Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

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

CLH-O-0000006713-73-01/F

Adopted

20 September 2019

20 September 2019

CLH-O-0000006713-73-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **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**

The proposal was submitted by **the United Kingdom** and received by RAC on **31 July 2018.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

The United Kingdom has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **8 October 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **7 December 2018**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Stine Husa**

Co-Rapporteur, appointed by RAC: **Laure Geoffroy**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **20 September 2019** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	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	
RAC opinion	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]	Acute Tox. 4 Eye Dam. 1 Aquatic Acute 1 Aquatic Chronic 1	H302 H318 H400 H410	GHS07 GHS05 GHS09 Dgr	H302 H318 H410		oral: ATE = 431 mg/kg bw M=10 M=10	
Resulting entry in Annex VI if adopted by Commission	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]	Acute Tox. 4 Eye Dam. 1 Aquatic Acute 1 Aquatic Chronic 1	H302 H318 H400 H410	GHS07 GHS05 GHS09 Dgr	H302 H318 H410		oral: ATE = 431 mg/kg bw M=10 M=10	

GROUNDS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

The DS included three oral toxicity studies with mecoprop-P in the rat, two of which were according to OECD TG401 and GLP and one study similar to OECD TG401, however not GLP. In addition, one study in mice according to OECD TG425 and GLP with the potassium salt of mecoprop-p was assessed.

LD_{50} values ranges from 431 to 1327 mg/kg bw in the rat, while in the mouse the LD_{50} value was greater than 3393 mg/kg bw. No human data for the evaluation of acute oral toxicity of mecoprop-p are available. On this basis the DS proposed to classify mecoprop-P as acute oral toxicity in category 4 (300<ATE 2000 mg/kg bw). Further, the DS proposed an ATE-value of 431 mg/kg bw based on the lowest observed LD_{50} value in the rat.

Comments received during public consultation

Three commenting Member States supported the proposed classification for acute oral toxicity and the proposed ATE value.

Assessment and comparison with the classification criteria

Four studies for the evaluation of acute oral toxicity are summarised in the table below.

***Table**: Summary table for animal studies on acute oral toxicity.*

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, dose levels, duration of exposure**	**Results – other than lethality**	**Value LD_{50} (mg/kg bw)**
OECD 401 (1987) Oral administration GLP Anonymous (1994) EU RAR B.6.2.1.1/02	Rat, SD 5/sex/group	mecoprop-P (purity 94.4%) Single oral administration 100, 180, 320, and 580 mg/ kg bw	180 and 320 mg/kg bw: piloerection, reduced motor activity and hunched posture observed on days 1 and 2. 580 mg/kg bw: piloerection, dyspnoea, prostration, absence of traction and grasping reflex, muscular atony, reduced motor activity and unconsciousness.	Males: 431 Females: 431
OECD 401 (1987) Gavage GLP Anonymous (1990a) EU RAR B.6.2.1.1/03	Rat, CD 5/sex/group	mecoprop-P (purity not stated) 450, 567, 714, and 900 mg/ kg bw	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.	Males: 803 Females: 756 Combined: 775

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results – other than lethality	Value LD_{50} (mg/kg bw)
			In the animals that died from the treatment, altered stomach and jejunum content, dark thymic lymph nodes and pale perineal staining were observed.	
Broadly similar to OECD 401 (1981) Gavage Non-GLP Anonymous (1983) EU RAR B.6.2.1.1/01	Rat, Wistar 5/sex/group	mecoprop-P (purity not stated) 681, 1000, 1470, and 2150 mg/kg bw	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.	Males: 1327 (interpolation) Females: 681< LD_{50} < 1000 Combined: 1050
OECD 425 (2001) as a limit test Dietary administration Anonymous (2009) EU RAR B.6.2.1.2	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.	No reports of clinical signs of gross toxicity, adverse pharmacologic effects, abnormal behaviour or macroscopic abnormalities. No deaths were observed.	>3993

The LD_{50} values ranged from 431 to 1327 mg/kg bw in 3 studies with rats. No LD_{50} value could be established from a limit test with dietary exposure of mice to mecoprop-P. On this basis rat appears to be more sensitive than the mouse to the acute effects of mecoprop-P via the oral route. No human data for classification of mecoprop-P for acute oral toxicity is available.

On this basis, RAC is of the opinion that a **classification of mecoprop-P with category 4 for acute oral toxicity with an ATE value of 431 mg/kg** is justified.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

For the assessment of repeated dose oral toxicity, the DS included several studies in the rat, mice and dog for mecoprop-P as well as racemic mecoprop. These studies are summarised in the table below.

***Table**: Summary table of animal studies and effects observed at dose levels relevant for classification as STOT RE.*

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results at dose levels relevant for classification for STOT RE**	**Guidance values for classification**
Studies with mecoprop-P			
Rats, Wistar (10/sex/group) Oral, diet OECD 407 (1981) Duration was extended from 28 days to 49 days. Non-GLP Anonymous (1986a) EU RAR B.6.3.1.	49 days mecoprop-P, purity 99.4% 0, 50, and 400 ppm equivalent to 0, 4.4/4.8, 35.2/38.0 mg/kg bw/day in m/f	No deaths were observed. No substance-related effects on food consumption, bodyweight or clinical signs. **50ppm (4.4/4.8 mg/kg bw/day in m/f)** ↑ absolute and relative kidney weight (males only, 5%) **400ppm (35.2/38.0 mg/kg bw/day in m/f)** ↓ 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) No adverse histopathological effect observed.	Cat 1 ≤ 20 mg/kg bw day 20 < Cat 2 ≤ 200 mg/kg bw/day
Rats, SD (15/sex/group) Oral, diet Similar to OECD 408 Non-GLP Anonymous (1979a) EU RAR B.6.3.2.1/01	90 days mecoprop-P, 100% purity 0, 200, 400, 800, 1600, and 3200 ppm equivalent to 0, 15.6/18.4, 31.9/37.8, 67.6/75.8, 146.4/170.1, 403.2/403.5	No treatment related increase in mortality. No adverse clinical signs or behavioural changes. **200ppm (15.6/18.4 mg/kg bw/day in m/f)** ↑ kidney weight (significant, males) (m – abs: ↑ 8%, rel: ↑ 7%; f – abs: ↑ 3%, rel: ↑ 12%) **400ppm (31.9/37.8 mg/kg bw/day in m/f)** ↓ body weight females 2.8% week 13, significant)	Cat 1 ≤ 10 mg/kg bw day 10 < Cat 2 ≤ 100 mg/kg bw/day

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results at dose levels relevant for classification for STOT RE	Guidance values for classification
	mg/kg bw/day in m/f	↑ 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 (m/f) **800ppm (67.6/75.8 mg/kg bw/day in m/f)** ↓ 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) No treatment related histopathological findings in any organs.	
Supplementary 3-month oral toxicity study Rats, SD (10/sex/group) Oral, diet Anonymous (1979b) EU RAR B.6.3.2.1/02	mecoprop-P, 99.9% purity 800, 1600, and 3200 ppm equivalent to 84.1/117.8, 178.1/239.9, 429.5/539.0 mg/kg bw/day in m/f	**800ppm (84.1/117.8 mg/kg bw/day in m/f)** ↓ 8% body weight in comparison to controls (females, significant)	Cat 1 ≤ 10 mg/kg bw day 10 < Cat 2 ≤ 100 mg/kg bw/day
Rat, Han Wistar (52/sex/dose) Oral, diet OECD 451 (1981) GLP Anonymous (2008) EU RAR B.6.5.1.1.	2 years mecoprop-P 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 m/f	**100ppm (5.3/6.6 mg/kg bw/day in m/f)** ↑ relative kidney weight (both sexes: m - ↑ 10%; f - ↑ 51%) with no supporting adverse histopathology 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	Cat 1 ≤ 1.25 mg/kg bw day 1.25 < Cat 2 ≤ 12.5 mg/kg bw/day
Mice, B6C3F1 (10/sex/group) Oral, diet OECD 408 (1981) GLP	3 months mecoprop-P, purity 96.5% 0, 100, 1000, and 2500 ppm equivalent to 0, 20/30,	**100ppm (20/30 mg/kg bw/day in m/f)** ↑ urea (females only, ↑ 22%), ↓ triglycerides (females only, ↓ 44%)	Cat 1 ≤ 10 mg/kg bw day 10 < Cat 2 ≤ 100 mg/kg bw/day

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results at dose levels relevant for classification for STOT RE**	**Guidance values for classification**
Anonymous (1993c) EU RAR B.6.3.2.2.	220/330, 740/930 mg/kg bw/day in m/f		
Mouse, B6C3F1 (50/sex/group) Oral, diet OECD 451 (1981) GLP Anonymous (1996) EU RAR B.6.5.2/01	18 months mecoprop-P, 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 m/f.	**25ppm (4/4 mg/kg bw/day in m/f)** ↑ relative kidney weight (↑ 10%/4% in m/ f), ↓ relative adrenal weight (21% in m)	Cat 1 ≤ 1.67 mg/kg bw day 1.67 < Cat 2 ≤ 16.7 mg/kg bw/day
Supplementary study to the original mouse carcinogenicity study Mice, B6C3F1 (50/sex/group) Oral OECD 451 (1981) GLP Anonymous (1999) EU RAR B.6.5.2/02	18 months, mecoprop-P, purity 92.7% 0 ppm or 700/800 ppm (m/f) Equivalent to 0/0 and 112/188 mg/kg bw/day in m/f	The doses tested is above the guidance values relevant for classification	Cat 1 ≤ 1.67 mg/kg bw day 1.67 < Cat 2 ≤ 16.7 mg/kg bw/day
Dog, beagle (5/sex/dose) Oral, diet OECD 452 GLP Anonymous (1997b) EU RAR B.6.3.3.1	1 year mecoprop-P (purity 89.9 %) 0, 60, 180 and 600 ppm corresponding to 0, 2, 5, 19 mg /kg bw/day	**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)	Cat 1 ≤ 2.5 mg/kg bw/day 2.5 < Cat 2 ≤ 25 mg/kg bw/day

