Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

phenmedipham (ISO);
methyl 3-(3-methylcarbaniloyloxy)carbanilate

EC Number: 237-199-0
CAS Number: 13684-63-4

CLH-O-0000001412-86-297/F

Adopted

20 September 2019

20 September 2019

CLH-O-0000001412-86-297/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: **phenmedipham (ISO); methyl 3-(3-methylcarbaniloyloxy)carbanilate**

EC Number: **237-199-0**

CAS Number: **13684-63-4**

The proposal was submitted by **Finland** and received by RAC on **12 November 2018.**

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

PROCESS FOR ADOPTION OF THE OPINION

Finland 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 **3 December 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **15 February 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Michal Martínek**

Co-Rapporteur, appointed by RAC: **Ignacio Tejero De La Flor**

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	Chemical name	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	616-106-00-0	phenmedipham (ISO); methyl 3-(3-methylcarbaniloyloxy)carbanilate	237-199-0	13684-63-4	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410			
Dossier submitters proposal	616-106-00-0	phenmedipham (ISO); methyl 3-(3-methylcarbaniloyloxy)carbanilate	237-199-0	13684-63-4	**Add** Carc. 2 Repr. 2 STOT RE 2 **Retain** Aquatic Acute 1 Aquatic Chronic 1	**Add** H351 H361d H373 (blood) **Retain** H400 H410	**Add** GHS08 **Retain** GHS09 Wng	**Add** H351 H361d H373 (blood) **Retain** H410		**Add** M=10 M=10	
RAC opinion	616-106-00-0	phenmedipham (ISO); methyl 3-(3-methylcarbaniloyloxy)carbanilate	237-199-0	13684-63-4	**Retain** Aquatic Acute 1 Aquatic Chronic 1	**Retain** H400 H410	**Retain** GHS09 Wng	**Retain** H410		**Add** M=10 M=10	
Resulting Annex VI entry if agreed by COM	616-106-00-0	phenmedipham (ISO); methyl 3-(3-methylcarbaniloyloxy)carbanilate	237-199-0	13684-63-4	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=10 M=10	

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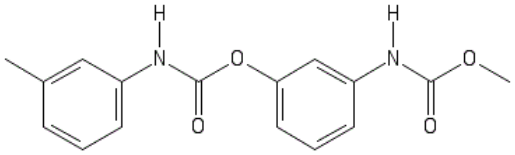
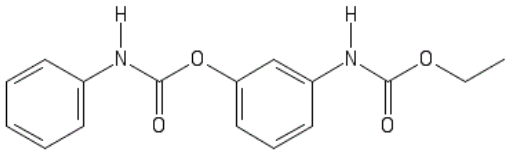
GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Phenmedipham (ISO); methyl 3-(3-methylcarbaniloyloxy)carbanilate is a herbicide from the phenylcarbamate group.

The Dossier Submitter (DS) used data on a structurally related substance desmedipham as supporting information in the assessment of several effects. According to the DS, the chemical structure, chemical properties, breakdown products and toxicological profiles of phenmedipham and desmedipham are similar. The structures of both substances are shown below.

	
phenmedipham	**Desmedipham**

As to the metabolic profile, RAC notes that although both substances are converted to aromatic amines and their derivatives, the metabolites are not identical or their relative amounts are different (see CLH report of phenmedipham, p. 10; CLH report of desmedipham, p. 10; summaries of absorption, distribution, metabolism, and excretion studies in both RARs). RAC further notes several differences between the toxic effects of phenmedipham and desmedipham: (1) although both substances are haematotoxic, desmedipham is more potent; (2) in addition to haematotoxicity, desmedipham affected the thyroid while phenmedipham did not in the available studies; (3) desmedipham, unlike phenmedipham, induced slightly increased incidence of several malformations such as micrognathia and cleft palate in rat prenatal developmental toxicity (PNDT) studies.

Since RAC considers the available information on repeat dose toxicity, carcinogenicity and developmental toxicity of phenmedipham to be sufficient upon which to draw conclusions, the Committee did not see any need to include data on desmedipham in the assessment.

The study numbers in the human health part refer to the respective sections of the RAR (draft Renewal Assessment Report under Regulation (EC) 1107/2009, RMS Finland, October 2017).

HUMAN HEALTH HAZARD EVALUATION

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

Summary of the Dossier Submitter's proposal

The repeat dose toxicity of phenmedipham via the oral route has been investigated in the rat, mouse and dog. Effects indicative of haemolytic anaemia were observed in all three species. Although the effects below the guidance values did not meet any of the individual criteria listed in the Guidance on the application of the CLP criteria v. 5.0 (CLP guidance), the DS proposed classification with STOT RE 2; H373 (blood) based on "generalised changes of a less severe nature involving several organs". Nevertheless, the DS indicated this to be a borderline case between Category 2 and no classification.

Comments received during public consultation

Comments were provided by 3 Member State Competent Authorities (MSCAs) and 1 Industry association.

While 2 MSCAs supported STOT RE 2 (blood), 1 MSCA and the Industry association did not find the haematologic effects sufficiently adverse to meet the classification criteria.

Assessment and comparison with the classification criteria

No significant effects below the guidance values for classification were observed in the available studies with phenmedipham except for slight haematotoxicity (reduced haemoglobin (Hb), increased haemosiderin deposition in the spleen, liver and kidney, increased extramedullary haematopoiesis, increased spleen weight). A detailed summary of effects below the guidance values (extrapolated according to the Haber's rule) is provided in Tables 29 and 30 of the CLH report. Additional information can be found in the RAR.

Haematological effects have been observed following exposure durations ranging from 4 weeks to 2 years. The CLP regulation provides guidance values for 90-day studies. For studies of a different duration, guidance values can be extrapolated using Haber's rule. Haber's rule says that the product of effective concentration (or dose) and exposure time is constant. However, haematological measurements in studies B.6.3.2/06 and B.6.5.1/07 show that the effective doses for Hb reduction are the same regardless of whether exposure duration is 1 month or 2 years (see 'Supplemental information'). Thus, the effect does not follow Haber's rule. For this reason, RAC does not consider extrapolation of the guidance values using Haber's rule appropriate in this particular case and the default guidance value of 100 mg/kg bw/d will be used in the assessment.

CLP provides specific guidance on classification of substances causing haemolytic anaemia. According to this guidance, if a haemolytic substance induces one or more of the serious health effects listed in the table below within the guidance values, classification is warranted. It is sufficient for classification that only one of these criteria is fulfilled. The table summarises the effects in studies with phenmedipham corresponding to the individual criteria.

Comparison of the haematotoxicity-related findings with the criteria of the CLP Guidance		
Criterion	**Corresponding effects in studies with phenmedipham**	**Reference(s)**
(1) Premature deaths in anaemic animals that are not limited to the first three days of treatment in the repeated dose study	None	–
(2) Clinical signs of hypoxia, e.g. cyanosis, dyspnoea, pallor, in anaemic animals that are not limited to the first three days of treatment in the repeated dose study	None	–
(3) Reduction in Hb at ≥ 20 % (4) Reduction in functional Hb at ≥ 20 % due to a combination of Hb reduction and MetHb increase	Maximum Hb reduction around/below 100 mg/kg bw/d by approx. 4-8 % No or only a slight increase in MetHb → Reduction in functional Hb by < 10 %	90-day rat study B.6.3.2/05, 1 000 ppm 90-day rat study B.6.3.2/06, 1 000 ppm 60-day dog study 6.3.1/02, 3 000 ppm

(5) Haemoglobinuria that is not limited to the first three days of treatment in the repeated dose study in combination with other changes indicating significant haemolytic anaemia (e.g. a reduction in Hb at ≥ 10 %)	None	–
(6) Haemosiderinuria supported by relevant histopathological findings in the kidney in combination with other changes indicating significant haemolytic anaemia (e.g. a reduction in Hb at ≥ 10 %)	None	–
(7) Multifocal or diffuse fibrosis in the spleen, liver or kidney	None	–
(8) Tubular nephrosis	None	–
(9) Marked increase of haemosiderosis in the spleen, liver or kidney in combination with other changes indicating significant haemolytic anaemia (e.g. a reduction in Hb at ≥ 10 %) in a 28-day study	No 28-day study available to see whether an increase in haemosiderosis occurs already after 28 days A possibly "marked" increase in haemosiderosis in some of the rat studies (B.6.3.1/01, /02) from ca. 100 mg/kg bw/d Hb reduction < 10 %	90-day rat studies 6.3.2/01, /02, /05, /06
(10) Significant increase in haemosiderosis in the spleen, liver or kidney in combination with microscopic effects like necrosis, fibrosis or cirrhosis	None Haemosiderosis increased, but not found in association with necrosis, fibrosis or cirrhosis (not even above the guidance values except for hepatic necrosis at ca. 1 000 mg/kg bw/d in the 60-day dog study B.6.3.1/02)	90-day rat studies 6.3.2/01, /02, /04, /05, /06 8-week mouse study 6.3.1/01 60-day dog study 6.3.1/02 2-year rat studies 6.5.1/03, /05, /07

The table above shows that none of the individual criteria for classification is fulfilled. This was also the DS's conclusion. Still, the DS argued that the CLP guidance also states that in the case where multiple less severe effects with regenerative capacity were observed, the classification should apply as, according to the CLP regulation (Annex I, 3.9.1.4), "*Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs*." However, RAC notes that the aforementioned guidance exemplifies this with criteria (9) and (10), neither of which is met here.

