Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

trifloxystrobin (ISO); methyl (*E*)-methoxyimino-{(*E*)-α-[1-(α,α,α-trifluoro-*m*-tolyl)ethylideneaminooxy]-*o*-tolyl}acetate

EC Number: -
CAS Number: 141517-21-7

CLH-O-0000001412-86-293/F

Adopted

20 September 2019

20 September 2019

CLH-O-0000001412-86-293/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: **trifloxystrobin (ISO);**
methyl (*E*)-methoxyimino-{(*E*)-α-[1-(α,α,α-trifluoro-*m*-tolyl) ethylideneaminooxy]-*o*-tolyl}acetate

EC Number: **-**

CAS Number: **141517-21-7**

The proposal was submitted by the **United Kingdom** and received by RAC on **27 November 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 **17 December 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **1 March 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Marja Pronk**

Co-rapporteur, appointed by RAC: **Kostas Andreou**

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	607-424-00-0	trifloxystrobin (ISO); (*E*,*E*)-α-methoxyimino-{2-[[[[1- [3-(trifluoromethyl)phenyl]ethylidene]amino]oxy]methyl]benzeneacetic acid methyl ester	–	141517-21-7	Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H317 H400 H410	GHS07 GHS09 Wng	H317 H410			
Dossier submitter's proposal	607-424-00-0	trifloxystrobin (ISO); methyl (*E*)-methoxyimino-{(*E*)-α-[1-(α,α,α-trifluoro-*m*-tolyl)ethylideneaminoo xy]-*o*-tolyl}acetate	–	141517-21-7	**Retain** Aquatic Acute 1 Aquatic Chronic 1	**Retain** H400 H410	**Retain** GHS07 GHS09 Wng	**Retain** H317 H410		**Add** M=10 M=10	
RAC opinion	607-424-00-0	trifloxystrobin (ISO); methyl (*E*)-methoxyimino-{(*E*)-α-[1-(α,α,α-trifluoro-*m*-tolyl)ethylideneaminoo xy]-*o*-tolyl}acetate	–	141517-21-7	**Retain** Aquatic Acute 1 Aquatic Chronic 1 **Add** Lact.	**Retain** H400 H410 **Add** H362	**Retain** GHS07 GHS09 Wng	**Retain** H317 H410 **Add** H362		**Add** M=100 M=10	
Resulting Annex VI entry if agreed by COM	607-424-00-0	trifloxystrobin (ISO); methyl (*E*)-methoxyimino-{(*E*)-α-[1-(α,α,α-trifluoro-*m*-tolyl)ethylideneaminoo xy]-*o*-tolyl}acetate	–	141517-21-7	Lact. Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H362 H317 H400 H410	GHS07 GHS09 Wng	H362 H317 H410		M=100 M=10	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Trifloxystrobin is a pesticide active substance that controls diseases caused by plant pathogenic fungi across a wide range of agricultural and horticultural crops. During the renewal process, concerns for classification for reproductive toxicity were raised (albeit, no new data were available), and M-factors were considered appropriate for the environmental classification. The CLH report therefore addresses only reproductive toxicity and hazardous to the aquatic environment.

Trifloxystrobin has an existing entry in Annex VI of CLP under the chemical name (*E*,*E*)-α-methoxyimino-{2-[[[[1- [3-(trifluoromethyl)phenyl]ethylidene]amino]oxy] methyl] benzeneacetic acid methyl ester. It is proposed to amend the name of the current Annex VI entry into methyl (*E*)-methoxyimino-{(*E*)-α-[1-(α,α,α-trifluoro-*m*-tolyl) ethylideneaminooxy] -*o*-tolyl}acetate, for consistency with the name used in the approval of the pesticide active substance and because the name includes a clerical error.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Sexual function and fertility

The potential of trifloxystrobin to adversely affect sexual function and fertility was investigated in a 2-generation study in rats, preceded by a 1-generation range-finding study.