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results at dose levels relevant for classification for STOT RE**	**Guidance values for classification**
Rabbit, New Zealand White (5/sex/group) Dermal, occlusive OCED 410 GLP Anonymous (1993d) EU RAR B.6.3.3	21 days mecoprop-P, purity 92.6%, 0, 10, 100, or 1000 mg/kg bw/day Covered for 6 hours/day	**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%)	Cat 1 ≤ 60 mg/kg bw/day 60 < Cat 2 ≤ 600 mg/kg bw/day
Studies with mecoprop (racemate)			
Rats, Wistar (10/sex/group) Oral, diet OECD 407 Deviation – the duration was extended from 28 days to 49 days. Non-GLP Anonymous (1986a) EU RAR B.6.3.1.	49 days mecoprop racemate, (purity 92.7%) 0, 50, and 400 ppm equivalent to 0, 4.4/4.8, 35.1/37.5 mg/kg bw/day in m/f	No mortalities. No observed adverse effects on food consumption, body weight or clinical signs. **50ppm (4.4/4.8 mg/kg bw/day in m/f)** ↑ absolute kidney weight (males only, ↑6%) **400ppm (35.1/37.5 mg/kg bw/day in m/f)** ↓ 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)	Cat 1 ≤ 20mg/kg bw/day 20 < Cat 2 ≤ 200mg/kg bw/day
Rats, SD (15/sex/group) Oral, diet Similar to OECD 408 Pre-GLP Anonymous (1979a) EU RAR B.6.3.2.1/01	90 days 0, 200, 800, and 3200 ppm mecoprop racemate, 93% purity equivalent to 0, 16.5/18.2, 67.9/75.9, 390.8/398.7	No adverse clinical signs or behavioural changes. No treatment-related increase in mortality or histopathological. **200ppm (16.5/18.2 mg/kg bw/day in m/f)** ↑ 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 m/f)** ↓ body weight (females, significant) ↑ kidney weight compared to control (m: abs: ↑11%, rel: ↑12%; f: abs: ↑4%, rel: ↑11%)	Cat 1 ≤ 10 mg/kg bw/day 10 < Cat 2 ≤ 100 mg/kg bw/day

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results at dose levels relevant for classification for STOT RE	Guidance values for classification
	mg/kg bw/day in m/f	↑ (frequency and degree) of blood urea nitrogen, serum alkaline phosphatase and alanine aminotransferase (both sexes)	
Supplementary 3-month oral toxicity study Rats, SD (10/sex/group) Oral, diet Anonymous (1979b) EU RAR B.6.3.2.1/02	mecoprop racemate (93% purity) 0, 800, and 3200 ppm equivalent to 0, 81.7/121.1 and 452.5/537.1 mg/kg bw/day in m/f.	No increased mortality, abnormal behaviour or ocular lesions. No decrease in food consumption. No treatment-related histopathological effects on the eye. **800ppm (84.1/117.8 mg/kg bw/day in m/f)** ↓ body weight (females, ↓8.3%, significant)	Cat 1 ≤ 10 mg/kg bw/day 10 < Cat 2 ≤ 100 mg/kg bw/day
Rats, Wistar (15/sex/group) Oral, diet 3 months OECD 408 Non-GLP Anonymous (1985) EU RAR B.6.3.2.1/03	mecoprop racemate (purity, 92.7%) 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 m/f	No treatment-related effects on mortality, clinical signs, food consumption or body weight Significantly increased albumin levels and significantly reduced levels of platelets at all dose levels in females were explained to be due to incidental abnormal control values. **150ppm (11.4/13.4 mg/kg bw/day in m/f)** ↑ relative kidney weight (14% males, 9% females) **450ppm (34.0/39.3 mg/kg bw/day in m/f)** ↑ creatine value (females) ↓ glucose concentration in plasma (males) ↑ relative kidney weight (↑17% males, ↑8% females)	Cat 1 ≤ 10 mg/kg bw/day 10 < Cat 2 ≤ 100mg/kg bw/day
Rat, Wistar (50/sex/dose) 2 years, Oral, diet Satellite group I (10/sex/dose) was dosed for 12 months Satellite group II (15/sex/dose) was dosed for 24 months. OECD 453 (1981) GLP Anonymous (1988) EU RAR B.6.5.1.	mecoprop racemate, purity 92.7%, 0, 20, 100, and 400 ppm equivalent to 0, 1.1/1.4, 5.5/6.9, 22.2/27.9 mg/kg bw/day in m/f.	No treatment-related mortality, clinical findings or histopathological changes. **20ppm (1.1/1.4 mg/kg bw/day in m/f)** ↑ levels of triglycerides (males, significant) ↑ relative kidney weight (males, at 12 months only, non-significant ↑ 10%) **100ppm (5.5/6.9 mg/kg bw/day in m/f)** ↑ levels of triglycerides (males, significant) ↑ relative kidney weight (males, non-significant, at 12 months only, ↑ 16%)	Cat 1 ≤ 1.25 mg/kg bw/ day 1.25 < Cat 2 ≤ 12.5 mg/kg bw/day

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results at dose levels relevant for classification for STOT RE	Guidance values for classification
Dog, beagle (4/sex/dose) Oral, diet 90 days Comparable to OECD 409 (1998) Non-GLP Anonymous (1979c) EU RAR B.6.3.2.3.	mecoprop racemate purity 93.3% 0, 4, 16 and 64 mg/kg bw/day	**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	Cat 1 ≤ 10 mg/kg bw day 10 < Cat 2 ≤ 100 mg/kg bw/day

↑ - increase; ↓ - decrease

In addition to the studies mentioned in the table above, the DS included two immunotoxicity studies and one haematology study. In the two immunotoxicity studies mecoprop (racemic) were administered by gavage to Wistar rats.

The first study consisted of 3 sub-studies (one acute, one 14-day and one 90-day, all non-guideline), and investigated organ 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 (Anonymous, 1989a). A significant decrease in thymus weight was observed at 1300 mg/kg bw/day in the acute study, at ≥ 320 mg/kg bw/day in the 14-day study,

at ≥ 8 mg/kg bw/day and 320 mg/kg bw/day in males and females, respectively in the 90-day study. At ≥ 320 mg/kg bw/day, degenerative processes consisting of decreased density of lymphocytes and increased decay of leucocytes were observed in the cortex. 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, a reduction in white pulp tissue was observed. 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 (decrease in lymphocytes and increase in neutrophilic granulocytes) in the 14- and 90-day studies.

In the second study (non-guideline) effects of mecoprop (racemic) on humoral and cell immunity in adrenalectomised animals were investigated in 3 sub-studies (Anonymous 1990c). 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 500 mg/kg bw/day). In the second sub-study, significant reductions in IgG and response in the ear test were observed (15 doses of 320 mg/kg bw/day). At 320 mg/kg bw/day in the control group in sub study 3, there were significantly reductions in spleen weight, IgG concentration and lymphocyte count compared to 0 mg/kg bw/day controls. None of these findings were noted in the adrenalectomised animals at 80 and 320 mg/kg bw/day.

The DS concluded that the findings have arisen due to a stress-induced release of steroid hormones secondary to general toxicity and insufficient to warrant classification for a specific effect on the immune system.

In a non-guideline in vitro haematology study (Anonymous, 1991) it was shown that racemic mecoprop has the potential to inhibit platelet aggregation in vitro. 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 0.5 mg/ml, no inhibition was observed. It was noted that details on the conduct of this study are limited.

In summary the DS considered that the available repeated dose studies via the oral route show that the liver and kidneys are target organs of toxicity, however, there are no evidence of impaired organ function within the dose levels relevant for a classification for STOT RE. The results from studies of racemic mecoprop were consistent with those from mecoprop-P.

No severe systemic effects were observed in rabbits exposed to mecoprop-P by the dermal route. Well-defined erythema, slight or well-defined oedema and diffuse acanthosis were seen at dose levels below the guidance values for classification, however these effects were not considered sufficient for classification by the DS.

As regards exposure by the inhalation route, no repeated dose studies were available to the DS.

On this basis, the DS did not propose any classification for STOT RE by the oral, dermal or inhalation route.

Comments received during public consultation

One commenting MSCA supported no classification for STOT RE.

Assessment and comparison with the classification criteria

The DS included several studies in rats, mice and dogs for the evaluation of STOT RE. These studies are summarised below.

Oral studies in rats

In rats one 49-day study (OECD TG 407), one 90-day study (OECD TG 408) and one 2-year study are available.

In the 49-days study (Anonymous, 1986a) with oral doses of 0, 50 and 400 ppm mecoprop-p (equivalent to 0, 4.4/4.8, 35.2/38.0 mg/kg bw/day in males/females) an increase in absolute kidney weights were observed at the low dose of 50 ppm (males only, 5%) and the high dose of 400 ppm (8% in both sexes, statistically significant). Significant decreases in cholesterol levels were observed in both sexes in the high dose group. Further, at this dose level, there was a significant increase in creatinine and urea values in females and in glutamic-pyruvic transaminase (alanine aminotransferase) in males. It should be noted that no histopathological changes in the kidneys were observed.

In the 90-day study (Anonymous, 1979a) with oral doses of 0, 200, 400, 800, 1600 and 3200 ppm (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) no adverse clinical signs or behavioural changes were observed, no treatment-related increase in mortality and no treatment-related histopathological changes in any organ including the kidneys were observed. 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. Increases of blood urea nitrogen, serum alkaline phosphatase and alanine aminotransferase were observed in both sexes from 400 ppm. The liver and kidneys were the target organs in this study, however, without supportive histopathological findings for the weight increases. Effects on liver weight was only observed at dose levels exceeding the guidance values for classification for STOT RE.