As the haematotoxic effects are below the guidance values and do not meet the criteria for classification and there were no relevant effects in other organs, **RAC proposes no classification for STOT RE**.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

Six carcinogenicity studies with phenmedipham were available, four in rats and two in mice. The DS proposed classification in Category 2 based on increased incidence of pituitary adenomas (male rats, study 6.5.1/07) and endometrial stromal carcinomas (rats, study 6.5.1/06).

Comments received during public consultation

Four MSCAs and 1 Industry association provided their comments.

Two MSCAs clearly supported classification in Category 2 while the other 2 MSCAs indicated this to be a borderline case between Category 2 and no classification.

Industry argued against classification. Regarding the uterine tumours, they pointed out lack of statistical significance in a trend test and a relatively high background incidence according to published historical control data (HCD). As for the pituitary adenomas, industry emphasised the high variability demonstrated by a relevant HCD, no increase in precursor lesions or adenocarcinomas and lack of a tumour increase in females. Further, they challenged the DS' assumption that the mode of action (MoA) of both tumours is related to disturbed homeostasis of the hypothalamus-pituitary-gonad (thyroid) axis.

In their responses to the comments, the DS agreed that the case is borderline and that a hormonally mediated MoA has not been clearly demonstrated.

Assessment and comparison with the classification criteria

The available carcinogenicity studies with phenmedipham are summarised in the following table.

Carcinogenicity studies		
Type of study; Reference; Year	**Method**	**Observations**
Rat		
2-year chronic toxicity/carcinogenicity, dietary B.6.5.1/07 2004	OECD TG 453 GLP Strain: Han Wistar Doses: 0, 100, 500, 2 500 ppm; equivalent to 4.6/6.4, 24/33, 118/171 mg/kg bw/d (m/f) 1-year: 20/sex/group 2-year: 50/sex/group	<u>Non-neoplastic findings</u> 2 500 ppm (118/171 mg/kg bw/d): • ↓ bw gain (f by 26 %, stat. sign.; males, by 7 %, not stat. sign.); ↓ food consumption (females, by 8 %) • ↓ Hb (by up to 10/12 % m/f); ↑ MetHb (up to 2-fold, max. 0.9 %), no Heinz bodies; ↑ reticulocytes; ↑ anisocytosis and hyperchromasia; ↑ lymphocytes • ↑ spleen weight (males, by ca. 20 %) • ↑ incidence of pigment in Kupffer cells, haemosiderosis in the spleen, extramedullary haematopoiesis in the spleen, splenic congestion, renal tubular pigmentation, renal pelvic epithelial mineralization and hyperplasia (males), renal interstitial inflammatory cells (males) 500 ppm (24/33 mg/kg bw/d): • ↑ incidence of renal interstitial inflammatory cells (males)

Carcinogenicity studies		
Type of study; Reference; Year	**Method**	**Observations**
		100 ppm (4.6/6.4 mg/kg bw/d): no adverse effects Neoplastic findings 2 500 ppm: • **Pituitary adenoma** (males) ≤ 500 ppm: no neoplastic effects
2-year chronic toxicity/carcinogenicity, dietary B.6.5.1/01,03,04 1988	OECD TG 453 GLP Strain: Sprague-Dawley Doses: 0, 60, 250, 1 000 ppm; equivalent to 3.1/4.1, 13/17, 50/68 mg/kg bw/d (m/f) 1-year: 20/sex/group 2-year: 50/sex/group	Non-neoplastic findings 1 000 ppm (50/68 mg/kg bw/d): • ↓ Hb (by ca. 7 % after 1 year) • ↑ incidence of haemosiderin deposition in Kupffer cells and renal tubular cells, urothelial hyperplasia (females), focal pituitary hyperplasia (males) (but no increase when hyperplasia and adenomas are combined), uterine endometrial stromal sclerosis Neoplastic findings None
2-year chronic toxicity/carcinogenicity, dietary B.6.5.1/02,05 1988 Conducted by the same laboratory as B.6.5.1/03 with animals of the same strain and source; the purity of the test substance was different	OECD TG 453 GLP Strain: Sprague-Dawley Doses: 0, 60, 250, 1 000 ppm; equivalent to 3.3/4.3, 14/18, 55/73 mg/kg bw/d (m/f) 1-year: 20/sex/group 2-year: 50/sex/group Deficiency: high incidence of autolysed or cannibalised animals (ca. 20 % of the males across groups in the 2-year study)	Non-neoplastic findings 1 000 ppm (55/73 mg/kg bw/d): • ↓ bw (females, by 10 % after 1 year) • ↓ Hb (by ca. 7 % after 1 year) • ↑ incidence of haemosiderin deposition in Kupffer cells (m/f) and renal tubular cells (males), renal pelvic epithelial hyperplasia (males), uterine endometrial sclerosis Neoplastic findings None (several tumour types discussed by the DS)
2-year chronic toxicity/carcinogenicity, dietary B.6.5.1/06 1980	OECD TG 453 GLP Strain: Sprague-Dawley Doses: 0, 20, 100, 500 ppm; equivalent to 1.1/1.4, 5.5/6.8, 28/34 mg/kg bw/d (m/f) 1-year: 10/sex/group 2-year: 50/sex/group	Non-neoplastic findings 500 ppm (28/34 mg/kg bw/d): • ↓ bw (females, by 6 % at termination) • ↓ Hb (females) Neoplastic findings None (endometrial stromal sarcoma discussed by the DS)

Carcinogenicity studies		
Type of study; Reference; Year	**Method**	**Observations**
Mouse		
18-month carcinogenicity, dietary B.6.5.1/08 1991	OECD TG 451 GLP Strain: CD-1 Doses: 0, 500, 2 000, 7 000 ppm; equivalent to 82/107, 331/443, 1 170/1 530 mg/kg bw/d (m/f) 50/sex/group	Non-neoplastic findings 7 000 ppm (1 170/1 530 mg/kg bw/d): • ↓ bw (females, by 10 % at termination) • ↑ incidence of amyloidosis (females) Neoplastic findings None
2-year carcinogenicity, dietary B.6.5.1/09 1987	OECD TG 451 GLP Strain: CD-1 Doses: 0, 10, 100, 1 000 ppm; equivalent to 1.1/1.2, 11/12, 110/117 mg/kg bw/d (m/f) 52/sex/group	Non-neoplastic findings No adverse effects Neoplastic findings None

Rat carcinogenicity study B.6.5.1/07

The top dose selection in this study (2500 ppm) was based on a dose range-finding 90-day study (B.6.3.2/06), where a body weight gain reduction of ca. 15 % was observed at 3 000 ppm. A dose of 10 000 ppm in the 90-day study caused a reduction in body weight and food consumption by ca. 20 % and Hb reduction by up to 18 %. Although the maximum tolerated dose (MTD) does not seem to have been reached in the carcinogenicity study itself, some toxicity was present at the top dose (haematotoxicity, haemosiderosis, histopathological findings in the kidney, minor effects on body weight in females) and taking into account the findings of the dose range-finding study, the top dose selection is considered acceptable.

The only neoplastic finding was increased incidence of pituitary adenoma in top dose males. The incidences are provided in the table below. The increase was statistically significant. The top dose incidence remained within a relevant HCD range and was close to the HCD mean. However, the concurrent control incidence was below the HCD range and the incidence at the low dose shows that the concurrent control was not aberrant. This, together with the apparent dose-response relationship, indicates that the increase was treatment-related. There was no increase in hyperplasia in males and no histopathological changes in the pituitary of females.

Neoplastic and hyperplastic findings in the pars distalis in study B.6.5.1/07					
Dose (ppm)	**0**	**100**	**500**	**2 500**	**HCD[a]**
Dose (mg/kg bw/d) (m/f)	0	4.6/6.4	24/33	118/171	
Males					
No. of animals examined	50	50	50	50	
Adenoma	7 (14 %)	7 (14 %)	12 (24 %)	19* (38 %)	Mean: 32 % Range: 19-45 %
Adenocarcinoma	0	0	0	0	
Focal hyperplasia	6	8	3	8	
Females					
No. of animals examined	50	50	50	49	
Adenoma	23	33	26	26	
Adenocarcinoma	3	0	1	2	
Focal hyperplasia	14	10	10	5*	

* Statistically significant difference from control, p≤0.05

[a] 17 studies within 5 years of the current study (studies starting 2001-2006; the current study started in 2001), the same laboratory, strain and supplier

Pituitary tumours were more frequent among top dose male early decedents than among control decedents, and pituitary tumours were a factor contributing to death of these animals according to the pathology report. There was no obvious group difference in females in this regard.

