Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

diflufenican (ISO); *N*-(2,4-difluorophenyl)-2-[3-(trifluoromethyl)phenoxy]-3-pyridinecarboxamide; 2',4'-difluoro-2-(α,α,α-trifluoro-*m*-tolyloxy) nicotinanilide

EC Number: -
CAS Number: 83164-33-4

CLH-O-0000001412-86-285/F

Adopted

13 June 2019

13 June 2019

CLH-O-0000001412-86-285/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: **diflufenican (ISO); *N*-(2,4-difluorophenyl)-2-[3-(trifluoromethyl)phenoxy]-3-pyridinecarboxamide; 2',4'-difluoro-2-(α,α,α-trifluoro-*m*-tolyloxy) nicotinanilide**

EC Number: **-**

CAS Number: **83164-33-4**

The proposal was submitted by **the United Kingdom** and received by RAC on **8 August 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: **Michael Neumann**

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 **13 June 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	616-032-00-9	diflufenican (ISO); *N*-(2,4-difluorophenyl)-2-[3-(trifluoromethyl)phenoxy]-3-pyridinecarboxamide; 2′,4′-difluoro-2-(α,α,α-trifluoro-*m*-tolyloxy) nicotinanilide		83164-33-4	Aquatic Chronic 3	H412	-	H412			
Dossier submitters proposal	616-032-00-9	diflufenican (ISO); *N*-(2,4-difluorophenyl)-2-[3-(trifluoromethyl)phenoxy]-3-pyridinecarboxamide; 2′,4′-difluoro-2-(α,α,α-trifluoro-*m*-tolyloxy) nicotinanilide		83164-33-4	**Modify** Aquatic Acute 1 Aquatic Chronic 1	**Modify** H400 H410	GHS09 Wng	H410		M=1000 M=100	
RAC opinion	616-032-00-9	diflufenican (ISO); *N*-(2,4-difluorophenyl)-2-[3-(trifluoromethyl)phenoxy]-3-pyridinecarboxamide; 2′,4′-difluoro-2-(α,α,α-trifluoro-*m*-tolyloxy) nicotinanilide		83164-33-4	**Modify** Aquatic Acute 1 Aquatic Chronic 1	**Modify** H400 H410	GHS09 Wng	H410		M=10000 M=1000	
Resulting Annex VI entry if agreed by COM	616-032-00-9	diflufenican (ISO); *N*-(2,4-difluorophenyl)-2-[3-(trifluoromethyl)phenoxy]-3-pyridinecarboxamide; 2′,4′-difluoro-2-(α,α,α-trifluoro-*m*-tolyloxy) nicotinanilide		83164-33-4	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=10000 M=1000	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Diflufenican belongs to the class of anilide herbicides. It acts as a specific inhibitor of phytoene dehydrogenase, a key enzyme of carotenoid biosynthesis. It is used for the control of broadleaf weeds and a few annual grasses in winter cereals. The dossier submitter (DS) has reviewed the existing entry in Annex VI of CLP for diflufenican as a result of the renewal assessment under Regulation EC 1107/2009. Hence this proposal only addressed the reproductive toxicity and environmental hazards.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Effects on sexual function and fertility

The DS included one GLP and OECD compliant two-generation study in the rat to assess the effects of diflufenican on sexual function and fertility. Diflufenican was administered in the diet at concentrations of 0, 500, 2 500 and 12 500 ppm (the corresponding doses in mg/kg bw/day are presented in the table "Mean achieved intakes of diflufenican for each generation", in the section "Assessment and comparison with the classification criteria", below). The DS noted that the top dose approached or exceeded the limit dose (1 000 mg/kg bw/d) for the study protocol.

Both males and females showed an overall reduction in food consumption and body weight gain in the mid and high dose groups. In the high dose group, an increased incidence of mortality was observed in females just prior to parturition and until post-partum day 8. This dystocia-related effect was considered by the DS to be treatment related. No other effects on fertility parameters were observed. However, other findings included a decrease in relative thymus weight in the high dose group which was associated with a depletion of thymic cortical tissue. Further, an increase in liver weight (adjusted for body weight) and some renal histopathology changes were observed in the high dose group. No relevant microscopic findings were found in the reproductive tract and no notable effects were associated with the endocrine system.

The dystocia was observed as perinatal death of several dams with no or incomplete delivery of their litters. In the high dose group, the incidence was 5.1 % (5/98 pregnant animals) spread across 2 generations and 3 matings (F0B, F1A and F1B). In addition, a single incidence was observed in the mid dose group in the F0 generation. The available historical control data indicate an incidence of dystocia up to 0.5 %, however in general dystocia is regarded as a rare event in rats.

Maternal toxicity was observed as reduced body weight of F0 dams by 11-17 % and for F1 dams by 10-18 % in the high dose group. No other clinical signs were observed. The individual body weight data for dams that died were not available to the DS, so the maternal toxicity of the affected dams could not be assessed on an individual basis.

As regards litter findings, a slight dose-dependent decrease in mean pup weight was observed at birth and during pup rearing. In the high dose group, the treatment was associated with a

marked reduction in the ability of litters to thrive up to weaning. The most consistent effect was on litter and mean pup weight, and on some occasions increased pup deaths. The decreased birth-weight of pups occurred only in conjunction with decreased maternal body weights. The DS therefore considered this effect to be secondary to maternal toxicity. No adverse effects were observed on sex ratios, the stages of pre-weaning development or the incidences of anomalous pups. A reduction of mean thymus or spleen weight and an increase in liver-weight were observed in the mid and high dose groups in some batches of weanlings in the parental generations. No effects on the reproductive tract were observed.

The DS included several short-term and long-term studies in the rat, mouse and dog as additional information on possible effects of diflufenican on reproductive organs and tissues. In most of these studies the ovaries, testes and pituitary gland were collected and weighed. In some studies, the uterus and cervix were also analysed for weight changes. None of the studies reported any findings on the reproductive organs analysed. The DS considered these studies as supportive/additional information for the evaluation of effects on sexual function and fertility.

The DS concluded that no classification is warranted for effects of diflufenican on sexual function and fertility. Although the incidence of dystocia seemed to be related to exposure to diflufenican, the finding was observed only at high doses (above the limit dose), together with maternal toxicity and was most likely a secondary, non-specific consequence of other toxic effects. This was further supported by the lack of evidence that diflufenican affects the reproductive tract, the endocrine system or other systems that might be involved in parturition in rats.

