information. While MCPP-P is a herbicide and Myriophyllum spicatum appears to be more sensitive than other aquatic plants, the formulation includes co-formulants in addition to water - the concentrations and impact of these substances in the studies is not clear. For example one co-formulant has an environmental self-classification (Aquatic Chronic 2 and 4) and the ecotoxicity to Myriophyllum spicatum is unknown.

As discussed in section 11.5 above degradants are not considered further for classification.

Table 41: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results	Remarks	Reference
Fish Early-Life Stage toxicity, OECD 210, GLP	Rainbow trout (*Oncorhynchus mykiss*)	MCPP-P (94.62%)	NOEC 11.1 mg/l MCPP-P (mm)	Valid	Anonymous, 2015
Daphnia magna Reproduction EEC XI/681/86 and OECD 202, GLP	*Daphnia magna*	MCPP-P (92.2%)	21-d NOEC 50 mg/l MCPP-P (n verified)	Valid	Dohmen, 1993
Daphnia magna Reproduction OECD 202, GLP	*Daphnia magna*	MCPP DMA salt (91.6%)	21-d NOEC 22.5 mg/l MCPP (n verified at exposure concentration)	Valid	Müllerschön (1990)
Freshwater Algal Growth Inhibition OECD 201, GLP	*Pseudokirchneriella subcapitata*	MCPP-P (92.2%)	72-h E_rC_{10} 145 mg/l MCPP-P (n verified)	Valid	Dohmen, 1993b
Freshwater Algal Growth Inhibition OECD 201, GLP	*Anabaena flos-aquae*	MCPP-P DMA salt (92.2%)	72-h NOE_rC 5.96 mg/l MCPP-P (mm)	Valid	Armstrong, 2000
Freshwater Algal Growth Inhibition OECD 201, GLP	*Navicula pelliculosa*	MCPP-P DMA salt (601.4 g MCCP-P/l)	72-h E_rC_{10} 40.2 mg/l MCPP-P (mm)	Valid	Jenkins, 2007
Freshwater Algal Growth Inhibition OECD 201, GLP	*Skeletonema costatum*	MCPP-P DMA salt (601.4 g MCCP-P/l)	72-h E_rC_{10} 86 mg/l MCPP-P (mm)	Valid	Burke, 2007
Lemna sp. Growth Inhibition Test OECD Guideline 221, GLP	*Lemna minor*	MCPP-P DMA salt (765.7 g MCCP-P/l)	7 day NOE_rC 0.18 mg/l MCPP-P (n verified)	Valid	Caley and Kelly, 1999

Lemna sp. Growth Inhibition Test FIFRA 122-2 and 122-3, GLP	*Lemna gibba*	MCPP-P DMA salt (65.62 % active salt)	**6 day E_rC_{10} 0.32 mg/l MCPP-P (mm)** **9 day E_rC_{10} 0.447 mg/l MCPP-P (mm)**	Valid	Hoberg and Witting, 1992
Myriophyllum spicatum Growth Inhibition Test OECD Guideline draft, GLP	*Myriophyllum spicatum*	Mecoprop-P K600 formulation (601.4 g/l active ingredient)	14 day E_rC_{10} 0.001 mg/l MCPP-P 14 day NOE_rC 0.009 mg/l MCPP-P (n verified)	Valid Additional information	Gonsior, 2015
Myriophyllum spicatum Growth Inhibition Test OECD 239 Guideline, GLP	*Myriophyllum spicatum*	Mecoprop-P K 600 g/l (582.9 g/l active ingredient)	14 day E_rC_{10} <0.00474 mg/l MCPP-P 14 day NOE_rC 0.00474 mg/l MCPP-P (n verified)	Valid Additional information	Seeland-Fremer and Mosch, 2015

Notes:
mm refers to mean measured concentrations
n refers to nominal concentrations
Bold values indicate most sensitive endpoint

11.6.1 Chronic toxicity to fish

Study 1 – Anonymous (2015)