Tumours of pituitary pars distalis in study B.6.5.1/07: time of the finding, contribution to unscheduled deaths				
Dose (ppm)	**0**	**100**	**500**	**2 500**
Males				
Adenoma in animals sacrificed after 52 weeks	0/20	0/20	1/20 (1 +)	1/20 (1 +)
Adenoma in animals sacrificed or dying between week 52 and 104	1/9 (1 +++)	3/8 (3 +++)	5/10 (5 +++)	6/7 (6 +++)
No. of animals for which pituitary adenoma was listed as a factor contributing to unscheduled death	1 (1 s)	3 (3 s)	5 (4 s)	6 (5 s)
Adenoma in animals sacrificed after 104 weeks	6/41 (2 +, 2 ++, 2 +++)	4/42 (2 +, 1 ++, 1 +++)	7/40 (2 +, 4 ++, 1 +++)	13/43 (4 +, 6 ++, 3 +++)
Week of death of animals sacrificed or dying between week 52 and 104	81	72, 88, 102	73, 78, 87, 94, 97	83, 93, 97, 98, 100, 102

Females				
Adenoma in animals sacrificed after 52 weeks	0/20	1/20	1/19	1/19
Adenoma or adenocarcinoma in animals sacrificed or dying between week 52 and 104	12/20 (9 a, 3 c)	9/12 (9 a)	9/15 (8 a, 1 c)	11/19 (9 a, 2 c)
No. of animals for which pituitary tumour was listed as a factor contributing to unscheduled death	7 (6 s)	6 (5 s)	8 (6 s)	7 (7 s)
Adenoma in animals sacrificed after 104 weeks	14/30	24/38	18/35	17/31

Size of tumour: +, not apparent on macroscopic investigation; ++, mass apparent macroscopically, no compression of the brain; +++ mass compressing the brain

s = pituitary adenoma was the sole factor contributing to death listed in the pathology report for the animal

a = adenoma, c = carcinoma

Rat carcinogenicity studies B.6.5.1/03, B.6.5.1/05 and B.6.5.1/06

These three carcinogenicity studies used top doses of 1 000 ppm, 1 000 ppm and 500 ppm respectively. The general toxicity at the top doses was rather limited and as the MTD in 90-day studies seems to lie around 5 000 ppm (B.6.3.2/04, /05, /06), none of these three carcinogenicity studies is considered to have fully investigated the carcinogenicity potential of phenmedipham.

While no treatment-related neoplastic findings were observed in study B.6.5.1/03, the DS pointed out some small increases in incidences of several tumours in study B.6.5.1/05, conducted by the same laboratory with animals of the same strain and source as B.6.5.1/03, but presumably with a test substance of a different batch or source. The neoplastic findings from study B.6.5.1/05 are presented in the table below. As none of the increases was statistically significant on pairwise comparison, the increases are limited to one sex and there was no increase in incidence of these tumours in other rat carcinogenicity studies at comparable or higher doses (B.6.5.1/03, /07), RAC does not consider these findings sufficient for classification.

Neoplastic findings in study B.6.5.1/05 (only premature decedents examined histopatologically in the low and mid-dose group)								
	Males				**Females**			
Dose (ppm)	**0**	**60**	**250**	**1 000**	**0**	**60**	**250**	**1 000**
No. of animals examined	48-49	20-21	23-24	49-50	47-50	17	21	50
Adrenal cortical tumour	0	0	0	2	1	0	2	1
Adrenal malignant phaeochromocytoma	0	0	1	2	2	0	0	0
Fibrosarcoma of the skin	1	2	0	4	1	0	0	0
Thyroid interstitial cell carcinoma	0	0	0	2	0	0	0	0
Thyroid interstitial cell adenoma, poorly differentiated	0	0	0	2	0	0	0	0
Thyroid interstitial cell adenoma, well differentiated	4	0	0	2	5	1	2	2

The increased incidence of endometrial stromal sarcoma in study B.6.5.1/06 (incidences 1, 0, 2 and 3 out of 49-50 animals at 0, 20, 100 and 500 ppm respectively) is not considered to warrant or contribute to classification as the increase was not statistically significant and was not seen at higher doses (1 000 ppm or 2 500 ppm) in three other rat carcinogenicity studies.

Mouse carcinogenicity studies B.6.5.1/08 and B.6.5.1/09

No significant increases in tumour incidences were observed up to doses exceeding 1 000 mg/kg bw/d in study B.6.5.1/08. The other mouse carcinogenicity study (B.6.5.1/09) was also negative but the top dose level was too low (ca. 110 mg/kg bw/d, no effect on body weight and no other adverse effects). Overall, phenmedipham is not considered carcinogenic in the mouse.

Mode of action

A brief overview of genotoxicity studies is provided under 'Supplemental information' in the Background Document. The mutagenicity hazard class was not open for public consultation and was presented only as background information for carcinogenicity assessment in the CLH report. Phenmedipham was negative for point mutations and positive for chromosomal aberrations *in vitro*. An *in vivo* mouse micronucleus assay using a dose of 15 000 mg/kg bw was negative. RAC, in line with the DS, does not consider the available data to raise a significant concern about genotoxicity.

The DS proposed that some changes in the weight of reproductive organs seen in some studies could be used to support a hormonally mediated MoA of the pituitary and uterine tumours. However, it is not clear from the RAR whether there indeed was a consistent pattern of effects on the weights of reproductive organs across studies at doses not causing marked body weight reductions. As there is no robust MoA information, RAC retains the default assumption of human relevance of any observed tumours.

Conclusion on classification

A treatment-related increase in the incidence of pituitary adenoma was observed in one sex (male) of one species (rat). Although the tumour is benign, it can lead to adverse consequences by compressing the surrounding tissue or by excessive production of hormones. Pituitary adenoma has a relatively high background incidence in both rats and humans.

A treatment-related increase in benign tumours can in principle lead to classification in Category 2. However, taking into account the benign nature of the pituitary tumours, the high background incidence, the lack of preneoplastic lesions and occurrence in only one sex of one species, RAC concludes that **no classification for carcinogenicity** is warranted.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Fertility

No effects on sexual function and fertility were observed in the three available generational studies with phenmedipham, and no effects on reproductive organs were reported in repeat dose toxicity studies except a dubious finding of increased aspermatogenesis in one carcinogenicity study. The DS proposed no classification for fertility. However, they noted that EFSA considered the data on fertility inconclusive, mainly because sperm parameters, affected by desmedipham, were not investigated in studies with phenmedipham (EFSA, 2018). In addition, the DS also pointed out low dosing in two of the three generational studies.

Development

Two rat and two rabbit prenatal developmental toxicity (PNDT) studies are available, all testing up to or above the limit dose of 1 000 mg/kg bw/d. The DS proposed classification in Category 2 based on runts (small foetuses less than half of the size of their littermates) occurring at a low incidence in one of the rat PNDT studies (B.6.6.2/02). According to the DS, classification is further supported by increased ossification and altered sex ratio in this study.

Lactation

The DS discussed a slight increase in early pup mortality associated with poor maternal care in one of the generational studies, but did not consider it to meet the criteria for classification.

Comments received during public consultation

Three MSCA and 1 Industry association provided their comments.

As to fertility, Industry and 1 MSCA supported no classification. The other two MSCAs considered the data on fertility inconclusive, one of them suggesting read-across from desmedipham.

Regarding developmental toxicity, 2 MSCAs supported Category 2 for development, while 1 MSCA questioned whether the data are sufficient for classification given the maternal toxicity, larger litter size at the high dose and occurrence of one small foetus in the control group of study B.6.6.2/02. This MSCA also pointed out the lack of developmental anomalies at higher dose levels in the other rat PNDT study (B.6.6.2/01).

The industry association proposed no classification for development, putting forward the following arguments:

- The incidence of runts did not show an obvious dose-response relationship and appeared to be associated with lower average weights of the whole litter.
- 'Runt' is not a malformation and the criteria for defining a 'runt' are subjective. Still, the ECETOC monograph 31 defines a 'runt' as a foetus, which weighs less than half of the average ligger weight. In study B.6.6.2/02, the weights of all foetuses called 'runts' were more than half of the mean foetal weight for the litter where the 'runt' was observed, when considering non-'runt' foetuses of the corresponding sex.
- Maternal corrected body weight gain was reduced by 17 % and 36 % at 450 and 1 350 mg/kg bw/d, respectively, which indicates significant maternal toxicity.
- This finding was not repeated in another rat study or in two rabbit studies that used equivalent doses.
- As to the altered sex ratio, the results did not markedly deviate from the expected percentage of 50 % for both sexes and the main reason for the statistically significant difference was the rather low percentage of males (or high percentage of females) in the control group. In addition, no such effect was observed in the pilot study or in the other rat PNDT study. This confirms that the observed changes are only due to a high variability.

The DS replied that runts occurred both in the preliminary and main study, and the individual animal data do not show a correlation between maternal toxicity and occurrence of runts. They, however, acknowledged that all pups defined as runts in the study report did not have body weights half of their littermates. Still, they were of the opinion that there is no indication that the occurrence of runts in phenmedipham-treated groups would be a secondary, non-specific consequence of maternal toxicity. As to the sex ratios, the DS admitted that the finding might be spurious due to high variability.

One MSCA supported no classification for effects on/via lactation.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

Generational studies

Two 2-generation studies (from 1987 and 1986), generally complying with OECD TG 416 (1983), and one pre-guideline 3-generation study (from 1979) are available for phenmedipham. All studies were reportedly conducted according to the principles of GLP. RAC notes that some sensitive parameters introduced into the OECD TG 416 in 2001, such as sperm parameters or sexual maturation, were not investigated in these studies.

None of these three studies reported adverse effects related to fertility. The top doses were ca. 80, 225 and 40 mg/kg bw/d in study B.6.6.1/01, /02 and /03 respectively. The top dose selection in study B.6.6.1/02 is considered acceptable as the body weight of parental animals in this study was reduced by up to 13 % compared to controls and the maximum tolerated dose in 90-day studies appears to lie around or above 400 mg/kg bw/d (B.6.3.2/04, /05, /06). RAC agrees with the DS that parental toxicity in the other two studies (B.6.6.1/01, /03) was rather limited and higher doses should have been tested.