In the 2-year study (OECD TG 451) with rats (Wistar) with doses of mecoprop-P in the diet 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), the liver and kidneys were found to be target organs (Anonymous, 2008). Reduced survival was reported in both sexes at the low dose with survival rates of 69/58% (m/f) compared to at least 80/70% (m/f) in the control, mid and high dose groups. An increase in relative kidney weight was observed in both sexes at 100 and 1200 ppm and in females only at 600 ppm. In this study, the only dose level relevant for classification for STOT RE is 100 ppm. At this dose level, an increase in relative kidney weight was observed in both sexes, however, without supportive histopathology. Abnormally high white cell counts were also observed at this dose level, which in isolation are not indicative of a specific target organ effect. Findings in other organs was minimal and are not considered to be of concern.

Oral studies in mice

In a 90 days study mice (B6C3F1) were exposed to mecoprop-P at dose levels equivalent to 0, 20/30, 220/330, 740/930 mg/kg bw/day in males/females (OECD TG 408) (Anonymous, 1993c). An increase in urea was observed in females only at the low dose and in both sexes at the mid and high doses. The liver and kidneys were the target organs of this study, however, at doses relevant for classification (only the low dose group), the only observations were changes in urea and triglyceride levels in females.

In a 18-month study, mice (B6C3F1) were exposed to 0, 25, 250, and 2500 ppm mecoprop-P (equivalent to 0/0, 4/4, 40/46 and 592/732 mg/kg bw/day in males/females) in the diet (OECD TG 451) (Anonymous, 1996). An increase in relative kidney weight compared to controls was observed in the low dose group (10%/4% in m/ f) and mid dose group (18%/20% in m/f). A

reduction in relative adrenal gland weight was seen in males only by 21% in the low dose group and 16% in the mid dose group. The kidney was the target organ in this study, however, at the dose level relevant for classification as STOT RE (only the low dose group) the only observations were a small increase in relative kidney weight and a decrease in relative adrenal weight.

Oral studies in dogs

In a 1-year study Beagle dogs (5/sex/dose) were exposed to mecoprop-P at dose levels equivalent to 0, 2, 5, 19 mg/kg bw/day (OECD TG 452) (Anonymous, 1997b). A few and incidentally occurring cases of diarrhoea and vomiting were reported. A decrease in bodyweight and bodyweight gain was observed in males at the high dose group. Absolute and relative liver weights were decreased in males at the low dose group. A decrease in absolute brain weight was observed in females in the mid dose group. Slight unilateral focal tubular degeneration of the kidneys was observed in one high dose male. No toxicologically significant haematological findings were observed. Slight focal atrophy of the prostate gland was observed in one male in each of the low, mid and high dose groups. 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. All dose levels in this study were within the guidance value for classification with STOT RE.

Dermal studies

New Zealand White rabbits were dermally exposed to mecoprop–P for 21/22 days (m/f) at doses of 0, 10, 100, or 1000 mg/kg bw/day (OECD TG 410) under occlusive conditions for 6 h/day (Anonymous, 1993d). No mortalities or effects on bodyweight were seen. A significant reduction in spleen weights in females were observed in the mid and high dose groups, 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 in the mid and high dose groups, respectively. At the low dose, slight erythema was observed from day 3 to day20 in 7 animals. At the mid dose, well-defined erythema and slight or well-defined oedema were 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 were observed in 1 animal. Desquamination (sloughing) of the stratum corneum was observed in majority of the rabbits.

Inhalation

No studies available.

Human information

No data available.

<u>Studies with mecoprop (racemate)</u>

In addition to the studies with mecoprop-p, 6 studies where rats and dogs were exposed orally to mecoprop (racemate) were included in the CLH dossier. These studies show comparable effects of mecoprop-p and mecoprop (racemate).

In a 49-day study (OECD TG 407) Wistar rats (10/sex/group) were exposed via diet to mecoprop (racemate, 92,7%) at dose levels of 0, 50, and 400 ppm (0, 4.4/4.8, 35.1/37.5 mg/kg bw/day in males/females) (Anonymous, 1986a). No deaths were reported and no substance-related effects on food consumption, bodyweight or clinical signs were observed. There was an increase in absolute kidney weight in the low dose group (males only, 6%) and the high dose group (7% in males and 2% in females). No histopathological changes in the kidney were observed. In the high dose group a significant decrease in levels of cholesterol and calcium in females, increase in urea concentration in males and a significant increase in glutamic-pyruvic transaminase

(alanine aminotransferase) in males were observed. In this study the kidney is considered to be the target organ, and this is consistent with the findings for a similar study with mecoprop-p.

In a 90-day study (similar to OECD 408), SD rats (15/sex/group) were exposed via diet to mecoprop (racemate, 93%) at dose levels of 0, 200, 800, and 3200 ppm (0, 16.5/18.2, 67.9/75.9, 391/399 mg/kg bw/day in males/females) (Anonymous, 1979a). No adverse clinical signs or behavioural changes were observed as well as no treatment-related increase in mortality or histopathological changes. Bodyweights of females were significantly reduced in the mid dose group. In the high dose group, body weights were significantly reduced (35%/30% in males/females). Increased kidney weights were observed in males/females at the low and mid doses. At the top dose, there was a significant decrease in kidney weight, although relative kidney weight was 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 groups. Due to technical problems, histopathological examination of the eyes was not performed. The liver and kidneys were the target organs in this study.

A supplementary study to the 90-day study described above, was conducted to perform histopathological examination of the eyes of SD rats (10/sex/group) exposed to up to 3200 ppm mecoprop (racemic, 93%) equivalent to 453/537 mg/kg bw/day in males/females (Anonymous, 1979b). A reduction in bodyweight was seen (8.3% in females in the low dose group and 37.8/20.3% in males/females in the high dose group). No adverse effects on the eyes were observed.

In another 90-day study (OECD TG 408) Wistar rats (15/sex/group) were exposed to mecoprop (racemic, 92.7%) at dose levels of 0, 50, 150 or 450 ppm (0, 3.8/4.4, 11.4/13.4, 34.0/39.3 mg/kg bw/day in males/females) (Anonymous, 1985). Relative kidney weight was increased at the mid dose (↑ 14%/9% in males/females) and high dose (↑ 17%/8% in males/females). In addition, an increased level of creatine in females and a decreased concentration of glucose in the plasma in males in the high dose group were observed. 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 a 2-year study (OECD TG 453), mecoprop (racemate, 92.7%) 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. In addition, 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. An increase in relative kidney weight was observed in males in the 20 ppm and 100 ppm dose groups at 12 months, however, not statistically significant. 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. No histopathological changes were observed in the kidneys. Significantly increased levels of triglycerides were observed in males at all doses. At the top dose, there was also a significant increase in levels of urea after 18 and 24 months.

In addition to the studies in the rat, one 90-day study (comparable to OECD TG 409) where Beagle dogs (4/sex/group) were exposed to mecoprop (racemate, 93.3) in the diet at dose levels of 0, 4, 16 or 64 mg /kg bw/day (Anonymous, 1979c) is available. In the high dose group, significant increases in the relative weights of the kidney (20%), liver (25%), heart (17.5%), lungs (16%) and brain (26%) were observed. Further, a non-significant dose-dependent reduction in absolute (47%) and relative (33%) thymus weight was observed. In the high dose group, there were decreases in total protein (9%), albumin (21%) and alkaline phosphatase (28%), which were significant only after 6 weeks, and an increase in levels of urea (59% after 6 weeks and 24% after 13 weeks). Bilirubin was decreased (25%) in the mid dose group, however, significant only after 6 weeks. An organ function test of the kidneys was indicative of an adverse

effect on kidney function, however, no supportive histopathological evidence were available. Liver function test was performed on the control and high dose groups at week 13. Bromosulphophthalein (BSP) retention was statistically significantly higher in the top dose group (6.2%) than in controls (3.0%). The increase in BSP retention was mainly attributable to a particularly high value in one male in the high dose group. Decreased packed cell volume (7% in the mid dose group, 24% at week 6 and 19% at week 13 in the high dose group) and red blood cell count (9 % in mid dose group, 25% at week 6 and 18% at week 13 in the high dose group) was observed. At the top dose, this was also accompanied by decreased haemoglobin (23% at week 6 and 16% at week 13) and decreased lymphocytes (32%, significant only after 6 weeks) and an increase in neutrophils (25%, significant only after 6 weeks). Further 3 dogs in the high dose group showed brown discolouration of adipose tissue in the mesentery. 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 of racemic mecoprop dosing and treatment with antibiotics.

Summary and comparison with the CLP criteria

Oral

The repeated dose studies evaluated for exposure by the oral route show that the liver and kidneys are the target organs following exposure to sufficiently high doses of mecoprop-P and mecoprop (racemate). However, at dose levels relevant for classification as STOT RE, the effects were limited to small changes in bodyweight, organ weight and clinical chemistry. There is no evidence of impaired organ function and the effects observed were not accompanied by adverse histopathological findings. RAC notes that Beagle dogs exposed to mecoprop (racemate) for 90 days showed a 23% decrease in haemoglobin after 6 weeks, however, after 13 weeks the decrease in haemoglobin was reduced to 16 % and no other significant indicators of haemolytic anemia were observed.

Dermal

No severe systemic effects were reported in rabbits exposed to mecoprop-P by the dermal route, and the effects observed at dose levels relevant for classification for STOT RE included well-defined erythema, slight or well-defined oedema and diffuse acanthosis. These finding are not considered sufficiently severe to justify a classification for effects by the dermal route.

Inhalation

No repeated dose studies by the inhalation route are available.

In conclusion, RAC is of the opinion that **no classification for STOT RE is warranted** for mecoprop-P.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Adverse effects on sexual function and fertility

The DS included two studies for the assessment of adverse effects on sexual function and fertility, one 2-generation study with mecoprop (racemate) and one preliminary 1- generation study with mecoprop-P. These studies are summarised in the table below.