A flow through chronic toxicity to fish study using MCPP-P following GLP and OECD Test Guideline 210 is available. The study ran for 89 days reflecting 60 days post hatch. The study used Rainbow trout (*Oncorhynchus mykiss*) and the following endpoints: hatching rate, development rate, survival and growth (length and dry weight). General observations were also recorded. It is noted the temperature slightly exceeded the test guideline range although it was not considered to have impacted the study. Additional study conditions were acceptable and validity criteria were met. The nominal exposure range was 0.12, 0.38, 1.2, 3.8 and 12 mg a.s./l. Exposure solutions were prepared with the aid of the solvent dimethylformamide (DMF) and a solvent control was included.

No statistically significant effects were observed for any parameter. On that basis, the study NOEC for all parameters was considered to be 11.1 mg a.s./l based on the highest treatment and mean measured concentrations.

11.6.2 Chronic toxicity to aquatic invertebrates

Study 1 – Dohmen (1993)

A semi-static chronic toxicity to *Daphnia magna* study is available using MCPP-P following GLP and EEC guideline XI/681/86 (in part also OECD Test Guideline 202). In addition, the study is considered to closely follow OECD Test Guideline 211. The nominal exposure range was 2.5, 10, 25, 50 and 100 mg/l. Analytical measurement verified nominal concentrations were within 20% of nominal. The study was reviewed under Directive 91/414/EC with conditions considered acceptable and the study is considered valid.

The 21-day NOEC based on reproduction and juvenile mortality was 50 mg/l based on nominal concentrations. It was not possible to calculate an EC_{10} value as effects were only observed at the highest treatment.

Study 2 – Müllerschön (1990)

A semi-static chronic toxicity to *Daphnia magna* study is available using MCPP as DMA salt. The study followed GLP and OECD Test Guideline 202 (1981). The study met validity criteria in the current OECD Test Guideline 211. The exposure concentration range was 2.5, 7.4, 22.2, 66.7 and 200 mg/l MCPP. Analytical verification was undertaken for the 2.5, 22.2 and 200 mg/l MCPP treatments for the first and last renewal periods of 0 to 48 hours. Measured concentrations were 100 to 104.5% of nominal for the 22.2 mg/l and 85.7 to 86.4 for the 200 mg/l treatments. The 21-day NOEC based on reproduction was 22.2 mg/l MCPP based on nominal concentrations.

The endpoint is based on MCPP which is the racemic mixture and it unclear what the concentrations of the R isomer were. However, this is unlikely to be <1mg/l the relevant cut off for aquatic chronic classification criteria.

11.6.3 Chronic toxicity to algae or other aquatic plants

One toxicity to algae study is available using MCPP-P. Full study details are presented in section 11.5.3 above with the chronic endpoint detailed below. Three further toxicity to algae studies with different species are available using MCPP-P DMA salt. As detailed previously, these are also presented because MCPP-P is a herbicide so algae and aquatic plants are key relevant species.

Toxicity to *Lemna* sp. studies are also available using MCPP-P DMA salt. Details are included below as a study with pure MCPP-P is not available and the endpoints are relevant for classification.

As described in section 11.5.2, the endpoints from two toxicity *Myriophyllum spicatum* studies are also presented as additional information. The studies used the formulation Mecoprop-P K 600 g/l with the endpoints quoted as MCPP-P active ingredient.

Where available, E_rC_{10} values are presented in preference to NOE_rC values.

Study 1 – Dohmen, (1993b)

Using *Pseudokirchneriella subcapitata*, the 72-h E_rC_{10} was determined to be 145 mg/l MCPP-P based on nominal concentrations.

Study 2 – Armstrong, (2000)

Using *Anabaena flos-aquae*, the 72-h NOE_rC was determined to be 5.96 mg/l MCPP-P based on mean measured concentrations.

Study 3 – Jenkins (2007)

Using *Navicula pelliculosa* the 72-h E_rC_{10} was determined to be 40.2 mg/l MCPP-P based on mean measured concentrations.