Repeat dose toxicity studies

According to the DS, there were no non-neoplastic histopathological findings in reproductive organs in the repeat dose toxicity studies with phenmedipham except for a slight increase in aspermatogenesis in one of the carcinogenicity studies (B.6.5.1/06), that was difficult to interpret due to poor reporting. RAC examined the study and found that the increase (9/50 vs 5/50) was not statistically significant. No such effect was seen in the other rat carcinogenicity studies testing higher doses. Thus, this finding is not relevant for classification.

Conclusion on classification for fertility and sexual function

In the absence of effects on sexual function and fertility in the available studies with phenmedipham, RAC agrees with the DS that **no classification is justified**.

Adverse effects on development

The available PNDT studies with phenmedipham are summarised in the following table.

PNDT studies		
Type of study; Reference; Year	**Method**	**Observations**
Rat		
PNDT study, gavage B.6.6.2/01 1989	OECD TG 414 GLP Strain: Wistar Doses: 0, 516, 1 160, 2 580 mg/kg bw/d Dosing GD 6-15 22 females/group Two batches of the test substance from two different sources were used; purity of one of the batches is not known	Maternal toxicity All doses: • ↓ corrected bw gain (at the top dose down to 31 g vs 41 g in control GD 0-20), ↓ food consumption (at the top dose by 12 % GD 6-15) Developmental toxicity All doses: • ↓ foetal weight (by up to 7 %) • Incomplete ossification of neck vertebrae

PNDT studies		
Type of study; Reference; Year	**Method**	**Observations**
PNDT study, gavage B.6.6.2/02 1988	OECD TG 414 GLP Strain: Wistar/HAN Doses: 0, 150, 450, 1 350 mg/kg bw/d Dosing GD 6-15 25 females/group	<u>Maternal toxicity</u> 1 350 mg/kg bw/d: • ↓ corrected bw gain (4.2 % vs 6.6 % in control), ↓ food consumption (by 7 % GD 6-16); corrected bw reduced by 3 % (not stat. sign.) 450 mg/kg bw/d: • ↓ corrected bw gain (5.5 % vs 6.6 % in control) 150 mg/kg bw/d: no adverse effects <u>Developmental toxicity</u> 1 350 mg/kg bw/d: • 2 'runts' in 1 litter • ↓ incidence of non-ossified metatarsalia 450 mg/kg bw/d: • 1 'runt' 150 mg/kg bw/d: • 1 'runt'
Rabbit		
PNDT study, gavage B.6.6.2/03 1992	OECD TG 414 GLP Strain: New Zealand White Doses: 0, 5, 71, 1 000 mg/kg bw/d Dosing GD 6-18 16-21 females/group	<u>Maternal toxicity</u> 1 000 mg/kg bw/d: • 2 out of 21 animals sacrificed due to poor condition • ↓ food consumption (by 8 % GD 6-18), ↓ bw gain 71 mg/kg bw/d: no adverse effects <u>Developmental toxicity</u> ≤ 1 000 mg/kg bw/d: no adverse effects
PNDT study, gavage B.6.6.2/04 1986	OECD TG 414 GLP Strain: New Zealand White Doses: 0, 50, 225, 1 000 mg/kg bw/d Dosing GD 6-18 15 females/group	<u>Maternal toxicity</u> 1 000 mg/kg bw/d: • ↓ food consumption (by 13 % GD 6-18), ↓ bw gain ≤ 225 mg/kg bw/d: no adverse effects <u>Developmental toxicity</u> 1 000 mg/kg bw/d: • ↓ foetal weight (by 14 %) • Reduced ossification (cranium) • Slight increase in misaligned pelvic halves 225 mg/kg bw/d: • Slight increase in misaligned pelvic halves 50 mg/kg bw/d: • Slight increase in misaligned pelvic halves

GD=gestation day

Rat PNDT study B.6.6.2/01

No effects warranting classification were observed in this study up to the very high top dose of 2 580 mg/kg bw/d. RAC notes that two different batches of the test substance from two different sources were used, and that purity of one of the batches is unknown.

Rat PNDT study B.6.6.2/02

The only finding potentially warranting classification is the occurrence of abnormally small foetuses ('runts'). The slightly changed sex ratio at the top dose (males 52 % vs 46 % in the control) reflects normal variability and the slightly reduced incidence of non-ossified metatarsalia is not an effect warranting classification.

Maternal toxicity was rather limited even at the top dose of 1 350 mg/kg bw/d. The data on the abnormally small foetuses are provided in the table below. Their weight was from 2.2 to 2.6 g (53-68 % of the average weight of their littermates of the same sex). For comparison, the lowest individual foetal weight in the control group was 3.3 g (no abnormalities on external and visceral examination; dam no. 16). Both 'runts' examined for skeletal anomalies showed retarded ossification and the mid-dose 'runt' additionally several malformations (ribs missing, ribs fused, fused vertebral centra). HCD from 2 years (1985-86) preceding the current study (1987) reported 3 'runts' among ca. 3 700 control foetuses.

Data on abnormally small foetuses in the rat PNDT study B.6.6.2/02				
Dose (mg/kg bw/d)	**0**	**150**	**450**	**1 350**
Number of foetuses (litters) examined	293 (24)	250 (23)	241 (21)	289 (25)
Runt: foetal (litter) incidence	0	1 (1)	1 (1)	2 (1)
Runt weight [g], sex	–	2.5 ♂	2.2 ♀	2.6 ♀; 2.4 ♀
Findings on visceral and skeletal examination of the runt	–	None	Retarded ossification and several anomalies	'runt' 1: none 'runt' 2: retarded ossification
Mean foetal weight for the "runt litter", only foetuses of the corresponding sex, runts excluded [g]	–	4.7	4.1	3.8
Range of foetal weights in the "runt litter", both sexes, runts excluded	–	4.2-4.8	3.6-4.8	3.7-4.5
Group mean foetal weight, combined sexes [g]; ±SD	4.6 (±0.3)	4.6 (±0.4)	4.7 (±0.4)	4.6 (±0.4)
Size of the affected litter	–	7	12	14
Group mean litter size	12.2	10.9	11.5	11.6
Corrected bw gain (GD 6-21) of the affected dam [% of weight on GD 6]	–	14.9	9.3	–0.4
Group mean corrected bw gain (GD 6-21) [% of weight on GD 6]; ±SD	6.6 (±3.7)	6.9 (±4.6)	5.5 (±6.1)	4.2 (±3.9)

Two small foetuses (2.6 g and 3.0 g) in one out of five litters were also observed at 1 000 mg/kg bw/d in the preliminary study. However, both these foetuses were malformed (hydrocephaly, one also had brachygnathia) and as malformed foetuses usually have lower weight, it is not clear whether this finding corresponds to 'runts' in the main study.

In summary, there were single incidences of abnormally small foetuses at the low- and mid-dose in the absence of maternal toxicity. The top dose of 1 350 mg/kg bw/d exceeds the limit dose for an OECD TG 414 study of 1 000 mg/kg bw/d, so the findings at this dose are considered less relevant for classification. Still, the two small foetuses at the top dose indicate that the findings at the low and mid-dose are treatment-related. The dose-response curve is rather shallow.

Rabbit PNDT studies B.6.6.2/03 and B.6.6.2/04

Study B.6.6.2/03 was negative regarding developmental toxicity, while study B.6.6.2/04 showed several relatively minor effects: reduced foetal weight, delayed ossification and slightly increased incidence of misaligned pelvic halves.

The foetal weight reduction by 14 % occurred in presence of some maternal toxicity, and is not considered to be of sufficient magnitude to warrant classification. The delayed ossification of the cranium is likely to reflect a slight general developmental delay. The incidences of pelvic anomalies are presented in the following table. The concern about these anomalies is reduced by their presence in the control group, lack of a dose-response relationship for misalignment with scoliosis, and lack of this effect in the other rabbit study. Therefore, the occurrence of misaligned pelvic halves in the treated groups is not considered to contribute to classification.

Pelvic anomalies in the rabbit PNDT study B.6.6.2/04				
Dose (mg/kg bw/d)	**0**	**50**	**225**	**1 000**
Number of foetuses (litters) examined	68 (13)	65 (13)	82 (15)	81 (15)
Misalignment of pelvic halves; scoliosis/incipient scoliosis at the lumbo-sacral border; foetuses (litters)	1 (1)	5 (5)	6 (6)	5 (4)
Misalignment of pelvic halves; no scoliosis	0	1 (1)	1 (1)	1 (1)
Slight misalignment of pelvic halves; no scoliosis	1 (1)	1 (1)	2 (2)	3 (3)

Conclusion on classification for developmental toxicity

The only finding to be considered for classification is the occurrence of abnormally small foetuses (weighing approx. half that of their litter mates) at doses without maternal toxicity in the rat PNDT study (B.6.6.2/02). The corresponding finding in humans, intrauterine growth restriction, is associated with increased risk of neonatal mortality and neurodevelopmental problems. Thus, although the finding is not a malformation (it does not necessarily lead to permanent damage), the level of concern is higher than with a variation.

On the other hand, the concern is reduced by the low incidence (only single incidences per group below the limit dose), very shallow dose-response curve (no increase in litter incidence from 150 to 1 350 mg/kg bw/d) and lack of such effects in the other rat PNDT study (B.6.6.2/01) testing up to 2 580 mg/kg bw/d.