The DS noted that the 2-generation study with racemic mecoprop is regarded as sufficient to assess the reproductive toxicity profile of mecoprop-P. Studies on both mecoprop (racemic) and mecoprop-P were taken into account in the assessment of reproductive toxicity.

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

<table>
<tr><th>Method</th><th>Results</th></tr>
<tr><td>Non-standard one-generation reproductive toxicity study

mecoprop-P, purity 92.8%
0, 500, 800 or 1200 ppm

Oral (dietary)

Rats, Han Wistar
12/sex/dose, 7-9 weeks old at the start of the study

Lactation period: the females were given diets containing nominal concentrations of 0, 300, 530 and 790 ppm (48.1, 85.8 and 130.2 mg/kg bw/day) mecoprop-P

OECD TG 415 (1983)

GLP

Deviations: 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><u>P0</u>

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>Dose (ppm)</th><th>0</th><th>500</th><th>800</th><th>1200</th><th rowspan="2">HCD[a] Range</th></tr>
<tr><th>mg/kg bw/day (females)</th><th>0</th><th>38.2</th><th>60.6</th><th>88.8</th></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</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</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.

1200 ppm

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

1200 ppm
↓ (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[n] = 800ppm
Reproductive NOAEL = 800ppm
Offspring NOAEL > 1200ppm</td></tr>
</table>

<table>
<tr><th>Method</th><th>Results</th></tr>
<tr><td>2-generation reproduction study

Rat: Wistar

25/sex/group, 35 days old at the start of the study

mecoprop racemate, purity 92.7%
0, 20, 100, or 500 ppm (1.7, 8.7 and 42.8 mg/kg bw/day)

Continuous dietary administration over 2 generations

OECD TG 416 (1983)

Deviations: 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 (1992a)

EU RAR B.6.6.1.1</td><td><u>P0</u>
No treatment-related differences in mating and fertility indices

500 ppm
↑ 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>
500 ppm:
↓ body weight gain of pups (significant (p<0.05) ↓ 6% on days 7-14 in F1a)
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>

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

<u>F1 parental animals</u>
500 ppm
↑ absolute and relative kidney weights (relative 10%/8% in m/f).

<u>F2 pups</u>

500 ppm
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 = 100ppm
Offspring NOAEL = 100ppm
Reproductive/fertility NOAEL > 500ppm</td></tr>
</table>

The one-generation study showed reductions in implantation sites and mean number of pups born. However, the DS considered the two-generation study to be more robust because no reduction in litter sizes were observed at 500ppm in any of the litters produced. The DS was of the opinion that when taking both studies into consideration, no clear evidence of a reproducible mecoprop-P-related adverse effect on sexual function and fertility in rats has been shown. This

was further supported by the repeated dose studies were no effects of concern for the reproductive system was observed. Therefore, the DS proposed no classification for adverse effects on sexual function and fertility.

Adverse effects on development

For the assessment of adverse effects on development, the DS included one study in the rat, two studies in the rabbit and one additional study in the mice, which were of lower quality. Further, one study in the rabbit and one study in the mice (of lower quality) using mecoprop (racemate) were included in the assessment. The studies are summarised in the table below.

***Table**: Summary table of animal studies in adverse effects on development*

Method	**Results**
Rat: Wistar, 25 females/group **mecoprop-P,** purity > 92.2% 0, 20, 50, or 100 mg/kg bw/day from GD6 to 15 Oral (gavage) OECD 414 (1981), GLP Deviations: 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	**<u>50 mg/kg bw/day</u>** Food consumption was significantly reduced (by about 9%) from day 6-8 post coitus ($p<0.05$) **<u>100 mg/kg bw/dday</u>** Food consumption significantly reduced (↓22%) from day 6-8 post coitus ($p<0.01$) 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 ($p<0.01$). No significant developmental toxicity in this study. NOAEL (foetotoxicity) = 50 mg/kg bw/day NOAEL (maternal toxicity) = 50 mg/kg bw/day
Developmental study Rabbit, Dutch-Belted, 15-30/ group **mecoprop (racemate)** 0, 12, 30 and 75 mg/kg bw/day from day 6-18 post insemination Oral, gavage Anonymous (1980)	No treatment related maternal effects at any dose level. No treatment-related clinical changes or deaths.. 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). ↓ mean number of implantations per doe in the mecoprop-treated groups (7.29, 7.00, 6.86 and 7.09 at 0, 12, 30 and 75 mg/kg bw/day). ↓ number of foetuses per dam (7.21, 6.36, 6.50 and 6.91 at 0, 12, 30 and 75 mg/kg bw/day) ↓ average litter weight in all treated groups (243.7, 220.7, 208.1 and 226.5 g at 0, 12, 30 and 75 mg/kg bw/day). 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 (maternal) = 75 mg/kg bw/day NOAEL (developmental) = 75 mg/kg bw/day
Preliminary dose range-finding study Rabbit, Himalayan, 5/dose	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,

Method	Results
mecoprop-P 0, 40, 80, 120 mg/kg bw/day on days 7 – 19 post insemination Dams were sacrificed on day 20 post insemination. Anonymous (1990b)	respectively. **<u>40 mg/kg bw/d</u>** Marginally reduced food consumption and body weight loss. **<u>80 mg/kg bw/d</u>** Overt signs of maternal toxicity (including increased kidney weight and increased creatinine, reduced food consumption and body weight). **<u>120 mg/kg bw/d</u>** 2/5 dams died (1 on 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, 2 dams that died and one 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 Rabbit, Himalayan, 15 females/group **mecoprop- P** (> 92.2% pure) 0, 5, 20, or 50 mg/kg bw/day (gavage) on days 7-19 post insemination. OECD 414 (1981) GLP Anonymous (1993b) EU RAR B.6.6.2.2	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. **<u>5 mg/kg bw/d</u>** No adverse effects reported. **<u>20 mg/kg bw/d</u>** No adverse effects reported. **<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) considered not to be toxicologically significant NOAEL (maternal toxicity) > 50 mg/kg bw/day NOAEL (foetotoxicity) > 50 mg/kg bw/day
Mice, NMRI, 22-59/group 0, 100, 200, 300, 400, 500, or 700 mg/kg bw/day **mecoprop racemate** or 0, 200, 300, 400, or 500 mg /kg bw/day **mecoprop-P** (gavage) from day 6 to day 15 of gestation. Guideline or GLP not stated Roll R & Matthiaschk G (1983). Published scientific article. The article was translated from German into English on 16/06/2017. EU RAR B.6.6.2.3	**mecoprop-P** ↓ foetal body weight in all treated groups **400 mg/kg bw/day** ↑ incidence of fused ribs and deformed thoracic vertebral nuclei **500 mg/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 **mecoprop (racemate)** ↓ maternal bodyweight gain in all treated groups ↓ foetal body weight in all treated groups **500 mg/kg bw/day** ↑ incidence of cleft palate **700 mg/kg bw/day** ↑ incidence of early resorptions and post implantation loss ↑ incidence of cleft palate and fused ribs

The DS is of the opinion that the available data are not sufficient for classification for adverse effects on development. This is based on the fact that there is no evidence of an effect on development in rats. Possible evidence for developmental toxicity was observed in a standard

study in rabbits, which showed an increased number of late resorptions in the absence of maternal toxicity in the high dose group. However, the number of live pups at the top dose was not significantly different from controls. The reproductive studies with mecoprop and mecoprop-P presented no reproducible evidence of an adverse effect on litter size. Further, in the repeated dose toxicity studies, the only findings relevant to reproductive toxicity are a slight increase in the incidence of benign uterine stromal polyps observed at 65 mg/kg bw/day in a 2-year rat study and the observation of cystic corpora lutea in 3/5 dogs administered 19 mg mecoprop-P/kg bw/day in a 1-year study.

Adverse effects on or via lactation

No studies available to the DS specifically investigate effects on or via lactation. The information available includes a limited 1-generation study with mecoprop-P and standard 2-generation study with mecoprop (racemate).

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. With the exception of 2 F1 parental dams (one who cannibalised 7 pups and one who did not nurse the pups properly), there is no evidence indicative of poor maternal care or adverse effects on nursing. It is possible that the pup deaths resulted from effects on or via lactation but there is no clear evidence to support this assertion.

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

On this basis no classification for effects on or via lactation was proposed by the DS.

Comments received during public consultation

One commenting MSCA was of the opinion that a classification in category 2 for development is justified, while another MSCA were of the opinion that it should be considered that the late resorptions in rabbits together with a trend for reduced number of live foetuses/rabbits could be sufficient for classification. A third MSCA noted an EFSA conclusion (EFSA Journal 2017; 15(5):4832) that mecoprop-P should be classified for developmental toxicity due to the late resorptions seen in the rabbit.

One individual submitted additional information on pup deaths in the two-generation study and supported the DS conclusion for no classification for reproductive toxicity.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

In the 2-generation study (OECD TG416, GLP) mecoprop (racemic) was administered at dose levels of 0, 20, 100 or 500 ppm in the diet. The table below show the doses in mg/kg bw/day.

***Table**: Test substance intake (mg/kg bw/day) 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 - lactation period*	 1.7 2.9	 8.7 14.4	 42.8 72.6
F0 females (F1b litter) - gestation period - lactation period*	 1.6 2.6	 8.0 13.2	 40.0 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 - lactation period*	 1.6 2.5	 8.5 13.3	 41.6 67.5

* days 0 - 14 post-partum only

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 were observed. In the high dose group, a small, inconsistent but statistically significant reduction in pup bodyweight gain were observed in the F1a group (6%, days 7-14) and in the F2 generation (8-11%, days 4-14). Further, the high dose group showed increased relative kidney weights in the F0 (12%/9% in males/females) and F1 parental animals (10%/8% in males/females). No treatment-related histopathological findings were observed.