Study 4 – Burke (2007)

Using *Skeletonema costatum* the 72-h E_rC_{10} was determined to be 86 mg/l MCPP-P based on mean measured concentrations.

Study 5 – Caley and Kelly (1999)

Using *Lemna minor* the 7-d NOE_rC was 0.18 mg/l MCPP-P based on verified nominal concentrations.

Study 6 - Hoberg & Wittering (1992)

The study data has been reanalysed NOE_rC and E_rCx endpoints were calculated based on Williams Multiple t-test and non-linear regression analysis (Exponent, 2017) and presented below based on growth rate (frond number) and mean measured concentrations of MCPP-P DMA salt, presented as MCPP-P acid.

Endpoints based on a 7 day duration are preferred for classification. However, observations are only available for days 3, 6, 9, 12 and 14. On this basis the day 6 and 9 E_rC_{10} endpoints are the closest and within the same classification range indicating the 7 day endpoint would fall within this range.

As effects were observed in all treatments at days 6 and 9, a NOE_rC could not be determined.

Table 42: *Lemna gibba* NOEC and ECx values (95% confidence limits) over study duration as mg/l MCPP-P acid (Hoberg & Wittering, 1992 and Exponent, 2017)

Endpoint	0 – 3 days	0 – 6 days	0 – 9 days	0 – 12 days	0 – 14 days
E_rC_{10}	0.0372 (0.00 – 4.1)	0.320 (0.08 – 1.3)	0.447 (0.17 – 1.2)	0.566 (0.29 – 1.1)	0.634 (0.33 – 1.2)
E_rC_{20}	0.174 (0.003 – 15)	0.871 (0.22 – 3.4)	1.01 (0.41 – 2.5)	1.06 (0.58 – 2.0)	1.09 (0.60 – 2.0)
NOE_rC	<0.438	<0.438	<0.438	<0.438	0.992

Study 7 - Gonsior (2015) – Additional information

The 14-d $E_rC_{10\ shoot\ length}$ was 0.0015 mg/l MCPP-P, with the 14-d $E_rC_{10\ wet\ weight}$ was 0.00106 mg/l MCPP-P based on verified nominal concentrations.

The 14-d NOE_rC for both shoot length and wet weight was determined as 0.009 mg/l MCPP-P, both based on verified nominal concentrations.

Study 8 – Seeland-Fremer and Mosch (2015) – Additional information

The study considered the 14-d E_rC_{10} for shoot length and wet weight to be <0.00474 mg/l MCPP-P for shoot length and wet weight based on verified nominal concentrations. It is noted that 2.1% inhibition was observed at the 0.00474 mg/l MCPP-P treatment and 17.9% at the next treatment of 0.015 mg/l MCPP-P.

The study determined the 14-d NOE_rCs for shoot length and wet weight to be 0.00474 mg/l MCPP-P, based on verified nominal concentrations. It is noted that all treatments were considered statistically significant compared to controls for growth rate based on wet weight (16.8% inhibition at 0.00474 mg/l MCPP-P 35.3% inhibition at the next treatment) and indicating the $NOE_rC_{wet\ weight}$ may be <0.00474 mg/l MCPP-P.

11.6.4 Chronic toxicity to other aquatic organisms

No data.

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

Acute toxicity data are available on technical MCPP-P for fish, invertebrates, algae and aquatic plants and all acute ecotoxicity endpoints were >1 mg/l. Considering these data alone would result in no Aquatic Acute classification.

Data are available for *Myriophyllum spicatum* using an aqueous formulation. Based on a 14-day E_rC_{50} of 0.0269 mg/l MCPP-P, this would result in a classification of Aquatic Acute 1 (M=10). However, while MCPP-P is a herbicide and *Myriophyllum spicatum* appears to be more sensitive than other trophic levels and aquatic plants, the formulation includes co-formulants (at unknown concentrations) in addition to water and the impact of these substances in the studies is not clear. Therefore it is not appropriate to use this data for hazard classification.