Taking into account the very low incidence of abnormally small foetuses, the very shallow dose-response curve and inconsistent results between studies, RAC is of the opinion that **classification for developmental toxicity is not warranted**.

Adverse effects on or via lactation

The 2-generation study (B.6.6.1/01) reported an increase in early pup mortality in the P/F1 generation correlating with deficient maternal care. There was no such effect in the second generation, or in the other 2-generation study (B.6.6.1/02) testing higher doses.

The 2-generation study (B.6.6.1/02) reported a reduction in F2 pup body weights. The birth weight was unaffected, but from PND 14 the pup weight started to differ significantly from controls at the top dose of 225 mg/kg bw/d (by 15 % on PND 14, by 18 % on PND 21). However, by that time the pups already start feeding on the maternal diet, so the effect cannot be unequivocally attributed to lactation. In addition, the dose was maternally toxic as indicated by a maternal body weight reduction by 13 % compared to controls, which might have adversely affected milk production or maternal care as a non-specific secondary effect.

Conclusion on classification for lactation

The slightly increased pup mortality in study B.6.6.1/01 was associated with poor maternal care and was not seen in study B.6.6.1/02 at a higher dose. The pup weight reduction in study B.6.6.1/02 was not observed before PND 14 and was associated with maternal toxicity. Therefore, RAC agrees with the DS that **no classification for effects on or via lactation is warranted**.

Overall conclusion on reproductive toxicity

RAC is of the opinion that **classification of phenmedipham for reproductive toxicity is not warranted.**

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Phenmedipham is a non-systemic contact herbicide and acts only via the foliage of emerged weeds. Root uptake is nearly excluded as phenmedipham is strongly absorbed by the soil and is fixed in the upper 5 cm.

The substance currently is classified in Annex VI of the CLP Regulation as Aquatic Acute 1; H400 and Aquatic Chronic 1; H410. The DS proposes to retain this classification and add an M-factor of 10 for both acute and chronic hazards.

Below, a summary of the studies included in the CLH report is provided. Only relevant and valid studies for the proposed classification of phenmedipham have been included from the RAR and CLH report.

Degradation

Hydrolysis

In the CLH Dossier, there are 3 studies where hydrolysis of phenmedipham is investigated.

In RAR B.8.2.1.1/03, the abiotic hydrolysis was investigated following OECD TG 111 in a sterile aqueous buffer at pH 4, 5, 7, and 9, following application of [amino Phenol-UL-14C]phenmedipham at a nominal concentration of 3 mg/L. Phenmedipham was hydrolysed at pH 4, 5, 7, and 9 to MHPC. The half-life of phenmedipham in aqueous buffers was calculated assuming first order kinetics. Half-lives were 259 days at pH 4, 47 days at pH 5, 12 hours at pH 7 and 7 min at pH 9.

In the study RAR B.8.2.1.1/04, the abiotic hydrolysis of phenmedipham was investigated following OECD TG 111 in a sterile aqueous buffer at pH 4, 5, 7, and 9, following application of [amino Phenol-UL-14C] and [methyl aniline-UL-14C]phenmedipham at the test concentration of 0.9 mg/L. The hydrolytic degradation of phenmedipham was strongly depended on the pH of the solution with slower degradation observed at lower pH. The mean calculated half-lives of phenmedipham assuming first order kinetics were 142 days, 18.5 days, 3 hours and 2 minutes at pH 4, 5, 7 and 9, respectively. Phenmedipham hydrolysed to two degradation products, MHPC and m-toluidine.

In the study RAR B.8.2.1.1/05, the hydrolysis of phenmedipham was investigated following OECD TG 111 at 20 °C in sterile aqueous buffer solutions at pH 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, and 8.0 in the dark for 30 days. The study was performed with [amino-Phenol -UL-14C]phenmedipham at nominal test concentration of 2.73 mg/L. The mean calculated half-lives of phenmedipham ranged from 1 011 days at pH 4.0 to 3.0 hours at pH 8.0. phenmedipham was hydrolytically relatively stable under acidic conditions (pH 4.0 and 4.5), labile in slightly acidic (5.0, 5.5 and 6.0) and neutral conditions (pH 6.5), and undergoes rapid hydrolysis above pH 7.

In addition, there are two studies with the degradant MHPC, which showed hydrolytical stability at different pHs.

Photochemical degradation

Phenmedipham was photochemically stable in the available studies (RAR B.8.2.1.2/01) and (RAR B.8.2.1.2/02) so direct photodegradation in water may contribute to a very limited extend to the degradation of phenmedipham in the environment.

Ready biodegradation

Two studies assess ready biodegradation of phenmedipham: RAR B.8.2.2.1/01 and RAR B.8.2.2.1/03.

Biodegradation of phenmedipham was 34.1 % (ThOD) and 54.3 % (DOC) after 14 days in RAR B.8.2.2.1/01. In this test, phenmedipham was investigated for its biodegradability in test concentration of 25 mg/250 mL in the Modified MITI-Test (I) following OECD TG 301C during 14 days (plateau phase was reached) in three replicates.

In test RAR B.8.2.2.1/03, the ready biodegradability of phenmedipham was studied following a Modified MITI-Test (I) following OECD TG 301C with a nominal concentration of 100 mg/L using an activated sludge. The degradation of phenmedipham after blank correction was between 23 % and 31 % of its ThOD after 35 days. Degradation of phenmedipham started on day 16 in both flasks. A plateau had not been reached by day 35. The results of the test were complicated by an inhibitory effect of phenmedipham on nitrification.

Inherent and enhanced ready biodegradability tests

The inherent biodegradability was studied using phenmedipham according to the OECD TG 302C during 28 days. Inherent biodegradation of phenmedipham was 39.5 % (BOD/ThOD) and 19.2 % (DOC) after 28 days (RAR B.8.2.2.1/02, 1990).

Water degradation data

In the study RAR B.8.2.2.2/01, the Degradation of [methyl aniline-UL-14C]phenmedipham and [amino Phenol-UL-14C]phenmedipham were studied according to OECD TG 309 in surface water under aerobic conditions in the dark for 63 days at 20.9 ± 0.2 °C. The pH in the water ranged from 7.50 to 8.74. Application rates were 0.1 and 0.01 mg/L. The experiment was also performed in addition under sterile condition at the high concentration (0.01 mg/L).

Primary degradation of phenmedipham was very fast. A single first order kinetics (SFO) DT_{50} value for methyl aniline labelled phenmedipham was 0.04 days and SFO DT_{50} value for amino Phenol labelled phenmedipham was 0.01 days and 0.04 days for low and high concentrations, respectively. Mineralisation was low, not higher than 15 % at day 63 for [methyl aniline-UL-14C] phenmedipham and 13.2 % AR at day 63 for [amino Phenol-UL-14C] phenmedipham. Two degradation products were found. SFO DT_{50} value of 499 days was evaluated for MHPC and SFO DT_{50} value of 47.6 days for m-toluidine.

Water-sediment degradation data

The degradation of [amino Phenol-UL-14C]phenmedipham (purity > 99 %) and [methyl aniline-UL-14C]phenmedipham (purity 97 %) (RAR B.8.2.2.3/02) was investigated in two different water/sediment systems (sandy loam silt and sand) under aerobic conditions over a period of 126 days at 20 °C with an initial phenmedipham concentration of 0.32 mg/L. The water pH in the systems were 6.9 and 7.0. The study was performed in line with OECD TG 308.

Mineralisation to CO_2 was 29.8-34.1 % at day 126 during the degradation of amino-Phenyl labelled phenmedipham. CO_2 formation was 12.6-13.8 % at day 70 during the degradation of methyl aniline labelled phenmedipham. Non-extractable residues in the sediment after 126 days were 50.8-55.3 % AR for amino-Phenyl labelled phenmedipham and after 70 days 69.7-73.4 % AR for methyl aniline labelled phenmedipham. The primary degradant was MHPC which accounted for approximately 1 % at day 126 in both systems. The dissipation half-lives in the water phase for [Amino Phenol-UL-14C]phenmedipham were first order multi-compartment (FOMC) DT_{50} of 0.16 and SFO DT_{50} 0.11 days and in total system FOMC DT_{50} of 0.069 and 0.15 days in sandy loam silt and sand systems, respectively. The half-lives of MHPC were SFO DT_{50} of 9.2-15.3 days in total system and SFO DT_{50} values of 11.6-13.8 days in the water phase.

In the study RAR B.8.2.2.3/03, the degradation of [amino Phenol-UL-14C]phenmedipham was studied in a water/sediment system, applied at a field rate of 4.9 kg a.s./ha, pH 6.0-6.50. This study was conducted according to OECD TG 308.

Mineralisation to CO_2 was low, 13.2 % at the end of the study period (84 days). The main degradant detected was MHPC, which accounted for 0.3 % at the end of the study period. Bound residues represented 74.8 % after 84 days. [Amino Phenol-UL-14C]phenmedipham half-life in the total system was FOMC DT_{50} of 0.023 days and dissipation half-life was FOMC DT_{50} of 0.012 days in water phase.

In the study RAR B.8.2.2.3/04, the degradation of phenmedipham was investigated according to OECD TG 308 in three freshwater water/sediment systems (silt loam, sand and sandy loam) using two labels, [amino Phenol-UL-14C]phenmedipham and [methyl aniline-UL-14C]phenmedipham, at 20 °C in the dark for up to 127 days and a pH ranging from 6.1 to 8.5. The application rate was 0.1 mg/L.