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 was statistically increased in the F1a 500 ppm group ($p<0.01$). In the F2 pups, the number of dead pups on day 1 was significantly increased ($p<0.01$) in the high dose group ($p<0.01$). It should be noted that number of implantation sites were not recorded in this study. RAC notes that the dose levels used in this study could be too low, considering that there are no indications that the substance exert serious effects up to the cut off levels for the STOT RE classification.

In the one-generation study, mecoprop-P was administered in the diet at dose levels of 0, 500, 800 and 1200 ppm. The table below show the doses in mg/kg bw/day. It is noted that the study only included 12 rats/sex/dose, which is not in line with the test guideline.

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

	Mean dose received mg mecoprop-P/kg/day		
P0	***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
During lactation	***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
F1	***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

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

Reduced bodyweight gain was observed during the pre-mating period 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). When considering the body weight changes it is noted that the

body weight of the dams of the P-generation was reduced from gestation day 0 (GD0) to lactation day 1 (LD), However, it is noted that also the control group show a similar pattern, which could question the reliability of the study.

***Table**: Group mean body weights, P-generation*

	GD0	**GD20**	**LD1**	**BW GD20-GD0**	**Estimated litter weight***	**BW LD1-GD0**
Control	250,6	341,7	241,8	91,1	99,9	-8,8
500 ppm	245,0	323,1	229,5	78,1	93,6	-15,5
800 ppm	243,5	321,7	233,6	78,2	88,1	-9,9
1200 ppm	229,8	295,3	217,8	65,5	77,5	-12,0

*Estimated litter weight calculated as weight on GD20 minus weight on LD1.

Group mean body weight and food intake were slightly lower than in 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%).

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

No clear dose response relationship was observed for the significant reductions in number of pups born at 500 and 1200 ppm (12.7, 11.2, 11.7 and 10.0 at 0, 500, 800 and 1200 ppm, respectively). The mean number of pups born in the low and high dose groups were within the historical control data (HCD) range (9.3-11.3%), however, the control and mid dose groups were above the HCD. A statistically significant dose-related reduction in the mean numbers of implantation sites compared to controls was observed in all treated groups (13.8, 12.5, 12.4 and 10.9 at 0, 500, 800 and 1200 ppm, respectively). Also for this observation the mean number of implantation sites in the high dose group were within the historical control data (HCD) range (10.3-12.0%), while the control, low and mid dose groups were above the HCD. Corpora lutea were not measured. The historical control data provided are considered to be of limited value since the concurrent control is outside the HCD range.

***Table**: Summary of findings in the 1-generation study*

Dose (ppm)	**0**	**500**	**800**	**1200**	
mg/kg bw/day (females)	**0**	**38.2**	**60.6**	**88.8**	**HCD[a] Range**
Mean implantation sites	13.8	12.5**	12.4**	10.9***	10.3-12.0
% implantation sites	N/A	9%↓	10%↓	21%↓	
Mean pups born	12.7	11.2*	11.7	10.0**	9.3-11.3
% pups born	N/A	12%↓	8%↓	21%↓	
Mean pups alive day 1	12.3	10.7	11.2	9.8	9.3-11.2
Mean pups alive day 4	11.1	9.7	11.0	9.0	9.0-10.9

* statistically significant compared to control: * = P<0.05, ** = P<0.01, *** = P<0.001
[a]HCD = historical control data (from 13 studies) for Han Wistar rats at Covance from the period 2000-2005.

As regards maternal toxicity, it is noted that around the time of implantation (GD5), maternal bodyweight gain was particularly affected. During GD 0-7, maternal bodyweight gain was lower than controls by 18.2%, 17.6% and 49.7% at the low, mid and high doses, respectively. The increased difference in body weight gain with increasing dose levels observed from GD0 to GD20 could partly be considered to be related to the reduction in mean implantation sites and mean number of pups born. It is however noted that the mean body weight of the dams on lactation day 1 is slightly lower than on gestation day 0 (see table below), indicating that the dams actually lost weigh during the gestation period.

Overall, this study show weak indications on effects on mean implantation sites. This reduction in implantation sites can be considered to be secondary to maternal toxicity. However, there are limitations in the study and the findings are considered inconclusive for a classification.

In summary, in the 2-generation study no effect on body weight gain was observed in parental animals. The mean number of pups delivered per litter did not vary between each treatment group and generation. It is noted that the number of implantation sites were not measured in this study. Further, it is noted that the highest dose tested in the 2-generation study was equivalent to the lowest dose tested in the one-generation study, and that the dose levels in this study are considered too low to reveal possible adverse effects on fertility.

In the 1-generation study, reduced body weight gain was observed in both sexes with increasing dose level. A statistically significant dose-related reduction in the mean numbers of implantation sites and decrease in the mean number of pups born was observed in all treated groups. However, the reduction in mean number of implantation sites and pups born were correlated to a reduction in the bw gain, which decreases the concern for this finding. The reduced body weight gain with increasing dose level can only partly be explained by a reduction in mean pups born.

Overall, when taking both studies into consideration, some evidence of adverse effect of mecoprop-P on sexual function and fertility in rats has been shown, however, these effects were observed alongside maternal toxicity. This is further supported by the repeated dose studies where no effects of concern for the reproductive system was observed. RAC notes that the dose levels used in the 2-generation study and possibly also the 1-generation study could be too low, considering that there are no indications that the substance exert serious effects up to the cut off levels for the STOT RE classification, and the robustness of the available studies could be limited.

In conclusion, RAC is of the opinion that, **no classification for effects on sexual function and fertility is warranted due to inconclusive data**.

Adverse effects on development

Rats

In the prenatal developmental toxicity study with female rats (OECD TG 414, 1981) exposed by gavage to mecoprop-P at dose levels of 0, 20, 50 or 100 mg/kg bw/day no deaths or clinical signs of toxicity were observed in dams. In the high dose group, body weight gain was reduced by 18%.

Weight of the foetuses was reduced by 2%, ($p<0.05$) in the high dose group. Dilated renal pelvis and/or hydroureter were reported in all groups, however not statistically significant. In the high dose group, the incidence of rudimentary cervical ribs and unossified sternebrae increased significantly. See the table below on results of the study.

***Table**: 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

In the two-generation study with rats (OECD TG416, GLP) mecoprop (racemic) was administered at dose levels of 0, 20, 100 or 500 ppm (corresponding to approximately 2, 10 and 50 mg/kg bw/day) in the diet (Anonymous 1992a). In this study, the high dose group in the F1a generation showed a statistically significantly increase in the number of pups which died or were cannibalized from day 1 to day 4 post-partum. Pup deaths were observed in 11 out of 24 litters. The viability index of this group was statistically significantly reduced (93% vs 98% in controls). In the F1b generation, a non-significant but dose-related increase in the sum of dead pups was observed. Pup deaths were observed across the litters and were seen in 11 out of 25 litters in the high dose group. In the F2 generation, the number of dead pups on day 0 was statistically significantly increased in the high dose group. In the low dose group, 16 pups were cannibalised (7/16 by one dam). One F1 parental dam in the mid dose group gave birth to 13 live pups, none of these 13 pups were alive on day 4. Auditory canal opening was delayed at the top dose in F2 pups only, which could be secondary to reduced bodyweight.

***Table**: Total dead pups in two-generation study in rats*

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

significance level 0.05, ## significance level 0.01

In the one-generation study rats were administered mecoprop-P at dose levels of 0, 500, 800 or 1200 ppm (approximately 0, 38.2, 60.6, 88.8 mg/kg bw/d) in the diet (Anonymous 2003). A statistically significant reduction in mean implantation sites were observed at all dose levels (13.8, 12.5, 12.4, 10.9 at 0, 500, 800, 1200 ppm, respectively), however within the HCD range (10.3-12.0). It is noted that the concurrent control is above the HCD range, which questions the relevance of the HCD data. Further, the mean number of pups born were statistically significantly reduced in the low and high dose group (12.7, 11.2, 11.7 and 10.0 at 0, 500, 800 and 1200 ppm, respectively), however within the HCD range (9.3-11.3). It is noted that the concurrent control is above the HCD range. The number of mean pups alive on day 1 and 4 were not statistically different in any dose group. It is noted that the 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).

Rabbits

In a developmental study (Anonymous, 1980), rabbits (Dutch-Belted, 15-30/group) were exposed to mecoprop (racemic) 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. An increase in post-implantation loss (1.1%, 9.2%, 5.2% and 2.6% at 0, 12, 30 and 75 mg/kg bw/day, respectively) was observed in all treated groups. The mean number of implantations per doe and the number of foetuses per dam were lower in the exposed groups compared to the controls (7.29, 7.00, 6.86 and 7.09 at 0, 12, 30 and 75 mg/kg bw/day, respectively), and consequently a decreased average litter weight (243.7, 220.7, 208.1 and 226.5g at 0, 12, 30 and 75 mg/kg bw/day, respectively) was observed in all treated groups. However, no dose-response relationship was evident for any of these observations. There was no increase in the incidence of external, visceral or skeletal variations and malformations.

In a preliminary dose range-finding study (Anonymous, 1990b), 5 rabbits/group were exposed to mecoprop-P at dose levels of 0, 40, 80 or 120 mg/kg bw/day on GD7-19. Maternal toxicity was reported at all dose levels and 2/5 females in the high dose group died. In the low dose group, a slightly reduced food consumption and body weight loss were observed. In the mid and high dose groups, 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 120 mg/kg bw/day, respectively. In the high dose group, only two rabbits were included (2/5 died and 1/5 did not get pregnant). No dose-response relationship in mean late resorptions was observed.