In the range finding study (non-guideline, non-GLP, Anonymous, 1995), trifloxystrobin was administered via the diet to groups of 15 rats/sex/dose at dietary concentrations of 0, 100, 1 000 or 2 000 ppm (equal to 0, 6, 53.5 and 109.6 mg/kg bw/d for males and 0, 7.9-16.5, 67.0-168.6 and 140.5-321.7 mg/kg bw/d for females). Food intake and body weight and body weight gain were reduced during treatment in the parental animals of the mid and high dose groups (food consumption 0-14 % and 0-15 %, respectively; body weight 0-5 % and 1-8 %, respectively). Mortality, clinical signs or remarkable observations at gross necropsy were not observed. Reproduction was not affected at any dose. At 2 000 ppm, pup body weight was statistically significantly decreased at lactation day (LD) 7 (by 12 %) and LD14 (by 15 %), with a decrease of 19 % over LD0-14. Based on the parental and offspring findings, 1 500 ppm was recommended as high dose level for a 2-generation study.

In the 2-generation study (OECD TG 416, GLP, Anonymous, 2001), groups of 30 rats/sex/dose were administered trifloxystrobin in the diet at concentrations of 0, 50, 750 or 1 500 ppm (equal to 0, 2.3-3.8, 32.9-58.4 and 73.1-126.7 mg/kg bw/d for males and 0, 3.1-8.0, 47.9-119.9 and 98.0-242.0 mg/kg bw/d for females). There were no treatment-related deaths or clinical signs among the F0 and F1 parental animals. Male and female reproductive parameters and organs were not affected by treatment. Parental toxicity at the mid and high dose consisted of slight reductions in food consumption and body weight as compared to controls at several time points during pre-/post-mating, gestation and lactation, and slight toxicity of the liver and kidneys. The decrease in food consumption was generally less than 10 %, but occasionally it was up to 16 % (F0) or 25 % (F1), mainly during the first week(s) of pre-mating and the third week of lactation.

Decreases in body weight mirrored these, and were up to 8 %/11 % in mid dose F0/F1, 5-13 % in high dose F0, and 15-20 % (but during the first weeks of pre-mating up to 30 %) in high dose F1. Pup toxicity was evident at these doses as retarded weight development during lactation (statistically significant from LD7 onwards), and F1a, F1b and F2 pups also showed a delay in eye opening of 0.6-0.7 days at the high dose.

In the absence of treatment-related effects on fertility, reproduction and pregnancy outcome, the dossier submitter (DS) concluded that trifloxystrobin does not meet the criteria for classification.

Developmental toxicity

The developmental toxicity of trifloxystrobin was investigated in rats and rabbits.

Rats

In a guideline study (OECD TG 414, GLP, Anonymous, 1999a), pregnant Tif:RAIf (SPF) rats (20-23/dose) received trifloxystrobin (in 0.5 % aqueous sodium carboxymethylcellulose) orally by gavage at dose levels of 0, 10, 100 or 1 000 mg/kg bw/d from gestation day (GD) 6-15. The dose levels in this study were chosen based on the findings in a preliminary range finding developmental study (7 pregnant Tif:RAIf (SPF) rats/dose, non-guideline, non-GLP, Anonymous, 1993), where there was no toxicity at 10 and 100 mg/kg bw/d, and 1 000 mg/kg bw/d resulted only in slight reductions in maternal food consumption and body weight gain throughout the treatment period. In the main study, there were no mortalities. Dams showed reduced food consumption (at mid and high dose) and body weight and bodyweight gain (at high dose) during the treatment period, resulting in a net weight change (weight gain over GD6-21 minus gravid uterus weight) that was 18 % and 32 % lower at the mid and high dose, respectively. Pregnancy status, numbers of implantations sites, pre-/post-implantation losses and live foetuses per litter were not affected by treatment, nor were foetal weights. No dead or aborted foetuses were noted, and external and skeletal examination revealed no treatment-related malformations, anomalies or variations. Upon visceral examination, the only apparently treatment-related finding was enlarged thymus in the high dose group, with a foetal incidence of 7.5 % and a litter incidence of 31.8 %. Although the increased foetal incidence reached statistical significance and both the foetal and litter incidences were slightly outside the historical control data (HCD) ranges (0-6.0 % and 0-29.2 %, respectively), the DS considered this finding a variation and in isolation not to be of toxicological significance. It therefore does not meet the criteria for classification.