Based on available data, degradation products of MCPP-P are not more acutely toxic than the parent substance and are not considered further for classification.

Overall, based on available, relevant data, MCPP-P does not require an Aquatic Acute classification.

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

MCPP-P is considered hydrolytically stable.

MCPP-P is susceptible to photodegradation. Study experimental DT_{50} values were 3.39 to 4.65 days based on southern Europe sunshine. In addition, the DT_{50} for the principle degradant *o*-cresol was determined as 41.91 days based on southern Europe sunshine. It is noted that the actual degree of photodegradation in the aquatic environment depends on local conditions and seasons and is difficult to quantify. Given the available data, there is insufficient information to evaluate photodegradation in the European environment in terms of mineralisation or transformation to non-classifiable substances.

In an OECD Test Guideline 301F study, MCPP-P was considered readily biodegradable meeting the 10 day window.

Limited mineralisation was observed in a surface water simulation study and water/sediment simulation studies using MCPP-P although this significantly less than 70% by day 28. Whole system DT_{50} values at 12 °C range from 44.4 to 463 days. Several aquatic degradants were observed although none at >5% AR.

While MCPP-P is considered readily biodegradable following a valid OECD 301F study with non-adapted inoculum, it is noted that limited mineralisation was observed in various simulations tests. Degradation half lives can be influenced and vary based on the test system media which may explain the observed difference. In general, chemicals that pass the OECD 301 ready biodegradation criteria under stringent test conditions are likely to undergo rapid degradation in the aquatic environment under most conditions.

Overall, on the basis of the ready biodegradation study, MCPP-P is considered to be rapidly degradable for the purpose of classification.

MCPP-P is considered to have a Log Kow below the CLP threshold of 4. An experimental BCF for MCPP is below the CLP threshold of 500. Overall, MCPP-P is considered to have a low potential for bioaccumulation.

Chronic toxicity data are available on technical MCPP-P for fish, invertebrates and algae and all chronic endpoints were >1 mg/l. Considering these data alone would result in no Aquatic Chronic classification.

Chronic endpoints are available for *Lemna* spp which would result in a classification of Aquatic Chronic 3 for a rapidly degradable substance. This is based on 6 and 9 day E_rC_{10} values in the range 0.1 to 1 mg/l.

Valid aquatic data are available for *Myriophyllum spicatum* using an aqueous formulation. Considering reliable chronic endpoints in the range 0.001 to 0.01 mg/l MCPP-P, this would result in a classification of Aquatic Chronic 1 (M=1) for a rapidly degradable substance. However, while MCPP-P is a herbicide and *Myriophyllum spicatum* appears to be more sensitive than other trophic levels and aquatic plants, the formulation includes

co-formulants in addition to water and the impact of these substances in the studies is not clear. Therefore it is not appropriate to use this data for hazard classification.

Overall, based on available, relevant data, MCPP-P should be classified as Aquatic Chronic 3.

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

No Aquatic Acute classification

Aquatic Chronic 3, Chronic M-Factor: not required

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

Not applicable, as an Ozone Depleting Potential (ODP) is not reported for MCPP-P and it is not listed in Annex I to Regulation (EC) No. 1005/2009 (recognising the Montréal Protocol).

12.1.1 Short summary and overall relevance of the provided information on ozone layer hazard

Not required.

12.1.2 Comparison with the CLP criteria

Not applicable.

12.1.3 Conclusion on classification and labelling for hazardous to the ozone layer

Not applicable.

13 ADDITIONAL LABELLING

No additional label.

14 REFERENCES

This section includes the non-confidential references. The confidential references (inducated in the text by 'Anonymous, XXXXx') are provided in Annex III.

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Draft Assessment Report – Mecoprop-P – Volume 3, Annex B.6: Toxicology and Metabolism, 2016

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15 ANNEXES

Annex I: Robust Study Summaries – not prepared as part of this report

Annex II: CONFIDENTIAL - Composition of mecoprop-p

Annex III: CONFIDENTIAL - Confidential references