In a prenatal developmental toxicity study (OECD TG 414, GLP) Himalayan rabbits (15 females/group) were exposed by gavage to mecoprop-P at dose levels of 0, 5, 20 or 50 mg/kg bw/d on days 7-19 post insemination (Anonymous 1993b). No effects on food consumption, body weight and bodyweight gain were observed. One doe in the low dose group died on day 7 post insemination. In the high dose group, minor skin lesions in the laryngeal area were observed in 2 dams. No substance-related differences in number of implantation sites, number of live foetuses, foetal weight or sex ratio were observed. No dose-related increases in malformations, variations or retardations was observed. Pre-implantation loss was increased in the mid and high dose groups, however not statistically significantly. In the high dose group, a slight but statistically significant increase in the number of late resorptions were observed. No dose-dependent response in total numbers of resorptions per rabbit was observed.

Table: Results of the Pre-natal developmental 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

Mice

NMRI mice (22-59/group) were exposed to 0, 100, 200, 300, 400, 500, or 700 mg mecoprop/kg bw/day or 0, 200, 300, 400, or 500 mg mecoprop-P/kg bw/day by gavage from day 6 to day 15 of gestation (Roll R & Matthiaschk G, 1983). There is no information on GLP-compliance or test guideline and the findings in this study were reported in little detail. Further, the 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. No information as regards impurities in the test substances used in this study is available.

In mice exposed to mecoprop-P, a statistically significant decreased bodyweight gain was observed in dams in the high dose group (24.2, 22.8, 26.6, 27.1 and 16.7g at 0, 200, 300, 400 and 500 mg/kg bw/day, respectively). There were statistically significant increases in the incidences of early resorptions and post implantation loss in the high dose group. An increased incidence of cleft palate was observed from 400 mg/kg bw/day and was significantly higher than in controls at the top dose. A statistically significantly increased incidence of deformed thoracic vertebral nuclei was observed in the two highest dose groups (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 300 mg/kg bw/day and was statistically significant at 400 and 500 mg/kg bw/day. In the high dose group, maternal body weight gain (16.7 g compared to 24.2 g in control) and foetal body weight was significantly lower than controls.

Table: *Results for mecoprop-P in mice pre-natal developmental toxicity study (Roll R & Matthiaschk G, 1983)*

Dose (mg/kg bw)	0	200	300	400	500
No of dams	59	25	33	36	34
Full term foetuses	749	317	414	500	390
Full term foetuses per dam	12.7	12.7	12.5	13.9	11.5
Full term foetuses removed	670	278	365	447	323
Early resorptions (%)	8.4	11.4	9.4	7.6	13.8##
Post implantation loss (%)	10.6	12.3	11.8	10.6	17.1#
Foetal weight (g)	1.17	1.12	1.11#	1.04##	1.00##

Dose (mg/kg bw)	0	200	300	400	500
Cleft palate (number of foetuses) (%)	 11 1.6	 3 1.1	 3 0.8	 11 2.5	 11 3.4#
Fused ribs (number of foetuses) (%)	 - -	 - -	 4 1.1	 20 4.5#	 28 8.7##
Deformed thoracic vertebral nuclei (number of foetuses) (%)	 2 0.3	 - -	 3 0.8	 18 4.0#	 23 7.1##
Exencephalies (number of foetuses) (%)	2 0.3	- -	- -	- -	1 0.3

significant p<0.009, ## significant p<0.0027

The results of the study with mice exposed to mecoprop (racemate) show that the toxicity profiles of mecoprop-P and racemic mecoprop are comparable. There were statistically significant increases in the incidences of early resorptions and post implantation loss in the high dose group only. Foetal weight was significantly reduced from 300 mg/kg bw/day. Significantly increased incidences of cleft palate were observed from 500 mg/kg bw/day. A significant increase in the incidence of fused ribs was reported at 700 mg/kg bw day. In the high dose group maternal body weight gain (15.4 g compared to 23.8 g in control) and foetal body weight was significantly lower than in controls.

***Table**: Results for mecoprop (racemate) in mice pre-natal developmental toxicity study (Roll R & Matthiaschk G, 1983)*

Dose (mg/kg bw)	0	100	200	300	400	500	700
No. of dams	24	37	34	30	27	34	22
Full term foetuses	300	432	411	319	293	371	252
Full term foetuses per dam	12.5	11.7	12.1	10.6	10.9	10.9	11.5
Full term foetuses removed	266	388	367	284	262	338	178
Early resorptions (%)	10.7	8.1	9.5	8.5	8.5	5.7	25.4##
Post implantation loss (%)	11.3	10.2	10.7	11.1	10.5	8.9	29.4##
Foetal weight (g)	1.17	1.16	1.12	1.09#	1.06#	1.03##	0.82##
Cleft palate (number of foetuses) (%)	 4 1.5	 8 2.1	 6 1.6	 3 1.1	 5 1.9	 13 3.8#	 35 19.7##
Fused ribs (number of foetuses) (%)	 - -	 1 0.3	 - -	 - -	 3 1.1	 2 0.6	 26 14.6##
Exencephalies (number of foetuses) (%)	- -	1 0.3	1 0.3	- -	1 0.4	1 -	- -

significant p<0.009, ## significant p<0.0027

It is noted that no HCD are presented in the study by Roll R & Matthiaschk G (1983), however the study author indicates that cleft palates occur relatively frequently spontaneously in the NMRI mouse strain used. In a study by Scheller et al. (2011) it is indicated that NMRI mice have a background incidence of 1-4% for cleft palate. The concurrent controls fall within that range.

The study by Roll R & Matthiaschk G (1983) has also previously been assessed by RAC (RAC opinion on MCPA-thioethyl (ISO), 2018), and at that time the relevance of this study was considered limited. The study describes developmental toxicity that in principle warrants classification. However, there are relevant reasons for a limited reliability of the study. The purity of the test substances is unknown, which is a rather essential reason for downgrading the relevance of the studies, as well as limited reporting. In addition, the stress-related mechanism

for eliciting cleft palate in mice is an additional aspect decreasing concern for a substance related effect. The results of Roll et al 1983 are very striking but no evidence of similar toxicity was seen in any of the other studies, which casts doubt on its reliability. For these reasons, the results of this study are not sufficient to support classification for developmental toxicity.

The available studies show equivocal evidence of an effect on development in rats and rabbits following exposure to mecoprop-P.

One study with rabbit (OECD TG 414) indicate a possible evidence for developmental toxicity observed as an increased number of late resorptions in the high dose group. The number of live pups in the high dose group was reduced, however, not significantly different from controls. No maternal toxicity was observed in this group.

The study with mice (Roll R & Matthiaschk G, 1983) show a statistically increased incidence of early resorptions and post implantation loss in the high dose groups (500/700 mg/kg bw/day for mecoprop-P/mecoprop (racemate)). Further, in the high dose groups a statistically significant increase in cleft palate, fused ribs and deformed thoracic vertebral nuclei was observed. However, at this dose level maternal body weight gain was statistically significantly reduced. There are significant limitations in the design and reporting of the study and the results are not used in support of a classification.

In the one-generation study with rats exposed to mecoprop-P there is a statistically significant reduction in mean implantation sites in all dose groups. Similarly, the mean number of pups born was statistically significantly reduced in the low and high dose group. The number of mean pups alive on day 1/4 was not statistically different in any dose group.

In the two-generation study with rats exposed to mecoprop (racemate) a statistically significant increase in the number of pups which died or were cannibalized from day 1 to day 4 were seen in the high dose group in the F1a generation. The viability index were statistically significantly reduced (93% vs 98% in controls). In the F1b generation, a non-significant but dose-related increase in the sum of dead pups was observed. Pup deaths were observed across the litters. In the F2 generation, the number of dead pups on day 0 was statistically significantly increased in the high dose group. In the low dose group, 16 pups were cannibalised (7/16 by one dam).

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 sufficient for an adverse effect on development.

The repeated dose toxicity studies showed a slight increase in the incidence of benign uterine stromal polyps at 65mg mecoprop-P/kg bw/day in a 2-year rat study and cystic corpora lutea in 3/5 at 19 mg mecoprop-P/kg bw/day in a 1-year dog study which could be of some concern, however in isolation not sufficient for classification.

Overall, these studies are equivocal for the assessment of adverse effects of mecoprop-P on development.

In conclusion, RAC is of the opinion that, **no classification for effects on development is warranted due to inconclusive data**.

Adverse effects on or via lactation

According to CLP criteria, classification for effects on or via lactation can be assigned based on:

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.

For mecoprop-P there is no human evidence indicating a hazard to babies during the lactation period.

No studies investigating effects on or via lactation is available. However, a limited 1-generation study with mecoprop-P and standard 2-generation study with mecoprop (racemate) is available.

The two-generation study showed a statistically significant increase in the number of pups which died or were cannibalized from day 1 to day 4 post-partum in the high dose group in the F1a generation, and consequently a significant reduction in the viability index. In the F1b and F2 generations, a non-significant but dose-related increase in the sum of dead pups was observed. There is no evidence indicating of poor maternal care or adverse effects on nursing, however, it is noted that one F1 parental dam cannibalised 7 pups and one F1 dam did not nurse her pups properly. It is possible that the pup deaths resulted from effects on or via lactation but there is no clear evidence to support this.

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

Overall, there is no evidence that mecoprop-P affects offspring through an effect on or via lactation.

RAC is therefore of the opinion that no classification for effects on or via lactation is justified.

Overall conclusion on toxicity to reproduction: RAC agrees with the DS that **no classification is warranted for effects on sexual function and fertility, development or lactation**. However, the available data did not enable RAC to justify this conclusion based on sufficient evidence.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Mecoprop-P (CAS: 16484-77-8) is a phenoxy herbicide intended for use against broadleaf weeds. Mecoprop-P, the pure R enantiomer, is included in the racemic mixture (S:R enantiomers) that is mecoprop (CAS: 93-65-2). The R enantiomer is herbicidally active. The S enantiomer is considered herbicidally inactive.