Adverse effects on development

Three developmental studies (OECD TG 414) were available to the DS, two in the rat and one in the rabbit. In the two studies with the rat, diflufenican was administered by oral gavage at doses up to 1 000 and 5 000 mg/kg bw/day respectively. In one study, clear signs of maternal toxicity were observed at 5 000 mg/kg bw/day. Litter size and litter weight were also slightly lower at this high dose level. This was possibly linked to maternal toxicity. However, no clear signs of developmental toxicity were observed even at the excessively high dose level of 5 000 mg/kg bw/day. In the same study, a reduction in maternal body weight gain were observed early in the treatment period at 500 mg/kg bw/day, however no effect on litter parameters were observed at this dose level. In the other study, no maternal toxicity or developmental effects were observed up to the highest tested dose of 1 000 mg/kg bw/day. Two different strains of rats were used in these two studies, which could explain the difference in maternal toxicity observed.

In the rabbit study, clear evidence of maternal toxicity such as pale faeces, red discoloration of the urine, reduced faecal output, reduced food consumption and clear reduction in body weight gain were observed at 2 500 mg/kg bw/day. However, no effects on litter parameters or other developmental effects were observed. It should be noted that the incidence of rudimentary extra ribs at the high dose was noted but was within the range of the historical control data (HCD) provided. Furthermore, the incidence in the concurrent control group was lower than expected.

Based on these three studies, the DS concluded that diflufenican did not show evidence of developmental toxicity in rats or rabbits although tested at doses well above the limit dose and showing clear maternal toxicity in two studies. No classification for developmental toxicity was proposed by the DS.

Effects on or via lactation

The DS concluded that no classification is warranted for effects on or via lactation. This is based on the absence of any substantial evidence from the information available to the DS indicating that diflufenican causes adverse effects in the offspring via lactation.

Comments received during public consultation

Comments were received from two MSCA and one Company-Manufacturer.

One MSCA supported the proposal that no classification is warranted for reproductive toxicity for diflufenican. Another MSCA however questioned the conclusion for no classification for fertility and suggested that a classification in category 2 for effects on sexual function and fertility based on the incidences of dystocia. This classification could be based on the incidence of dystocia being clearly above the HCD and that the top dose only slightly exceeded the limit dose. Further, they questioned the relevance of maternal toxicity for dystocia and considered that the relevance of potential bioaccumulation should be assessed.

The Company-Manufacturer supported no classification for reproductive toxicity as proposed by the DS. They considered the dystocia observed to be secondary to the excessive general toxicity of diflufenican.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

The DS included one 2-generation study (conducted according to GLP and OECD TG 415, 416) in Sprague Dawley rats for the assessment of effects on sexual function and fertility (Anon. 1985). In addition, histopathology of the reproductive tract in F0 and F1A adult rats were examined in Anon. (1987). Diflufenican was administered in the diet at dose levels of 0, 500, 2 500 and 12 500 ppm. The mean achieved intakes of diflufenican are summarised in the table below. It is noted that the high dose group approached or even exceeded the limit dose.

Table: *Mean achieved intakes of diflufenican for each generation.*

Generation/phase	Mean diflufenican intake (mg/kg bw/day)					
	Males			Females		
	500 ppm	2 500 ppm	12 500 ppm	500 ppm	2 500 ppm	12 500 ppm
F0/premating	35.5	175.6	888.0	41.9	206.1	1 042.0
F1A/premating	38.8	198.4	1 035.0	47.3	223.7	1 168.0
F2A/rearing	42.9	209.8	1 044.0	50.8	244.2	1 316.0

F0 animals (32/sex/group), 6 weeks of age, were treated for 10 weeks pre-mating until sacrifice after weaning of F1B pups. F1A animals (28/sex/group), 4 weeks of age, were treated for 12 weeks during the pre-mating period until sacrifice after weaning of the F2B pups. F2A animals were treated from 4 weeks of age for 90 days before sacrifice while F2B animals were treated from 4 weeks of age for 14 days before sacrifice.

Findings of parental toxicity are summarised in the table below.

Table: *Summary of parental toxicity*

F0 generation			
	500 ppm	**2 500 ppm**	**12 500 ppm**
Perinatal mortality	1 female on day 18 of the first mating period. Not pregnant.	1 female, second mating at GD 22	Second mating: 1 female PND8 (humane sacrifice), 1 female GD 22.
Food consumption, bw and bw gain	No effect observed	Males/females: reduced food consumption and bw gain (~10 % compared to controls).	Males/females: reduced food consumption (~10-15 % compared to controls) and bw gain (~15 % compared to controls).
Organ findings	Significantly reduced relative thymus weight*, dose-dependent ranging from 8 % at 500 ppm to 15 % at 12 500 ppm		
Histopathology of the reproductive tract	No adverse effects observed in males or females (only investigated in the control and high dose groups)		
F1 generation			
	500 ppm	**2 500 ppm**	**12 500 ppm**
Perinatal mortality	1 female (first mating)	None	First mating: 1 female PND3 (humane sacrifice), 1 female PND8. Second mating: 2 females PND1
Food consumption, bw and bw gain	No effect observed	Males/females: reduced food consumption (~10-20 % compared to controls) and bw gain (~15 % compared to controls).	Males/females: reduced food consumption (~10-20 % compared to controls) and bw gain (~10-15 % compared to controls).
Organ findings	No adverse effects observed	Males: 15.5 % reduced thymus weight (relative to brain) compared to control.	F1A males: 7 %* increased relative (to bw) kidney weight compared to controls 25 % reduced relative (to brain) thymus weight compared to controls; F1A females: 11.5 % reduced relative (to brain) thymus weight compared to controls.
Histopathology (lungs, thymus, liver, spleen, kidneys and reproductive tract)	No treatment related effects observed	Dilated renal medullary collecting ducts (1/28 females).	Dilated renal medullary collecting ducts (2/24 females), associated with mineral casts in one of the affected females. Minimal depletion of cortical tissue in thymus in 4/28 males and 6/24 females, associated with lower relative thymus weights in both sexes. No adverse effects on reproductive tract (males/females).