Phenmedipham degraded very quickly with MHPC and m-toluidine being the major degradation products. Mineralisation was not higher than 31.2 % for any of the labelled phenmedipham. Bound residue formation reached a maximum of 52.1 %. The half-lives for [amino Phenol-UL-14C]phenmedipham were calculated following the FOCUS degKinetics (RAR B.8.2.2.3/01). The half-lives in the total system were FOMC DT_{50} of 0.0001 and 0.0007 days in the

silt loam and sand systems, respectively, and SFO DT_{50} of 0.35 days in the sandy loam system. The half-lives for MHPC were calculated between SFO DT_{50} of 8.7-21 days in the total system and SFO DT_{50} of 8.8-20.2 days in water phase.

In the study RAR B.8.2.2.3/05, the aerobic degradation of [amino Phenol-UL-14C]phenmedipham and [methyl aniline-UL-14C]phenmedipham was investigated according to OECD TG 308 in river and a pond water-sediment systems at 20.7 ± 2 °C in the dark for 98 days. pH values were 8.35 and 7.83. The nominal application rate was based on the maximum field application rate of 1 kg a.s./ha.

Amino Phenol-UL-14C]phenmedipham: phenmedipham was completely dissipated after day 1 in the water phase and it was not detected in the sediment of test systems at any sampling point. Mineralisation to CO_2 was 24.2 % maximum. Non-extractable residues in sediment were, in proportion, 65.6 % and 68.6 % AR after 98 days. The only major degradant was MHPC, which reached, in the total system, at the end of the study 5.1 % AR. Two additional degradation products were identified in the pond system, namely 3-[(methoxycarbonyl) amino]Phenyl(3-hydroxyPhenyl)carbamate (M1) and 3-aminoPhenol (M2). Both reached maximum amounts of 0.5 % AR.

The half-lives for the parent in the total system was 0.12-0.09 days for the river and pond system respectively. The degradant MHPC had half-lives SFO DT_{50} of 13.3 and 17.6 days in total system in river and pond, respectively.

Methyl aniline-UL-14Cphenmedipham was not detectable from day 3 onwards in the water phase of the river and the pond test systems. One major degradant (m-toluidine) was found representing 2.0 % at day 40 in water and 2.9 % in sediment day 7. Mineralisation to CO_2 accounted for 54.8 and 13 % AR for phenmedipham in the river and the pond systems at day 98, respectively. Non-extractable residues in sediment were, in proportion, 31.8 % and 67.7 % AR after 98 days.

The degradation half-life for methyl aniline labelled phenmedipham was SFO DT_{50} of 0.21 and 0.14 days in total system for river and pond, respectively. The degradant m-toluidine had half-lives SFO DT_{50} of 1.5 and 4.7 days in total system in river and pond, respectively.

Soil degradation data (including simulation studies)

There were four soil degradation studies included in the CLH report. Half-lives in soil for phenmedipham ranged from 4 to 53.2 days with the maximum mineralisation to CO_2 25.5 % AR after 224 days.

Conclusion on degradation

Phenmedipham is considered to be not rapidly degradable, for classification purposes, because:

- it is not readily biodegradable;
- hydrolysis degradation half-lives were not under 16 days in the whole pH range of 4.0-9.0 and the hydrolysis product m-toluidine fulfils the classification criteria as hazardous for the aquatic environment;
- it was not demonstrated that phenmedipham is ultimately degraded > 70 % within 28 days in the aquatic environment and the degradation product m-toluidine fulfils the classification criteria as hazardous for the aquatic environment. In the surface water simulation test, primary degradation was fast but the mineralisation to CO_2 was at maximum 15 % AR.

Bioaccumulation

In the study RAR B.9.2.2.3/01, juvenile fish (*Oncorhynchus mykiss*) were exposed in a flow-through system to a nominal concentration of [amino Phenol -UL-14C]phenmedipham of 0.02 mg/L (115 fish) and 0.2 mg/L (106 fish) for 64 hours. The test was done according to OECD TG 305.

In the test, phenmedipham was rapidly hydrolysed to MHPC (more than 86 % radioactivity after 21 and 68hours). Therefore the results mainly represent the bioaccumulation potential of the degradation product MHPC. A BCF of 321 for the low concentration and 121 for the high concentration was obtained. The BCF was not lipid normalised or corrected for fish growth and thus BCF could different depending on the test fish lipid content and/or fish growth during the test period.

In the study RAR B.9.2.2.3/02, juvenile fish (*Lepomis macrochirus*) were exposed in a flow-through system to methyl-Phenol ring and Phenyl ring labelled phenmedipham with nominal concentration of 0.03 mg/L for 10 days according to OECD TG 305.

In the test, a BCF value of 165 for the whole fish was obtained. The BCF was not lipid normalised or corrected for fish growth and thus BCF could be different depending on the test fish lipid content and/or fish growth during the test period.

A measured valid n-octanol/water partition coefficient is also available Log K_{ow} of 2.7 at 20 ± 1 °C (RAR B.2.7/01) and it does not meet the CLP criteria (Log K_{ow} ≤ 4). It is noted that n-octanol/water partition coefficients determined for the major degradation products MHPC and m-toluidine also indicate low potential to bioaccumulate (Log K_{ow} < 1.6).

Conclusion on bioaccumulation

The DS concluded that based on BCF and Log K_{ow} values the substance has a low potential to bioaccumulate.

Aquatic toxicity

The next two tables provide a summary of the most relevant acute and chronic studies provided for phenmedipham in the CLH Dossier.

Table*: Acute aquatic toxicity*

Method	Species	Test material	Results[1]	Remarks	Reference
Acute toxicity to fish - phenmedipham					
OECD TG 203; US EPA OPPTS 835.1075 GLP	*Oncorhynchus mykiss* (rainbow trout)	phenmedipham technical (purity 97.7 % w/w)	**LC_{50}:** 1.84 mg/L (mm)[1]	Validity criteria met	2016 dRAR B.9.2.1/XX M-564852-01-1
Acute toxicity to *Daphnia magna* - phenmedipham					
OECD TG 202; JMAFF 12 Nounan No. 8147 GLP	*Daphnia magna* (cladoceran)	phenmedipham (technical) Purity 97.4 % (w/w)	**EC_{50}:** 2.033 mg/L (mm)[1]	Validity criteria met	2004 B.9.2.4.1/05 M-233654-01-1
Acute toxicity to *Americamysis bahia* – phenmedipham					
OPPTS 850.1035 GLP	*Americamysis bahia* (mysid shrimp)	phenmedipham (technical) Purity 99.1 % (w/w)	**EC_{50}:** 0.23 mg/L (mm)[1]	Validity criteria met	2010 B.9.2.4.2/01 M-409871-01
Acute toxicity to aquatic macrophytes – phenmedipham					
ASTM guideline E 1415-91 (1991)	*Lemna minor* (duck weed)	phenmedipham (technical) Purity 99.4 % (w/w)	**7d EC_{50} (biomass):** 0.109 mg/L (geo)[2]	Validity criteria met	2004 dRAR B.9.2.7/02 M-493457-01-1

GLP			**7d EC_{50} (growth rate):** >0.157 mg/L (geo)[2](geo)[2]		
OECD TG 239 GLP	***Myriophyllum spicatum* (Eurasian watermilfoil)**	phenmedipham (technical) Purity 97.7 % (w/w)	**EC_{50} (biomass):** 0.0519 mg/L (geo)[2] **EC_{50} (growth rate):** 0.0705 mg/L (geo)[2](geo)[2]	Validity criteria met	2017 dRAR B.9.2.7/06 M-580251-02-1 **Key study**

[1] mm = mean measured concentration
[2] geo = geometric mean concentrations

Table: *Chronic aquatic toxicity*

Method	Species	Test material	Results	Remarks	Reference
Chronic toxicity to fish – phenmedipham					
OECD TG 210; US EPA OCSPP 850.1400; US EPA-FIFRA OPP 72–4 GLP	*Oncorhynchus mykiss* (rainbow trout)	phenmedipham technical (purity 99.1 % w/w)	**$NOEC_{(fry\ survival)}$:** 0.096 mg/L (mm)[1] **$NOEC_{(percent\ hatch)}$:** 0.361 mg/L (mm)[1] **$NOEC_{(percent\ swim\text{-}up)}$:** 0.181 mg/L (mm)[1] **$NOEC_{(standard\ length\ growth)}$:** 0.041 mg/L (mm)[1] **$NOEC_{(dry\ weight\ growth)}$:** 0.096 mg/L (mm)[1] **$NOEC_{(morphological\ and\ behavioural\ effect)}$:** 0.041 mg/L (mm)[1]	Validity criteria met	2014 dRAR B.9.2.2.1/01 M-481742-01-1 **Key study**
Chronic toxicity to *Daphnia magna* - phenmedipham					
OECD TG 211; USEPA OCSPP 850.1300 GLP	***Daphnia magna* (cladoceran)**	phenmedipham (technical) Purity 99.1 % (w/w)	**$NOEC_{(reproduction)}$:** 0.005 mg/L (mm)[1] **$NOEC_{(survival)}$:** 0.026 mg/L (mm)[1]	Validity criteria met	2014 dRAR B.9.2.5.1/03 M-482048-01-1 **Key study**
Chronic toxicity to aquatic macrophytes – phenmedipham					
ASTM guideline E 1415-91 (1991) GLP	*Lemna minor* (duck weed)	phenmedipham (technical) Purity 99.4 % (w/w)	Biomass **7d EC_{10}:** 0.022 mg/L (geo)[2] **7d NOEC:** 0.024 mg/L (geo)[2] Growth **7d EC_{10}:** 0.044 mg/L (geo)[2] **7d NOEC:** 0.024 mg/L (geo)[4]	Validity criteria met	2004 dRAR B.9.2.7/02 M-493457-01-1
OECD TG 239 GLP	*Myriophyllum spicatum* (Eurasian watermilfoil)	phenmedipham (technical) Purity 97.7 % (w/w)	Biomass **EC_{10}:** 0.028 mg/L (geo)[2] **NOEC:** 0.0128 mg/L (geo)[2] Growth **EC_{10}:** 0.0208 mg/L (geo)[2] **NOEC:** 0.0128 mg/L (geo)[2]	Validity criteria met	2017 dRAR B.9.2.7/06 M-580251-02-1 **Key study**

[1] mm = mean measured concentration
2 geo = geometric mean concentrations

Acute toxicity to fish

One acute toxicity test with phenmedipham, three with the degradant MHPC and one with degradant m-toluidine on different fish species were considered valid in the RAR.