Some environmental fate studies were conducted with the racemic mixture mecoprop whilst some ecotoxicity studies were conducted with mecoprop-P dimethylamine (DMA) salt and mecoprop-P formulations.

The water solubility of mecoprop-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 TG 112, the dissociation constant for mecoprop-P is 3.7 (Comb, 2000a). It is likely the substance will be largely ionised within an environmentally relevant pH range.

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

The substance had a low potential for bioaccumulation and was considered rapidly degradable.

The Dossier Submitter (DS) proposed to classify mecoprop-P as Aquatic Chronic 3 based on available and relevant data. There were reliable acute data for all three trophic levels and all the endpoints were below 1mg/L leading to no classification for aquatic acute toxicity.

Experimental chronic toxicity endpoints were available for all three trophic levels. The lowest values were observed with *Lemna.* in the range 0.1 to 1 mg/L, which had resulted in a classification of Aquatic Chronic 3 for a rapidly biodegradable substance.

Data are available for *Myriophyllum spicatum* using an aqueous formulation. Based on a 14-day E_rC_{50} of 0.0269 mg/L mecoprop-P and a NOE_rC in the range 0.001 to 0.01 mg/L mecoprop-P, classification as Aquatic Acute 1 (M=10) and Aquatic Chronic 1 (M=1) is derived. However, this study is performed with mecoprop-P K 600 and this formulation includes co-formulants in addition to water. The DS considered this study as not appropriate for hazard classification due to the unknown impact of the co-formulants.

Degradation

A summary of reliable valid studies considering the aquatic fate of mecoprop-P and presented by the DS are listed in the table below.

***Table**: Summary of relevant information on rapid degradability (in bold: key study)*

Method	Results	Remarks	Reference
Abiotic transformation			
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	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	Obrist, 1986, 1988, 1990
Aquatic photolysis, FIFRA Subdivision N: 161-2, GLP, MCPP-P (99.2-99.3%)	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 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	MCPP-P Valid	Connor, 1996b and Hazlerigg, 2015
Biotic degradation			
Ready biodegradation OECD TG 301F, GLP, MCPP-P (91.7%)	**84-86% mineralisation day 28** **Readily biodegradable meeting 10 day window**	**MCPP-P** **Valid**	**Feil, 2010**

Method	Results	Remarks	Reference
Abiotic transformation			
Freshwater aerobic mineralisation in surface water OECD TG 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	MCPP-P Valid	Hazlerigg and Garratt, 2014
Freshwater-sediment mineralisation simulation, OECD TG 308, GLP, MCPP-P (99.64%)	DT_{50} whole system: 83.2 to 244 days at 20°C	MCPP-P Valid	Roohi, 2015

Mecoprop is considered by the DS as hydrolytically stable at an environmentally relevant pH and study temperatures between 25 and 70°C. On this basis, mecoprop 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 mecoprop, the data are read-across and mecoprop-P is considered hydrolytically stable.

Mecoprop-P is susceptible to photodegradation. Based on southern European sunshine, study experimental DT_{50} values were 3.39 to 4.65 days for mecoprop-P and 41.91 days for the principle degradant o-cresol.

Four experimental studies performed according to OECD guidelines and GLP are presented by the DS. In an OECD TG 301F study, mecoprop-P was considered readily biodegradable meeting the 10-day window. However, a limited mineralisation, significantly less than 70% by day 28, was observed in a surface water simulation study (OECD TG 309) and water/sediment simulation studies (OECD TG 308) using mecoprop-P. Whole system DT_{50} values at 12°C range from 44.4 to 463 days. Several aquatic degradants were observed although none at >5%. The DS noticed the limited mineralisation observed and considered that the difference of degradation half-lives might be explained by the test system media.

Based on the ready biodegradability test result, the DS considered mecoprop-P as rapidly degradable for the purpose of classification.

Bioaccumulation

Table: *Summary of relevant information on bioaccumulation*

Method	***Results***	***Remarks***	***Reference***
Partition coefficient, EC A.8, OECD TG 107 (shake flask) purity 99.8%	Log K_{ow} 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 K_{ow} prediction, KOWWIN	**2.94**		**RAR, 2017**
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**

Whereas no experimental data are available for mecoprop-P, a bioconcentration study in fish using radiolabelled mecoprop, a racemic mixture including mecoprop-P, was considered relevant by the DS. After a 28-day exposure period, the whole fish bioconcentration was determined to be 3 L/kg based on ^{14}C-mecoprop equivalents without lipid normalisation.

The DS also presented a Log K_{ow} value estimated with KOWWIN of 2.94 and an octanol:water partition was determined following the shake flask method (OECD TG 107) at pH4, 7, and 9 at 20°C. The quoted Log K_{ow} values are 2.19, -0.19 and -0.64 at pH 4, 7 and 10 respectively. Due to the surface-active property of mecoprop-P, the DS questioned the reliability of these results.

Based on the experimental BCF and the Log K_{ow} estimation, the DS considered that mecoprop-P has a low potential for bioaccumulation.

Aquatic toxicity

Acute aquatic hazard

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

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 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 by the DS as their validity has not been clarified. No other significant degradants were identified.

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

***Table**: Summary of relevant information on acute aquatic toxicity*

Method	Species	Test material	Results	Remarks	Reference
Acute toxicity to fish, OECD TG 203, GLP	Rainbow trout (*Oncorhynchus mykiss*)	MCPP-P (98.6%)	96h 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%)	96h LC_{50} >100 mg/L MCPP-P (n verified)	Valid	Anonymous, 1989b
Daphnia sp. Acute Immobilisation OECD TG 202, GLP	*Daphnia magna*	MCPP-P (89.7%)	48h 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%)	48h EC_{50} >100mg/L MCPP-P (n verified)	Valid	Elendt-Schneider, 1991
Freshwater Algal Growth Inhibition OECD TG 201, GLP	*Pseudokirchneriella subcapitata*	MCPP-P (92.2%)	72h E_rC_{50} >729 mg/L MCPP-P (n verified)	Valid	Dohmen, 1993b
Freshwater Algal Growth Inhibition OECD TG 201, GLP	*Anabaena flos-aquae*	MCPP-P DMA salt (92.2%)	72h E_rC_{50} 23.9 mg/L MCPP-P (mm)	Valid	Armstrong, 2000
Freshwater Algal Growth Inhibition OECD TG 201, GLP	*Navicula pelliculosa*	MCPP-P DMA salt (601.4 g MCCP-P/l)	72h E_rC_{50} 105 mg/L MCPP-P (mm)	Valid	Jenkins, 2007
Freshwater Algal Growth Inhibition OECD TG 201, GLP	*Skeletonema costatum*	MCPP-P DMA salt (601.4 g MCCP-P/l)	72h E_rC_{50} 102 mg/L MCPP-P (mm)	Valid	Burke, 2007
Lemna sp. Growth Inhibition Test OECD Guideline TG 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

The DS reported two acute toxicity to fish studies and mentioned 5 further acute toxicity studies with fish using MCPP racemic and MCPP-P DMA salt presented in the RAR. As the studies are not more sensitive than endpoints from studies using mecoprop-P, details are not included in the CLH report.

Both studies used mecoprop-P and followed OECD TG 203 for the rainbow trout (*Oncorhynchus mykiss*) test, and US EPA Test Guideline Subdivision E 72-1 for the Bluegill sunfish (*Lepomis macrochirus*). A nominal exposure range 31.6, 46.4, 68.1, 100, 147, 215 and 316 mg/L was employed in a static system. At 72 hours, a 100% mortality is observed at nominal treatment 215 mg/L (mean measured 207 mg/L). The reliability of the test is reduced due to the undissolved material. Two nominal exposure concentrations of 50 and 100 mg/L were employed in a static system. 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 96h LC_{50} was considered to be >100 mg/L.

Two static acute toxicity to *Daphnia magna* studies are available following OECD TG 202 or considered closely follow this guideline. The exposure range was nominally from 1 to 100 mg/L and the concentrations were analytically verified. The 48h EC_{50}s were >91 mg/L and >100 mg/L as mecoprop-P.

There were seven reliable tests presented for algae and aquatic plants. For algae, the static algal growth inhibition tests following GLP and OECD TG 201 were performed with different species: the freshwater algae *Pseudokirchneriella subcapitata, Anabaena flos-aquae, Navicula pelliculosa* and the marine algae *Skeletonema costatum.* The lowest E_rC_{50} was obtained with *Anabaena flos-aquae* and mecoprop-P DMA salt and was calculated to be 23.9 mg/L MCPP-P based on mean measured concentrations.

A semi-static 7 day toxicity to *Lemna minor* study using mecoprop-P DMA salt is available following GLP and OECD TG 221. The nominal exposure range was 0.1, 0.32, 1.0, 3.2, 10, 32 and 100 mg mecoprop-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 7d E_rC_{50} was above the highest exposure concentration and considered to be >56 mg mecoprop-P/L based on nominal concentrations.

A semi-static 14 day toxicity to *Lemna gibba* study using mecoprop-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 mecoprop-P DMA salt with equivalent concentrations as mecoprop-P acid. The study has been reanalysed (Exponent, 2017) to determine the 7 day E_rC_{50} based on growth rate (frond number) and mean measured mecoprop-P DMA salt with equivalent concentrations as mecoprop-P acid.

The DS presented as additional information, two studies assessing growth inhibition to the aquatic plant *Myriophyllum spicatum* using the product Mecoprop-P K 600. The studies are considered valid and reliable.

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 TG 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. The DS considered that the active ingredient remained in the water phases sufficiently for the quoted endpoint to be reliable. The lowest endpoint is the 14d $E_rC_{50\ \text{shoot length}}$: 26.9 µg/L (0.0269 mg/L) mecoprop-P.