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (Kruskal-Wallis test intergroup comparison with the control)

An overall reduction in food consumption was observed in both males and females at 2 500 and 12 500 ppm (~10-15 % compared to controls). In F0 adult animals food consumption decreased during the pre-mating phase in males and females in the mid and high dose. In the F1 and F2 males a similar decrease in food consumption was seen in all treated groups. For F1 and F2 females there was a decrease in food consumption of 10-20 % and 5-10 % in the mid and high dose groups respectively. Body weight gain was also reduced (10-20 %) in both males and females in all generations in the mid and high dose groups, however, similar findings were not observed for the corrected bodyweight gain (see the table below).

Table: *Corrected body weight gain (g) GD 0-20*

	Litter	0 ppm	500 ppm	2 500 ppm	12 500 ppm
F0	F1A	42.7 g	39.4 g	43.3 g	49.7 g
	F1B	48.1 g	47.6 g	53.6 g	47.8 g
F1	F2A	41 g	41.2 g	46.6 g	47.1 g
	F2B	43.3 g	42.2 g	42.8 g	47.5 g

Mating performance and pregnancy rate were unaffected in all pairings. No effects on the reproductive tract of females in the control and high dose groups were revealed in the histopathological examination (Anon. 1987). No treatment-related effects were observed in the males; over the two generations, the number of males which failed to induce pregnancy at either mating was 1, 2, 3 and 1 at 0, 500, 2 500 and 12 500 ppm, respectively. Two males in the mid dose group showed reduced spermatogenesis with reduced numbers of spermatozoa in the epididymides. For all other animals failing to mate, no histopathological findings of the reproductive tract outside normal limits were reported.

As regards mortalities, nine females died or were killed prematurely during the study. Two of these were clearly incidental, whilst up to 6 of the 7 remaining female deaths were plausibly linked to dystocia. The female deaths are further described in the table below. In addition, two males died during the study (one F1A generation control male in week 30, one F0 generation male at 500 ppm in week 29) but these were not considered treatment related.

The gestation period was unaffected by treatment in all four pairings. Five out of 7 dams found dead at or near parturition were found to have died during delivery of the pups resulting from the second mating of the F0 or F1 adults, and 6 of the 7 animals were in the high dose group (1 042/1 168 mg/kg bw/day in F0/F1 females).

In the high dose group, 4 out of 6 dams that died had failed to deliver all their offspring and were therefore clearly diagnosed with dystocia. Of the remaining two females that died, one female (second mating) was humanely sacrificed at PND8 due to poor condition linked to paralysis of the hind-limbs. A distended uterus was observed at autopsy. No clear information was available regarding whether the paralysis occurred before, during or after parturition. The paralysis could be linked to difficult parturition and dystocia cannot be ruled out. The other female displayed no evidence of difficult parturition.

A single incidence of dystocia (incomplete parturition) occurred at the mid-dose level in the F0 generation but no evidence of dystocia was seen at this dose in the F1 generation.

Table: *Incidence of perinatal mortality and potential dystocia in F0 and F1 dams*

Dose level	Dam ID	Time/cause of death/clinical sign	Dystocia
Control	-		
500 ppm	F0A 172	Humanely sacrificed day 18 of first mating period. Not pregnant. Death caused by poor clinical condition and dorsal injury.	No
	F1A 422	Right eye prominent and congested. Autopsy – right eye ruptures and haemorrhagic. Left lower molar, crown missing.	No
2 500 ppm	F0B 221	Found dead day 22 of second gestation period. All 15 foetuses undelivered.	Dystocia plausible.
12 500 ppm	F0B 235	Humanely sacrificed on PND8. Paralysis of hind limbs. No delayed gestation, no undelivered foetuses. All pups died by PND7, likely due to starvation.	Dystocia cannot be dismissed.
	F0B 237	Found dead on day 22 of the second gestation. All 14 foetuses undelivered.	Dystocia plausible.
	F1A 479	Found dead PND8 of first litter. No undelivered foetuses, though only 2 born. No increase in the duration of gestation.	Not dystocia.
	F1A 459	Humanely sacrificed PND3. Duration of parturition extended. 6 foetuses undelivered. 2 foetuses undelivered at necropsy. Other findings: pallor, piloerection, blood staining of the fur around vaginal opening.	Dystocia plausible.
	F1B 474	Found dead PND1 of second mating. Parturition incomplete, 3 foetuses delivered, 12 undelivered. No increase in duration of gestation.	Dystocia plausible.
	F1B 478	Found dead on PND1 of second mating. Parturition incomplete. 1 pup born, 13 undelivered. No increase in duration of gestation.	Dystocia plausible.

Regarding historical control data for dystocia in rats, data collected from 3 preliminary one-generation studies and 7 definitive two-generation studies from the same laboratory, in the same strain of animals from 1981-1988 were compiled by the study sponsor. Dystocia was identified in control animals in 2/10 studies with one incidence in a study from 1981 and two incidences in a study from 1983. The animal supplier indicated the incidence of perinatal mortality in their breeding colonies of approximately 0.2-0.5 %.

In comparison, the incidences of assumed dystocia identified in the two-generation study with diflufenican are summarised in the table below. It should be noted that there was no overall effect of diflufenican on the duration of gestation in any group.

Table: *Incidence of diagnosed dystocia in F0 and F1 dams in the study.*

	Dystocia/litters/mated female rats			
Mean diflufenican intake	**0 ppm**	**500 ppm**	**2 500 ppm**	**12 500 ppm**
F0 first mating % incidence of dystocia	0/32/32 0	0/30/32 0	0/31/32 0	0/29/32 0
F0 second mating % incidence of dystocia	0/25/32 0	0/21/31 0	1/23/32 4.3	2/23/32 8.7
F1 first mating % incidence of dystocia	0/26/28 0	0/25/28 0	0/24/28 0	1/24/28 4.2
F1 second mating % incidence of dystocia	0/26/28 0	0/26/28 0	0/26/28 0	2/22/26 9.1
Total number (%) incidence of dystocia in pregnant rats across matings/ dose a)group	0/109/120 (0)	0/102/120 (0)	1/104/120 (1)	5/98/120 (5.1)

Findings of litter toxicity are summarised in the table below.