In the study RAR B.9.2.1/XX, the acute toxicity of phenmedipham to *Oncorhynchus mykiss* (rainbow trout) was studied in 96-hour semi-static test conducted according to OECD TG 203 (1992) and US EPA OPPTS 835.1075 (1996) and in compliance with GLP. Ten fish in each group, were exposed to water control, solvent control and nominal concentrations of 0.128, 0.282, 0.620, 1.36 and 3.00 mg a.s./L, corresponding to the geometric mean measured concentrations of 0.117, 0.250, 0.600, 1.24 and 2.73 mg a.s./L.

The 96h LC_{50} value of 1.84 mg a.s./L was based on geometric mean measured concentration of phenmedipham.

For the degradant MHPC, experimental LC_{50} values of ≥ 75 mg/L were determined using *Oncorhynchus mykiss*, *Cyprinus carpio* (common carp) and *Pimephales promelas* (fathead minnow). For the degradant m-toluidine, an experimental LC_{50} value of 93.3 mg/L was determined in *Cyprinus carpio*. In this test, satisfaction of validity criteria and test substance stability were not reported.

Acute toxicity to invertebrates

One acute toxicity study for water flea *Daphnia magna* (RAR B.9.2.4.1/05 (2004)) and mysid *Americamysis bahia* (RAR B.9.2.4.2/01 (2010)) were considered valid in the RAR for phenmedipham. The lowest toxicity was 96h EC_{50} value of 0.23 mg/L for *Americamysis bahia* based on mean measured concentrations. For the degradant MHPC, two acute toxicity studies for *Daphnia magna* and for degradant m-toluidine one *Daphnia magna* study were considered valid in the RAR. In the last one the EC_{50} = 0.1 mg/L.

In the study RAR B.9.2.4.1/05, the acute toxicity of phenmedipham to *Daphnia magna* was studied in 48h semi-static test according to OECD TG 202 and in compliance with GLP. *Daphnia magna* (< 24 hours old) were exposed to nominal concentrations of 0.00625, 0.0625, 0.625, 1.25, 2.50, 5.00 and 10.0 mg/L at pH 6.0-6.5 in 4 replicates of 5 daphnids in each.

The 48h EC_{50} was determined to be 2.033 mg/L for phenmedipham based on mean measured concentrations.

In the study RAR B.9.2.4.2/01, the acute toxicity of phenmedipham to *Americamysis bahia* was studied in 96h flow-through test according to OPTTS guideline 850.1035 and in compliance with GLP. Juvenile *Americamysis bahia* (20 per treatment level) were exposed to nominal test concentrations 0.063, 0.13, 0.25, 0.50, 1.0 and 2.0 mg/L. The mean measured test concentrations were 0.028, 0.10, 0.23, 0.48, 0.88, 2.0 (non-centrifuged) and 1.9 mg/L (centrifuged).

The 96h EC_{50} was determined to be 0.23 mg/L for phenmedipham based on mean measured concentrations.

There were two studies with Daphnia magna with degradant MHPC RAR B.9.2.4.1/06 and RAR B.9.2.4.1/07. Both studies were done according to OECD TG 202. The 48h EC_{50} were 14 mg/L based on nominal concentrations and 25.6 mg/L based on mean measured concentrations, respectively.

In the study RAR B.9.2.4.1/08, the acute toxicity of the degradant m-toluidine (purity 99.1 % w/w) to *Daphnia magna* was studied in a 48h static test according to OECD TG 202 and in compliance with GLP. *Daphnia magna* 1st instars were exposed to nominal concentrations of 0.02, 0.04, 0.08, 0.16, 0.32 and 0.64 mg/L, corresponding to mean measured test concentrations of 0.0175, 0.0342, 0.0684, 0.142, 0.295 and 0.582 mg/L.

The 48h EC_{50} was determined to be 0.1 mg/L based on mean measured concentrations.

Chronic toxicity to fish

In the study RAR B.9.2.2.1/01, the toxicity of phenmedipham to *Oncorhynchus mykiss* was studied in 92-day (60 days post hatch) flow-through test conducted according to OECD TG 210 (1992), US EPA OCSPP 850.1400 (1996) and US EPA-FIFRA OPP 72-4 (1982) and in compliance with GLP. Four replicates, each with 35 eggs at experiment start and thinned to 15 alevins after hatch, were exposed to nominal (mean measured concentrations) of 0.025 (0.024), 0.050 (0.041), 0.100 (0.096), 0.200 (0.181) and 0.400 (0.361) mg/L. The concentration of the test material in the test medium was determined as a sum of phenmedipham and degradant MHPC. Mean measured recoveries were within the range of 87 to 104 % of the nominal concentrations.

The 92-day exposure resulted in NOEC values of 0.041 and 0.096 mg a.s./L for growth and survival, respectively, based on the arithmetic mean measured concentrations of phenmedipham and the metabolite MHPC. The same NOEC would apply to phenmedipham.

In the study RAR B.9.2.2.1/02, toxicity of the degradant MHPC to *Oncorhynchus mykiss* was studied in 95-day (62 days post hatch) flow-through. The test was conducted according to OECD TG 210 (1992), US EPA OCSPP 850.1400 (1996) and US EPA-FIFRA OPP 72–4 (1982) in compliance with GLP. Four replicates, each with 35 eggs at experiment start and thinned to 15 alevins after hatch, were exposed to control and nominal (mean measured concentrations) of 0.625 (0.798), 1.25 (1.26), 2.50 (2.74), 5.00 (5.34) and 10.0 (10.4) mg/L. The 95-day exposure resulted in a NOEC value of 2.74 mg a.s./L for (dry weight) growth based on the arithmetic mean measured concentrations of MHPC.

Chronic toxicity to invertebrates

There is one valid chronic toxicity study available for aquatic invertebrate *Daphnia magna* in the RAR (B.9.2.5.1/03) with a 21d NOEC 0.005 mg/L for reproduction based on mean measured concentrations. This is the lowest chronic endpoint and it is used as the key study for the long-term aquatic hazard classification of phenmedipham. For degradation products, one 21d Daphnia magna study for m-toluidine and one 28d *Chironomus riparius* study were considered valid in the RAR.

In the study RAR B.9.2.5.1/03, the chronic toxicity of phenmedipham to *Daphnia magna* was studied in 21d flow-through test following OECD TG 211 and in compliance with GLP. *Daphnia magna* 1st instars were exposed to nominal concentrations of 0.0125, 0.0250, 0.050, 0.10 and 0.20 mg/L. The mean measured concentrations of phenmedipham were 39.2-45.8 % of nominal concentrations and the endpoints were recalculated by the request of the RMS based on arithmetic mean measured concentrations of phenmedipham instead of sum of phenmedipham and MHPC, as originally calculated in the study. A NOEC 0.005 mg/L was determined for reproduction based on mean measured concentrations.

In the study RAR B.9.2.5.1/04, the chronic toxicity of m-toluidine to *Daphnia magna* was studied in 21d semi-static test following OECD TG 211 and in compliance with GLP. *Daphnia magna* 1st instar neonates were exposed to nominal concentrations of 2.0, 4.0, 8.0, 16.0, 32.0 and 64.0 µg/L, corresponding to time-weighted mean measured concentrations of 1.19, 1.77, 2.87, 4.67, 8.04 and 14.16 µg/L. A NOEC value of 0.00467 mg/L for total offspring per parent animal and an EC_{10} = 0.00478 mg/L for time to first brood were determined based on TWA.

In the study RAR B.9.2.5.3/05, the chronic toxicity of the degradant MHPC to *Chironomus riparius* was studied in 28d static test according to OECD TG 219 and in compliance with GLP. The substance degraded more than 80 % during the test. The 28d NOEC value of 32 mg/L and EC_{10} value of 29.1 mg/L for emergence ratio for pooled sex, the NOEC of 32 mg/L for development rate

of males, the 28 days NOEC value of 18 mg/L, and EC_{10} value of 53.78 mg/L for development rate of females were determined based on nominal concentrations of MHPC.

Toxicity to algae or other aquatic plants

During the Peer Review of phenmedipham the validity of available algae studies was discussed and studies where the geomean measured concentrations were calculated based on mean initial concentrations and LOQ/2 were not considered valid. Hence, studies with no intermediate samples with measurable residues were not considered valid and were not included in the CLH dossier. The above two studies with *Lemna minor* and *Myriophyllum spicatum* were considered valid in the CLH dossier (RAR B.9.2.7/02 and RAR B.9.2.7/06).