The second study is a 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 TG 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. The lowest endpoint is the 14d $E_rC_{50\ \text{biomass dry weight}}$: 32.9 µg/L mecoprop-P.

Mecoprop-P is a herbicide and *Myriophyllum spicatum* appears to be more sensitive than other aquatic plant/algae species. The DS emphasized that this formulation includes co-formulants in addition to water and one of them accounting for around 0.004% w/w has an environmental self-classification (Aquatic Chronic 2 and 4). Thus, the DS estimated that the impact of the co-formulants in the studies is unknown.

Long-term aquatic hazard

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

Valid studies relevant for the classification of MCPP-P are presented in Table below.

Table: *Summary of relevant information on chronic aquatic toxicity*

Method	Species	Test material	Results	Remarks	Reference
Fish Early-Life Stage toxicity, OECD TG 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 TG 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 TG 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 TG 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 TG 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 TG 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 TG 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 TG 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 TG 239, 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

In a flow through chronic toxicity study with fish using MCPP-P following GLP and OECD TG 210, the NOEC for all parameters was considered to be 11.1 mg a.s./L, based on the highest treatment and mean measured concentrations. 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.

There were two reliable chronic *Daphnia* studies available.

A semi-static chronic toxicity to *Daphnia magna* study is available using mecoprop-P following GLP and EEC guideline XI/681/86 (in part also OECD TG 202). In addition, the study is considered to closely follow OECD TG 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 considered acceptable and 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.

The second study is a semi-static chronic toxicity to *Daphnia magna*. The study followed GLP and OECD TG 202 (1981). The study met validity criteria in the current OECD TG 211. The exposure concentration range was 2.5, 7.4, 22.2, 66.7 and 200 mg/L mecoprop. Analytical verification was undertaken for the 2.5, 22.2 and 200 mg/L mecoprop treatments for the first and last renewal periods of 0 to 48 hours. The 21 day NOEC based on reproduction was 22.2 mg/L mecoprop based on nominal concentrations. The DS noticed that the endpoint was based on mecoprop, which was the racemic mixture and the concentrations of the R isomer were unknown. However, this is unlikely to be <1 mg/L the relevant cut off for aquatic chronic classification criteria.

As previously described, there were seven reliable tests presented for algae and aquatic plants. For algae, the static algal growth inhibition tests following GLP and OECD TG 201 were performed with different species the freshwater algae *Pseudokirchneriella subcapitata, Anabaena flos-aquae, Navicula pelliculosa* and the marine algae *Skeletonema costatum*. The endpoints are presented

in the table below. There were two duckweed studies available. Using *Lemna minor* the 7d NOE_rC was 0.18 mg/L mecoprop-P based on verified nominal concentrations and using *Lemna gibba* the 6d E_rC_{10} was 0.32 mg/L mecoprop-P and the 9d E_rC_{10} was 0.32 mg/L mecoprop-P based on mean measured concentrations.

Endpoints for *Myriophyllum spicatum* with studies using the formulation mecoprop-P K 600 g/L are presented by the DS as additional information. For the first study, the 14d $E_rC_{10\ \text{shoot length}}$ was 0.0015 mg/L mecoprop-P, with the 14d $E_rC_{10\ \text{wet weight}}$ was 0.00106 mg/L mecoprop-P based on verified nominal concentrations. The 14d NOE_rC for both shoot length and wet weight was determined as 0.009 mg/L mecoprop-P, both based on verified nominal concentrations. For the second one, the study considered the 14d E_rC_{10} for shoot length and wet weight to be <0.00474 mg/L mecoprop-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 mecoprop-P treatment and 17.9% at the next treatment of 0.015 mg/L mecoprop-P. The study determined the 14d 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 mecoprop-P 35.3% inhibition at the next treatment) and indicating the $NOE_rC_{\text{wet weight}}$ may be <0.00474 mg/L mecoprop-P.

Mecoprop-P is a herbicide and *Myriophyllum spicatum* appears to be more sensitive than other aquatic species. The DS emphasized that this formulation includes co-formulants in addition to water and one of them accounting for around 0.004 % w/w has an environmental self-classification (Aquatic Chronic 2 and 4). Thus, the DS estimated that the impact of the co-formulants in the studies is unknown.

Comments received during public consultation

Three Member States (MSs) supported the classification proposed by the Dossier Submitter; two of them considered that due to the mode of action of mecoprop-P, the classification should be based on the toxicity for aquatic macrophyte *Myriophyllum spicatum*. However, the MS shared the DS's concern of basing the classification on the data from *Myriophyllum spicatum* growth inhibition tests (OECD TG 239) conducted with a formulation including co-formulants as these substances might have contributed to the observed toxicity. Therefore, this data was not appropriate, in their opinion, to be used for hazard classification. As there were no study results for mecoprop-P and *Myriophyllum spicatum*, the *Lemna sp.* growth inhibition test (FIFRA 122-2 and 122-3) with *Lemna gibba* should be used as the key study. According to the study, the chronic toxicity 6 and 9 day E_rC_{10} values for mecoprop-P and its salts are in the range of 0,1-1,0 mg/L; thus, resulting in classification of Aquatic Chronic 3 for a rapidly degradable substance.

The DS noted that the difference between hazard classification using the formulation data (Aquatic Acute 1, M=10, Aquatic Chronic 1, M=10) is markedly different to hazard classification based on data (*Lemna*) using the active ingredient (Aquatic Chronic 3). However, the DS considered that it is not straightforward to compare the formulation data to hazard classification criteria given the above uncertainties. On this basis, at present, the hazard classification proposal was based on ecotoxicity data using the active ingredient. If ecotoxicity testing using the active ingredient and additional aquatic plants such as *Myriophyllum spicatum* became available in the future, the classification should be reassessed.

Assessment and comparison with the classification criteria

Degradation

In a valid and reliable OECD TG 301F study, mecoprop-P was considered readily biodegradable meeting the 10-day window. However, a limited mineralisation, significantly less than 70% by day 28, was observed in a surface water simulation study (OECD TG 309) and water/sediment simulation studies (OECD TG 308) using mecoprop-P. Whole system DT_{50} values at 12°C range from 44.4 to 463 days. Several aquatic degradants were observed although none at >5%. The DS noticed the limited mineralisation observed and considered that the difference of degradation half-lives might be explained by the test system media.

RAC notes the limited mineralisation in a surface simulation study and water/sediment simulation studies. However, as mecoprop-P is considered readily biodegradable following a valid OECD TG 301F with the 10-day window criteria being fulfilled and as the OECD TG 301 test is considered to be performed under stringent conditions, RAC is of the opinion that mecoprop-P should be considered as rapidly degradable, for classification purposes.

Bioaccumulation

Mecoprop-P has an experimental BCF (=3 L/kg, performed with the mecoprop racemic mixture) below the CLP threshold of 500 and a Log K_{ow} below the CLP threshold of 4. Consequently, RAC agrees that mecoprop-P has a low potential for bioaccumulation.

Aquatic Toxicity

As already reported in the current opinion document, the DS concluded that the *Myriophyllum* studies should be taken into account only as additional data, due to the uncertainty regarding the toxicity of the co-formulants. This is especially the case with the co-formulants present at around 0.004% w/w with environmental self-classifications of Aquatic Chronic 2 and 4. However, RAC is not of the same opinion as the DS on this matter, namely it concludes that this study should not be considered as additional, but as key.

The reasons for this are:

(i) The **specific mode of action** of mecoprop-P as a herbicide: Indeed, mecoprop-P is an aryloxyalkanoic acid herbicide that is known and has been used as an inhibitor of auxin synthesis in plants. This chemical is a herbicide intended for use against dicotyledons. Consequently, dicotyledonous aquatic plants, such as *Myriophyllum*, should be more sensitive than algae or duckweeds;

(ii) The **low concentration** of the co-formulants: The concentrations of the co-formulants are very low and even if an environmental self-classification (Aquatic chronic 2 and 4) is proposed, the impact of their toxicity compared to the specific mode of action of the substance should be low. It should also be noticed that the trophic level triggering the aquatic chronic self-classification of the co-formulants is not known in the dossier;

(iii) The similar toxicities of the active substance and the formulated product in other algae species as reported in the DAR document: In the pesticidal peer review performed by EFSA and summarised in https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2017.4832, several studies performed with Mecoprop-P K 600 g/L were quoted and no evidence of a higher toxicity of the mixtures as opposed to the active substance could be highlighted;

(iv) The high purity of the technical product

To conclude, RAC considers that dicotyledons would be the most sensitive organisms due to the mode of action of mecoprop-P, hence, also considering the other reasons stated above, the *Myriophyllum* studies will be considered as key studies for environmental classification purposes. Indeed, the data indicate that the dicotyledon *Myriophyllum spicatum* is the most sensitive species under both acute and chronic aquatic toxicity testing.

Thus, for acute toxicity, data are available for fish, invertebrates, algae and aquatic plants. *Myriophyllum* is the most sensitive species. With the lowest endpoint, the 14d $E_rC_{50\ \text{shoot length}}$: 26.9 µg/L (0.0269 mg/L) mecoprop-P, the acute ecotoxicity endpoint is below the CLP cut-off value of 1 mg/L. Consequently, RAC considers that based on available and relevant data, the classification **Aquatic Acute 1** with an **M factor of 10** is warranted for mecoprop-P.

For chronic toxicity, data are available for fish, invertebrates, algae and aquatic plants. RAC considers *Myriophyllum* as the most sensitive species. The 14 day E_rC_{10} 0.001 mg/L is in the range from 0.0001 to 0.001 mg/L and since mecoprop-P is considered as rapidly biodegradable, RAC considers that the classification **Aquatic Chronic 1** with a **M factor of 10** is warranted.

Additional references

K. Scheller, A. Schubert, J. Schubert: In vitro investigation of the secondary palate development in two strains of mice. Int. J. Oral Maxillofac. Surg. 2011; 40: 737–742

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).