Table: *Summary of litter toxicity*

	F1 pups (excluding total litter loss)			
		500 ppm	**2 500 ppm**	**12 500 ppm**
	Pup weight			
		No effect observed	F1A ↓** & F1B ↓*** litter and mean pup weight day 21.	F1A ↓** & F1B ↓*** litter and mean pup weight day 21. F1A ↑** cumulative pup loss/pup mortality (day 0-21).
		Dose dependent decrease in mean pup-weight observed in F1A and F1B from birth up to PND21 (weaning)		
	Organ findings (relative organ weight adjusted to bodyweight)			
F1A young		Females ↓* spleen weight (10 % reduction compared to controls)	Females ↓** spleen weight (11 % reduction compared to controls); males ↓* spleen weight (10 % reduction compared to controls).	Females ↓** spleen weight (14 % reduction compared to controls) ↓* thymus weight (17 % reduction compared to controls); males ↓* spleen weight (13 % reduction compared to controls).
		Note: Thymus weight change was dose-dependent in both sexes.		
F1A adults		No effect observed	No effect observed	Males ↑* kidney weight (7 % increase compared to controls).
	F2 pups (excluding total litter loss)			
		500 ppm	**2 500 ppm**	**12 500 ppm**
	Pup weight			
		No adverse effects observed	F2A & F2B ↓* mean pup weight day 21	F2A ↓** litter weight ↓*** mean pup weight day 21; F2B ↓*** litter weight, ↓* mean pup weight day 21, ↑** cumulative pup loss/pup mortality (day 0-21).
		Dose-dependent decrease in mean pup weight observed at F2A & F2B from birth up to post-natal day 21 (weaning)		
	Organ findings			
F2A young		No adverse effect observed	Male ↓** spleen weight (15 % reduction compared to controls)	Male ↑** liver weight (10 % increase compared to controls) ↓** spleen weight (12 % reduction compared to controls)
F2 adult		Males ↑** kidney weight (9.3 % increase compared to controls); females ↑** liver weight (12 % increase compared to controls).	Males ↑* kidney weight (11 % increase compared to controls); females ↑** liver weight (14 % increase compared to controls).	Males ↑* kidney weight (8.4 % increase compared to controls); females ↑** liver weight (20 % increase compared to controls). Increase in liver weight was dose-dependent.
F2B young		500 ppm: no adverse effect observed	Males ↑** liver weight (9 % increase compared to controls).	↑** liver weight (9 % increase compared to controls).
	Histopathology (lungs, thymus, liver, spleen, kidneys) F2A weanlings			
		No treatment-related effects observed	Dilated renal medullary collecting ducts in 2/24 females associated with mineral casts in the dilated collecting ducts of one female.	Dilated renal medullary collecting ducts in 1/19 males and 2/17 females associated with mineral casts in all affected weanlings. Wedge-shaped areas of dilated cortical tubules were also observed in 2/19 male weanlings and 1/17 female weanlings.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (Kruskal-Wallis test intergroup comparison with the control)

A generally low incidence of total litter loss was reported. Overall the incidence was 0, 0, 0, 0 (F0, 1st mating) and 1, 0, 0, 1 (F0, 2nd mating) in control, low, mid and high dose group and 1, 4, 0, 3 (F1A, 1st mating) and 0, 0, 1, 1 (F1A, 2nd mating) in the control, low, mid and high dose group, respectively. Mean pup weights at birth were decreased in a dose-dependent manner and were statistically significantly different for all matings in the high dose groups. This was also generally the case but to a lesser extent in the mid dose groups. The reduced pup weight was associated with a statistically significant decrease in mean litter weight in 2/4 matings, while litter size at birth was unaffected.

Pup weight gain from birth up to day 21 was statistically significantly lower in the high dose group, and to some degree also in the mid-dose group, in both generations. In the high dose groups a statistically significant increase in pup mortality (cumulative pup loss between days 0-21) at the first mating of the F0 generation and second mating of the F1A generation were noted. However, no clear dose-response relationship was seen for the cumulative pup loss at day 21 (across 4 matings) and they were statistically significantly different from control only in 2/4 matings in the high dose groups.

Overall, the litter effects observed in the high dose group are likely to be the consequence of the markedly lower pup weight observed at birth compared to controls, resulting in a marked reduction in the ability of litters to thrive up to weaning (day 21). Maternal weight was affected in a dose-dependent manner during gestation, however no effect was observed for the corrected maternal body weight gain. Despite their initially reduced bodyweight at birth, the surviving pups in the high dose group gained weight in a similar pattern to the other dose groups up to weaning.

No treatment-related effects were seen on sex ratio or pre-weaning development. The incidence of structural anomalies recorded at autopsy of excess F1 and F2 offspring did not indicate any adverse relationship to dietary concentration of diflufenican.

Table: *Litter data up to day 21*

Dose (ppm)	**0**	**500**	**2 500**	**12 500**
F1 pups 1st mating				
Litter size at birth	11.8	12.0	12.0	11.9
Mean pup weight at birth (g)	6.0	5.9	5.7*	5.2***
Cumulative pup loss (day 0-21) %	3.4	5.6	6.4	11.2**
Mean litter weight (g)	504.6	497.3	444.7***	408.0***
Mean pup weight day 21 (g)	43.8	42.7	38.0***	34.8***
F1 pups 2nd mating				
Litter size at birth	10.7	11.8	10.2	10.3
Mean pup weight at birth (g)	6.1	5.9	5.8*	5.7**
Cumulative pup loss (day 0-21) %	11.8	8.4	15.1	7.9
Mean litter weight day 21 (g)	486.1	497.2	395.8**	377.3***
Mean pup weight day 21 (g)	45.8	43.7	40.9**	38.4***
F2 pups 1st mating				
Litter size at birth	11.0	11.7	12.0	10.5
Mean pup weight at birth (g)	5.8	5.8	5.6	5.4**
Cumulative pup loss (day 0-21) %	7.3	5.7	4.9	13.0
Mean litter weight (g)	459.7	482.1	455.5	369.8**
Mean pup weight day 21 (g)	43.3	42.4	39.0*	36.0***
F2 pups 2nd mating				
Litter size at birth	12.4	12.3	12.4	9.5**
Mean pup weight at birth (g)	5.9	5.8	5.8	5.4**
Cumulative pup loss (day 0-21) %	6.4	9.2	4.2	26.4**
Mean litter weight day 21 (g)	480.7	484.4	449.6	329.3***
Mean pup weight day 21 (g)	39.3	40.4	36.5*	35.3*

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (Kruskal-Wallis test intergroup comparison with the control)

In F1A weanlings a decrease in thymus weight was observed in the high dose group. Male F1A and F2A weanlings showed a reduction in spleen weights in the mid and high dose groups, and female F1A weanlings showed a reduction of spleen weights in all dose groups. No histopathology findings were associated with these organ weight changes.