In the study RAR B.9.2.7/02, the toxicity of phenmedipham to *Lemna minor* was studied in 14d semi-static test according to ASTM guideline E 1415-91 and in compliance with GLP. *Lemna minor* were exposed to initial mean measured concentrations of 1.76, 0.020, 0.048, 0.11, 0.28, 0.69 and 1.76 mg/L.

The 7d EC_{50} value of > 0.157 mg/L for growth rate and the 7d EC_{50} value of 0.109 mg/L for biomass growth inhibition was determined. For chronic toxicity, the 7d EC_{10} = 0.044 mg/L and the 7d NOEC = 0.024 mg/L for growth rate of *Lemna minor*. The 7d EC_{10} value of 0.022 mg/L and the 7d NOEC value of 0.024 mg/L for biomass growth inhibition were determined. Results are based on geometric mean concentrations. The study fulfilled the validity criteria set in OECD TG 221.

In the GLP test RAR B.9.2.7/06, the toxicity of phenmedipham to *Myriophyllum spicatum* was studied in 14 d semi-static test according to OECD TG 239 except for the pH, which was lower than recommended 7.9. The pH of the test solution was purposely decreased in order to prevent the hydrolysis of phenmedipham as much as possible. Shoots of *Myriophyllum spicatum* were exposed via the water phase to nominal concentrations of 3.0, 9.49, 30.0, 94.9 and 300 µg/L of test item. The corresponding geometric mean measured concentrations were 0.898, 3.85, 12.8, 46.4 and 170 µg/L. Endpoints were provided based on geomean concentrations.

For growth rate, the most sensitive parameter was the 14d EC_{50} value of 0.0705 mg/L. For chronic endpoints, biomass growth inhibition resulted in an EC_{10} of 0.028 mg/L and a NOEC of 0.0128 mg/L. Growth rate reduction resulted in an EC_{10} of 0.0208 mg/L and a NOEC of 0.0128 mg/L.

For the degradant MHPC, two valid algal and one duckweed study were available in the RAR. For degradant m-toluidine one valid duck weed study was available in the RAR (RAR B.9.2.7/04 (2015)). All of the metabolites were observed to be less toxic than the parent.

Conclusion of the Dossier Submitter (DS)

Aquatic acute toxicity data are available for all the trophic levels for phenmedipham and its degradants MHPC and m-toluidine. The most acutely sensitive species is aquatic macrophyte *Myriophyllum spicatum* with a 14 day E_rC_{50} of 0.0705 mg/L based on geometric mean measured concentrations.

For acute aquatic hazard, on the basis of this acute aquatic macrophyte endpoint being in the range 0.01 mg/L < $L(E)C_{50}$ ≤ 0.1 mg/L, the DS proposed that phenmedipham should be classified as Aquatic Acute 1; H400 with an M-factor of 10.

Phenmedipham is considered to be not rapidly degradable and to have a low bioaccumulative potential. There are adequate chronic toxicity data available for all three trophic levels. The lowest valid chronic toxicity for fish is 92d NOEC value of 0.041 mg/L for *Oncorhynchus mykiss*. The lowest chronic toxicity for aquatic invertebrates is 21d NOEC value of 0.005 mg/L for reproduction of *Daphnia magna* and for aquatic macrophytes a 14d NOEC value of 0.0128 mg/L for biomass growth inhibition and growth rate reduction and a 14d EC_{10} value of 0.0208 mg/L for biomass

growth inhibition of *Myriophyllum spicatum*. Thus, a classification of Aquatic Chronic 1; H410 is applicable for phenmedipham, according to the DS, based on the lowest NOEC value of 0.005 mg/L for *Daphnia magna* (≤ 0.1 mg/L) with a chronic M-factor of 10 (0.001 < NOEC ≤ 0.01 mg/L).

Comments received during public consultation

Three MSCAs commented during public consultation, one of which agreed with the proposed classification.

Another MSCA asked if an E_rC_{10} (dry weight) endpoint was available for the *Myriophyllum spicatum* study. It also asked if a statistically based EC_{10} might be more appropriate given the steep toxicity profile. Furthermore, they asked if measurements of test item concentrations in sediment were available to support the use of water phase concentrations which declined over the study period pinpointing that this is important to consider exposure routes.

The DS answered that a growth rate E_rC_{10} (dry weight) value of 0.0048 mg/L was calculated in the original *Myriophyllum spicatum* study report. However, the control coefficient of variation of this parameter was higher than the respective effect level. Thus, the EC_{10} endpoint for growth inhibition (dry weight) is not considered reliable.

The DS further indicated that measurements were only available in water. According to the DS, the observed loss of test item during the study occurred mainly because of hydrolytic degradation of phenmedipham and the shoots of *Myriophyllum spicatum* were exposed via water phase and, thus, they considered that water phase is relevant exposure route.

RAC took note of the fact that a reliable EC_{10} dry weight cannot be obtained although it cannot check the raw data. RAC considered that the *Myriophyllum* test is adequate for classification.

The third MSCA agreed with the proposed classification. Yet since the metabolite m-toluidine 21d NOEC value of 0.00478 mg/L for *Daphnia magna* appears to be more toxic than the parent, they asked if this value should be considered for chronic classification.

The DS reviewed the test available both for parent and metabolite and answered that toxicity of the parent substance phenmedipham and degradant m-toluidine is within the same order of magnitude for aquatic invertebrates, and both toxicity values would result in the same classification of Aquatic Chronic 1 with a chronic M-factor of 10. Nevertheless in this case they preferred to classify phenmedipham according to the lowest toxicity value for the parent substance (21d NOEC 0.005 mg/L).

RAC agreed in using phenmedipham data for classification since for the parent there is full a data set whereas for the metabolite there is no chronic data for fish.

Assessment and comparison with the classification criteria

RAC agrees with the DS that the data on phenmedipham and not its metabolites should be used for classification since the most reliable and complete data set is available for the parent compound, which is not less toxic than any of the degradation products.

Acute toxicity

Aquatic acute toxicity data are available for all three trophic levels for phenmedipham. The lowest acute endpoints are:

- Fish: *O. mykiss* 96h LC_{50} = 1.84 mg a.s./L
- Invertebrates: *Americamysis bahia* 96h EC_{50} = 0.23 mg/L

- The most acutely sensitive species is the aquatic macrophyte, *Myriophyllum spicatum* with a 14 day E_rC_{50} of 0.0705 mg/L based on geometric mean measured concentrations. RAC considers that the water sediment *Myriophyllum* test is suitable for classification for various reasons (although exposure via sediment cannot be totally ruled out): the substance is a herbicide acting only via the foliage of emerged weeds and *Myriophyllum* has been demonstrated to be the most sensitive acute species, application of the test substance is done via the water column and substance concentration reduces mainly because of hydrolysis.

Hence, according to the Classification criteria, phenmedipham warrants classification as **Aquatic Acute 1; H400, M-factor 10** (0.01 mg/L < L(E)C_{50} ≤ 0.1 mg/L).

Chronic toxicity

RAC agrees with the DS that phenmedipham in **not rapidly degradable**:

- The substance it is not readily biodegradable;
- Hydrolytical degradation half-lives were not under 16 days in the whole pH range of 4.0-9.0 and the hydrolysis product m-toluidine fulfils the classification criteria as hazardous to the aquatic environment;
- It was not demonstrated that phenmedipham is ultimately degraded > 70 % within 28 days in the aquatic environment (under neutral and alkaline conditions, phenmedipham undergoes fast primary degradation with a half-life below 16 days) and the degradation product m-toluidine fulfils the classification criteria as hazardous for the aquatic environment.

With a BCF of 165 below the trigger value of 500 and a Log K_{ow} of 2.7, below the trigger value of 4, RAC agrees with the DS and considers that phenmedipham has **a low potential to bioaccumulate.**

There are adequate chronic toxicity data available for all three trophic levels:

- Fish: *Oncorhynchus mykiss* 91d NOEC = 0.041 mg/L
- Invertebrates: *Daphnia magna* 21d NOEC = 0.005 mg/L (there is no chronic data with the acute most sensitive species for invertebrates *A. bahia;* a chronic study with *A. bahia* might potentially lead to a lower NOEC than *Daphnia*)
- Algae or other Aquatic Plants: *Myriophyllum spicatum* 14 days EC_{10} (growth) = 0.0208 mg/L

The lowest chronic toxicity value is the 21d NOEC = 0.005 mg/L for reproduction of *Daphnia magna*. Based on this value and the substance being non-rapidly degradable, a classification of **Aquatic Chronic 1; H410, M-factor of 10** (≤ 0.1 mg/L) with a chronic (0.001 < NOEC ≤ 0.01 mg/L) is warranted.

RAC agrees with the DS that phenmedipham warrants **classification as Aquatic Acute 1; H400, M = 10 and Aquatic Chronic 1; H410, M = 10.**

Additional references

EFSA (2018) Peer review of the pesticide risk assessment of the active substance phenmedipham.

EFSA Journal, doi: 10.2903/j.efsa.2018.5151

Muller *et al.* (2006) Hazard classification of chemicals inducing haemolytic anaemia: an EU regulatory perspective. Regulatory Toxicology and Pharmacology 45:229-241

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).