Increased liver weights were observed in young males in the F2A and F2B generations at the higher doses (less than 10 % increase compared to controls). In adult F2A female animals a significant increase in liver weight was seen in all treatment groups, however the control value appeared to be low in this group (10-20 % increase compared to controls). No microscopic changes in the liver were observed.

Kidney changes were apparent in the F2A weanlings which were considered to be treatment related, including dilated collecting ducts in 2/17 females and 1/19 males in the high dose groups; this was associated with mineral casts in all weanlings. Wedge-shaped areas of dilated cortical tubules were seen in 2/19 male weanlings and 1/17 female weanlings. In the mid dose group, dilated medullary collecting ducts were observed in 2/24 weanling females.

RAC noted the repeated dose toxicity studies included by the DS (summarised under "Supplemental information" in the background document; for further detail see Section 10.10 of the CLH report). Overall, these studies did not show any evidence on effects on reproductive organs.

Comparison with the CLP criteria

No human data was available, therefore, classification as Repr. 1A is not warranted.

In a GLP and OECD TG compliant two-generation study in the rat, diflufenican was administered via the diet up to a high dose level which were up to or above the limit dose. Dystocia were observed in one dam of the mid dose groups and 5 dams in the high dose groups. The dystocia was observed together with some maternal toxicity observed as reduced food consumption and reduced body weight gain. It is noted, however, that no clear effect on corrected maternal body weight gain on GD 0-20 was observed.

RAC is of the opinion that classification in Category 1B is not justified since the findings of dystocia do not provide sufficiently clear evidence of an adverse effect on sexual function and fertility.

As regards a classification in category 2 or no classification, RAC considers the cases of dystocia to be related to the exposure to diflufenican. Five animals in the high-dose group were affected across generations and matings. In addition, one single incidence was observed in the mid-dose group in the F0 generation. The incidence in the high dose group was clearly above the HCD provided. However, it is noted that the high dose group exceeded the limit dose. Maternal toxicity was evident at this dose as body-weights of the dams were up to 17 % lower than the control animals throughout the study. However, no clear effect was seen on the corrected maternal body weight gain (GD 0-20). There is no evidence from the reproductive toxicity or repeated-dose toxicity studies indication that diflufenican acts through a specific mode-of-action that might result in dystocia. No other effects on reproduction or fertility were observed in this study.

In conclusion, RAC is of the opinion that the findings in this study provide some evidence of an effect on sexual function or fertility. However, other toxic effects observed in the dams and the fact that the effect is mainly observed at a dose level exceeding the limit dose decrease the concern. Therefore, RAC is of the opinion that **no classification** is justified for adverse effects on sexual function and fertility.

Adverse effects on development

Three developmental toxicity studies were available for the evaluation of adverse effects on development, two studies in the rat and one study in the rabbit. These studies have been summarised in table below.

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

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**
Oral gavage OECD TG 414 (1981) Sprague Dawley rats Pregnant females 25 / group Anon. 1984a	Diflufenican (purity 98.1 %) 0, 50, 500 and 5 000 mg/kg bw/day Administered by gavage at dose volume of 2 mL/100g bw Treated between days 6 and 15 of pregnancy	Maternal toxicity: Dose-related ↑salivation (post-dosing); not seen beyond the last dosing day. Pale faeces in high dose animals over days 7 to 16. No treatment-related deaths. ≥ 500 mg/kg bw/day: dose-related ↓bodyweight gain throughout treatment. Food consumption at 5 000 mg/kg bw/day slightly lower than controls (~10 % reduction) (days 6 - 10). No gross necropsy findings. Developmental toxicity: No statistically significant differences in litter size, litter weight or pre- or post-implantation losses between the treated and the control groups. Sex ratio unaffected by treatment. No dose-related increase and no pattern to the malformations observed. Dose-dependent mean increase (%) in **visceral anomalies** observed although no obvious pattern or relationship between the anomalies seen. No historical control data available. No treatment-related increase in skeletal anomalies observed.
Oral gavage OECD TG 414 (1981) Wistar rats Pregnant females 28/group Anon. 2002	Diflufenican (purity 98.8 %) 0, 250, 500 and 1 000 mg/kg bw/day Administered by gavage at dose volume of 5 mL/kg bw Treated between days 6 and 15 of pregnancy	Maternal toxicity: No clinical signs. No treatment-related deaths. Food consumption / bodyweight gain comparable to the control group at all doses. Comparable mean number of corpora lutea, implantations, early and late resorptions, pre- and post-implantation loss and dams with any/all resorptions to the respective vehicle control values in all treatment groups. No gross necropsy findings Developmental toxicity: No statistically significant differences in litter size, litter weight between the treated and the control groups. Sex ratio unaffected by treatment. No treatment-related external observations. No visceral observations or major skeletal malformations.
Oral gavage OECD TG 414 (1981) New Zealand White rabbits Pregnant females Anon. 1984b	Diflufenican (purity 98.1 %) 0, 50, 350 and 2 500 mg/kg bw/day Administered at dose volume of 10 mL/kg bw Treated between days 6 and 18 of pregnancy	Maternal toxicity: No treatment-related deaths. 2 500 mg/kg bw/day: pale faeces (up to day 19), red discoloured urine (11/16 animals towards end of treatment, persisting few days post dosing period), reduced faecal output associated with reduced food consumption. 350 mg/kg bw/day: red discoloured urine (3/13 animals) at immediate post-dosing period. 2 500 mg/kg bw/day: food consumption and bodyweight gain clearly reduced throughout the treatment period but recovered once treatment ceased. 50-350 mg/kg bw/day: food consumption lower than controls, however not considered treatment related because the reduction was observed during the pre-treatment period and remained as such throughout treatment. One dam at 350 mg/kg bw/day aborted its litter on day 24 (10 abortion sites in the uterus). No treatment-related increase in post-implantation losses and litter size.

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results
		No treatment-related gross necropsy findings Developmental toxicity: No treatment-related effect on litter weight, mean foetal weight or sex ratio. No treatment related skeletal observations. Variant sternebrae incidence not increased by treatment. ↑ Extra ribs incidence in all treated groups in a dose-related pattern (statistically significant at 2 500 mg/kg bw/day), however within historical control data range provided. Incidence in control animals relatively low.

In a study conducted according to OECD TG 414 and GLP, rats (Sprague Dawley, 25/group) were exposed to diflufenican (98.1 %) at dose levels of 0, 50, 500 and 5 000 mg/kg bw/day (Anon., 1984a). A dose-related increase in salivation were observed in the in the post-dosing period, accompanied by brown facial staining on many occasions. The increased salivation was not observed beyond the last day of dosing. In the high dose animals, pale faeces were also reported over GD 7 to 16. Food consumption was slightly reduced (~10 %) in the high dose group over GD 6 to 10. Bodyweight gains were reduced in a dose-related pattern in the mid and high dose groups, beginning from day 6 and persisting throughout the treatment period (to GD 15). However, these effects showed at least partial recovery after the cessation of treatment. There were no gross necropsy findings in dams. No statistically significant effects on litter size, litter weight or pre- or post-implantation loss were observed and sex ratio was not affected by treatment. There was no dose-related increase and no pattern to the malformations observed. Skeletal anomalies were not increased. The number of young with visceral anomalies was increased in all treated groups in a dose-related pattern (3.2 %, 4.7 %, 5.8 % and 9.6 % at 0, 50, 500 and 5 000 mg/kg bw/day respectively, see the table below), however there was no obvious pattern or relationship between the anomalies seen. No HCD were available to put this finding into context. The incidence of foetuses with additional ribs or sternebral abnormalities was not affected by treatment.

Table: *Group mean incidence of malformations and anomalies*

Group (mg/kg bw/day)				**0**	**50**	**500**	**5 000**
# litters				19	21	19	21
# pups with	**Malformations**		Examined	199	205	195	207
			Total (N)	3	5	1	3
			Mean (%)	1.5	2.6	0.7	1.4
	Anomalies	**Skeletal**	Examined	98	101	97	102
			Total (N)	13	16	12	14
			Mean (%)	14.3	16.1	13.9	13.3
		Visceral (Wilson technique)	Examined	98	99	97	102
			Total (N)	3	5	5	10
			Mean (%)	3.2	4.7	5.8	9.6
			# litters affected	2	5	5	7

In another study according to OECD TG 414 and GLP, rats (Wistar, 28/group) were exposed to diflufenican (98.8 %) by oral gavage at doses of 0, 250, 500 and 1 000 mg/kg bw/day (Anon. 2002). No evidence of developmental toxicity in rats were observed. There were no clinical signs or treatment-related deaths observed, no effects on body weight and body weight gain or food

consumption. There were no effects on the mean number of corpora lutea, implantations, early and late resorptions, pre- and post-implantation loss and dams with resorptions. There were no treatment-related gross visceral lesions in the rats sacrificed at term. Litter parameters such as mean litter size, number and weight of the foetuses and sex ratio were statistically comparable between exposed and control groups. No treatment-related changes in external observations (including major malformations), skeletal variant parameters, visceral malformations or anomalies were observed in exposed groups compared to the control group.

In a study conducted according to OECD TG 414 and GLP, New Zealand White rabbits were exposed to diflufenican (98.1 %, oral gavage) at doses of 0, 50, 350 and 2 500 mg/kg bw/day (Anon., 1984b). There were no treatment-related deaths. In the high dose group, clinical signs included pale faeces (for most animals during most of the treatment period, persisting as far as GD 19) and red discoloured urine (in 11 out of 16 animals towards the end of the treatment period, persisting a few days into the post-dosing period). In addition, reduced faecal output was observed. This was associated with reduced food consumption, which was clearly reduced at 2 500 mg/kg bw/day throughout the treatment period but recovered once treatment ceased. Bodyweight gain was markedly lower in the high dose group compared to controls during the treatment period, especially early in the treatment period. This effect recovered once treatment ceased. A single animal in the mid dose group aborted on GD 24. There was no treatment related gross necropsy findings in dams and no treatment-related effect on post-implantation losses, litter size, litter weight, mean foetal weight or sex ratio. One or 2 incidences of malformations were observed in each dose group. The pattern of anomalies identified by gross dissection or skeletal examination did not indicate any effect of treatment. The incidence of variant sternebrae was not affected by treatment. The incidence of the common variation rudimentary extra ribs was higher than controls in all treated groups, and statistically significant in the high-dose group (see table below). However, the incidences were within the historical control range.

Table: *Incidence of extra ribs and sternebrae variants*

Dose (mg/kg bw/day)	**N**	**Foetuses examined**	**12 ribs**		**13 ribs**		**Normal sternebrae**		**Variant sternebrae**	
			Total	Mean %	Total	Mean %	Total	Mean %	Total	Mean %
0	12	96	80	81.2	16	19.0	66	71.7	30	28.3
50	16	111	74	63.6	37	36.4	89	85.6	22	14.4
350	13	97	65	60.9	32	39.1	73	78.0	24	22.0
2 500	16	124	73	57.8	51	**42.2***	114	92.5	10	7.5

* $p < 0.05$

HCD for extra ribs from 21 rabbit teratology studies from the same laboratory (Jan. 1983 – Jan. 1984) showed a mean incidence of 34.3 %, ranging from 13.8-50 %.

Comparison with the CLP criteria

In one of the two rat developmental toxicity studies, the highest dose of diflufenican greatly exceeded the limit dose. Maternal toxicity was observed in the high dose group, including pale faeces, reduced body weight gain and food consumption. Litter size and litter weight were also slightly lower. The incidence of visceral anomalies was increased in all treated groups in a dose-related pattern (3.2 %, 4.7 %, 5.8 % and 9.6 % at 0, 50, 500 and 5 000 mg/kg bw/day respectively), however there was no obvious pattern or relationship between the anomalies seen and no HCD were available. In the other rat developmental toxicity study, no maternal toxicity or developmental effects were observed up to the maximum dose tested of 1 000 mg/kg bw/day. In the rabbit, there was clear evidence of maternal toxicity at the high dose of 2 500 mg/kg bw/day. No effects on litter parameters or signs of abnormalities in development were observed.

In conclusion, based on the available studies, RAC agrees with the DS assessment that **no classification for effects on development is warranted.**

Effects on or via lactation

There was no human evidence indicating a hazard to babies during the lactation period. A two-generation study in rats showed reduced pup weight gain and reduced litter weights in the mid and high dose group from birth up to post-natal day 21. This was consistent with the reduced maternal body weight reported during gestation. In the high dose group, a cumulative pup loss (day 0-21) was observed, however the findings were not consistent between F0 and F1 generations. No significant changes at any dose in effects such as surface righting, startle reflex, air righting, and pupil reflex were observed. Diflufenican has lipophilic properties, which indicates that residues could be present in milk. Toxicokinetic studies did not indicate that diflufenican was present at a relevant level in mammary glands or breast milk.

In conclusion, there is no evidence that diflufenican affects offspring through an effect on or via lactation. The reduced pup weight gain observed during the post-natal period could be associated with reduced body weight at birth rather than a result of effects on or via lactation. RAC is therefore of the opinion that **no classification for effects on or via lactation is justified**.

Overall, RAC is of the opinion, in line with the DS that **diflufenican does not warrant classification for reproductive toxicity**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Diflufenican has for environmental hazard a current Annex VI entry with a harmonised classification as Aquatic Chronic 3; H413.

The DS proposed to classify diflufenican as Aquatic Acute 1; H400 with an M-factor of 1 000 and as Aquatic Chronic 1; H410 with an M-factor of 100.

Rapid degradability

The dossier submitter proposed to consider diflufenican as <u>not</u> rapidly degradable for classification purposes. The basis for this proposal is that all the available information on the behaviour of diflufenican in water (hydrolysis, photolysis, aerobic mineralisation in surface water and natural water/sediment studies) indicate that diflufenican is stable to hydrolysis, undergoes very slow primary degradation in water or sediment and has enhanced but slow degradation under illumination.

Three aqueous hydrolysis studies were submitted (Reeves and Savege, 1985; Reeves and Savege, 1986; Juozenaite, 2008). All three studies showed consistent behaviour for diflufenican to be stable to hydrolysis even at environmental unrealistic temperature of 50 °C.

In two ready biodegradability studies (Lebertz, 1989, OECD TG 301D; Desmares-Koopmans, 2008, OECD TG 301B). Diflufenican is not readily biodegradable with only 5.2 % and 9 to 21 % biodegradation after 28 days. Both studies were conducted appropriately and to GLP; they are thus considered to be reliable.

Two reliable aerobic mineralisation simulation studies in surface water, conducted to OECD TG 309 and GLP compliant, are available for diflufenican (Hein and Kasel, 2016; Ilieva, 2016b). Both studies showed consistent results for diflufenican with virtually no degradation.

Five valid water/sediment studies are available for diflufenican (Knoch, 1996; Crowe, 2003; Unsworth, 2006; Mamouni, 2003; Adam, 2008. All were conducted according to OECD TG 308 or other internationally recognised guidelines very similar to OECD TG 308. They indicate that significant partitioning from water into sediment occurs. The decline of diflufenican in the water layer was primarily due to partitioning to sediment. Primary degradation is slow in the entire water/sediment systems. The kinetics in the whole system were typically biphasic with DT_{50} values ranging from 86 up to 1 000 days and DT_{90} values of 341 up to 1 000 days.

Overall, the information on degradation show that diflufenican is not degraded under any environmentally realistic conditions. Consequently, diflufenican is considered to be 'not rapidly degradable' according to the CLP criteria.

Aquatic Bioaccumulation

The dossier submitter proposed to consider diflufenican as having a high bioaccumulation potential in the aquatic environment for classification purposes. The basis for this proposal is two studies with experimentally determined whole-fish, lipid-normalised BCF values of 1 650 L kg^{-1} and 2 583 L kg^{-1} and a measured Log K_{ow} of 4.2 at 20 °C.

Acute Aquatic Toxicity

The dossier submitter proposed to classify diflufenican as Aquatic Acute 1; H400 for the aquatic environment with an M-factor of 1 000. The basis for this proposal are acute studies that were provided both for the original approval for diflufenican under Dir. 91/414/EEC, and for the renewal of the active under Regulation (EC) 1107/2009. The dossier submitter selected only those studies of highest reliability/ quality. The studies have been evaluated, considered reliable and deemed suitable for hazard classification purposes. Only studies testing the technical substance, diflufenican, have been selected and studies testing any kind of formulation have not been considered.

For fish, there are sufficient suitable studies to allow classification of the acute hazard. The endpoint selected for use in hazard classification is LC_{50} > 0.0985 mg a.s./L from an OECD TG 203 acute toxicity test (96-hour) with common carp (*Cyprinus carpio*) under static conditions from Anon. (1998c). It is noted that fish are not the most acutely sensitive taxa and therefore not critical for setting the hazard classification.

For aquatic invertebrates, there are sufficient suitable studies for classification purposes. The endpoint selected for use in hazard classification is EC_{50} > 0.240 mg a.s./L from an OECD TG 202 acute toxicity test (48 hours) with (*Daphnia magna*) under static conditions by Odin-Feurtet (1999f). It is noted that aquatic invertebrates are not the most acutely sensitive taxa and therefore not critical for setting the hazard classification.

For algae and other aquatic plants, there are sufficient suitable studies for classification purposes. The endpoint selected for use in hazard classification is the E_rC_{50} = 0.0006 mg a.s./L from an algal growth inhibition assay (OECD TG 201) by Wilby (2007g), with *Raphidocelis subcapitata* (formerly *P. subcapitata*, as referred to in the report, and *S. capricornutum*). Consequently, algae are the most acutely sensitive taxa and therefore are critical for setting the hazard classification.

However, the dossier submitter noted that *R. subcapitata* may not represent the most sensitive algal species. Within the dossier submitted to support diflufenican under Reg. (EC) 1107/2009 a study was available testing *Ankistrodesmus falcatus* that exhibited an E_rC_{50} of 0.000064 mg a.s./L, approximately 10 fold lower than that for *R. subcapitata*. The study was not considered valid due

to failure to meet the validity criterion related to the mean coefficient of variation for section-by-section growth rates specified in the OECD TG 201. *A. falcatus* is a novel test species not normally used under OECD TG 201 and it was noted in the study report that there appeared to be a lag phase to the development of the cultures which may have explained the failure to meet the validity criterion. However, the study was not considered valid and so has not been used for hazard classification, but it is highlighted that this information suggests that other test species may exhibit greater sensitivity to diflufenican than *R. subcapitata*.

For other aquatic organisms there is one study on African clawed frog (*Xenopus laevis*) available. Since no specific guideline was available for this species the test protocol was based on the guidelines OECD TG 203 and US EPA 850.1075. The study was conducted according to GLP. The LC_{50} is > 0.0705 mg a.s./L and the NOEC is 0.0705 mg a.s./L indicating that it is not the most acutely sensitive species and therefore not critical for setting the hazard classification.

Chronic Aquatic Toxicity

The dossier submitter proposed to classify diflufenican as Aquatic Chronic 1 (H410) for the aquatic environment with an M-factor of 100, based on studies meeting the criteria already described in the introductory paragraph for Acute Aquatic Toxicity.

For fish, there are sufficient suitable studies to allow classification for chronic/long-term hazard. The endpoint selected for use in hazard classification is the EC_{10} = 0.00543 mg a.s./L (length and mean measured concentrations) from a fish early life stage toxicity test (OECD TG 201) for *Fathead minnow* by Anon. (2007c). It is noted that fish are not the most long-term sensitive taxa and therefore not critical for setting the hazard classification.

For aquatic invertebrates, there are sufficient suitable studies to allow classification for chronic/long-term hazard. The endpoint selected for use in hazard classification is the NOEC = 0.0124 mg a.s./L (geometric mean measured) for sediment dwelling chironomid larvae (*Chironomus riparius*) by McElligot (1996b). It is noted that aquatic invertebrates are not the most long-term sensitive taxa and therefore not critical for setting the hazard classification.

For algae and other aquatic plants, there are sufficient suitable studies to allow classification for chronic/long-term hazard. The endpoint selected for use in hazard classification is the E_rC_{10} = 0.000157 mg /L from an Algal growth inhibition assay (OECD TG 201) by Wilby (2007g), this is based on the most sensitive taxon to *Raphidocelis subcapitata* (formerly *P. subcapitata*, as referred to in the CLH report, and *S. capricornutum*). Consequently, algae are the most long-term sensitive taxa and therefore are critical for setting the hazard classification.

No chronic toxicity studies on other organisms were considered valid for use in the hazard assessment.

Comments received during public consultation

The public consultation obtained three comments from MSCAs and one comment from industry on the proposals for environmental classification. All three MSCAs agreeing with the proposed classification for diflufenican as Aquatic Acute 1; H400 with an M-factor of 1 000 and as Aquatic Chronic 1; H410 with an M-factor of 100.

RAC agrees that 20 °C or higher test temperature may not be environmental realistic temperatures for European surface water bodies and that DT_{50} values should always be normalised to 12 °C as it was agreed within RAC to be more environmentally realistic temperatures. However, in the case of diflufenican, RAC notes that this deficit clearly does not affect the conclusion on rapid degradability.

RAC notes the comment that the normalised BCF value for the Anon. (2008) study may be unreliable. RAC has not assessed this further because this would not impact the conclusion that diflufenican has a high potential to bioaccumulate.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the proposal of the dossier submitter to consider diflufenican as not rapidly degradable for classification purposes, based on three aqueous hydrolysis, two ready biodegradability, two aerobic mineralisation in surface water and five water/sediment studies that all slowed very slow biotic and abiotic degradation.

Aquatic Bioaccumulation

RAC agrees with the proposal of the dossier submitter to consider diflufenican as having high bioaccumulation potential in the aquatic environment for classification purposes, based on two studies with experimentally determined whole-fish, lipid-normalised BCF values of 1 650 L kg^{-1} and 2 583 L kg^{-1} and a measured Log K_{ow} of 4.2 at 20 °C.

Acute Aquatic Toxicity

RAC evaluates the new available OECD TG 201 study on *Ankistrodesmus falcatus* by Eckenstein (2016) as valid, robust and relevant for acute classification. RAC concludes to base the acute classification on the 72-h EC_{50} value of 0.000071 mg/L (growth rate) and that diflufenican warrants **classification as Aquatic Acute 1; H400 with an M-factor of 10 000.**

Chronic Aquatic Toxicity

RAC evaluates the new available OECD TG 201 study on *Ankistrodesmus falcatus* by Eckenstein (2016) as valid, robust and relevant for chronic classification. RAC concludes to base the chronic classification on the 72-h EC_{10} value of 0.000029 mg/L (growth rate), to consider diflufenican as not rapidly degradable and as having high potential for bioaccumulation. RAC concludes that **diflufenican warrants classification as Aquatic Chronic 1; H410 with an M-factor of 1 000**.

RAC evaluation of hazards to the ozone layer

Summary of the Dossier Submitter's proposal

The dossier submitter proposed <u>not</u> to classify diflufenican as hazardous to the ozone layer. The basis for this proposal is that there are no data provided regarding the hazard of diflufenican to the ozone layer and the Ozone Depleting Potential (ODP) of diflufenican has not been measured. However, diflufenican is a solid, with a corresponding extremely low vapour pressure (4.25×10^{-6} Pa at 25 °C). No boiling point could be determined below 360 °C. Hence, it is unlikely that diflufenican would be available in the stratosphere.

In addition, diflufenican does not contain any other halogen functionality other than fluorine. A substance is considered hazardous to the ozone layer if the available evidence concerning its properties and its predicted or observed environmental fate and behaviour indicate that it may present a danger to the structure and/or the functioning of the stratospheric ozone layer.

Any substances having an ODP of greater than or equal to the lowest ODP (i.e. 0.005) of the substances currently listed in Annex I to Regulation EC No 1005/2009 should be classified as hazardous to the ozone layer. Although no specific data have been provided for this hazard,

considering the chemical structure and other available information on the physico-chemical properties, diflufenican is not expected to be hazardous to stratospheric ozone.

Comments received during public consultation

No comments have been received on the DS's proposal to not classify diflufenican as hazardous to the ozone layer.

Assessment and comparison with the classification criteria

RAC agrees with the proposal of the dossier submitter that diflufenican **does not warrant classification as hazardous to the ozone layer**.

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).