Regarding the retarded body weight development in the pups during the lactation period in the 2-generation study, the DS considered that likely to be a non-specific secondary effect of maternal toxicity (i.e., reduced food consumption and lower body weights during gestation and lactation in the parental females). A direct effect arising from pups consuming treated diet during weaning was also likely to be a contributing factor. The DS considered the minor delays in eye opening secondary to the retarded pup body weight development. As there was no evidence of a specific effect on development in this study, and the effect on pup weight did not appear to have had any long term adverse effects in these animals (i.e., the pups survived to adulthood and produced viable offspring), classification was not considered warranted.

Rabbits

In a preliminary range finding developmental study (non-guideline, non-GLP, Anonymous, 1994a), trifloxystrobin was administered by gavage to pregnant Russian (Chbb:HM) rabbits (5/group) at dose levels of 0, 20, 100, 500 or 1 000 mg/kg bw/d from GD7-19. There were no deaths at any dose. Clinical signs such as reduced locomotor activity and haemorrhagic discharge occurred at 1 000 mg/kg bw/d. Dose dependent effects on food consumption and body weight were observed at doses from 100 mg/kg bw/d, at 500 mg/kg bw/d resulting in body weight loss throughout the treatment period. At 500 mg/kg bw/d, the number of post-implantation losses

(1 dam with total resorptions) was increased, the number of foetuses was decreased and foetal body weight was reduced. At 1 000 mg/kg bw/d, all pregnant animals had total resorptions; food consumption and body weight data were not reported. Based on these results, 500 mg/kg bw/d was selected as high dose level for the main developmental toxicity study with trifloxystrobin.

In the main study (OECD TG 414, GLP, Anonymous 1999b), pregnant Russian (Chbb:HM) rabbits (17-19/dose) received trifloxystrobin (in 0.5 % aqueous sodium carboxymethylcellulose) orally by gavage at dose levels of 0, 10, 50, 250 or 500 mg/kg bw/d from GD7-19. No treatment-related mortality or clinical signs occurred. At doses from 250 mg/kg bw/d there was a dose-related reduction in bodyweight gain and a significant bodyweight loss during the treatment period. The findings were associated with reduced food consumption. Pregnancy status was not affected by treatment, nor were the numbers of corpora lutea, implantation sites, pre- and post-implantation losses and live foetuses per litter. There were no dead or aborted foetuses in any group, and foetal weights were unaffected by treatment. Foetal external and visceral examinations revealed no treatment-related or toxicologically significant findings, and the same was found for skeletal malformations and variations. The incidence of skeletal anomalies (consisting mainly of fused or asymmetric sternebrae) was however slightly increased in the two higher dose groups, and occasionally slightly outside the HCD range. Statistical significance was reached only for the occurrence of fused sternebrae-3 and -4 in the high dose group. Additional analysis of the individual foetal data showed that severe sternebrae fusions were not reported and that there was no evidence of a treatment-related effect of fusion of all segments of the sternum (sternebrae 1 to 5). There were some differences from controls in the foetal incidence of partially fused and asymmetrically shaped sternebrae at the two higher doses, but these represent small deviations from normal sternal development, and are common variations in this rabbit strain (as shown by HCD) that have no effect on survival and do not persist postnatally. Given further that the findings occurred only in the presence of marked maternal toxicity, the DS concluded that, overall, this minor developmental change does not support classification.

Adverse effects on or via lactation

In the 2-generation study in rats, a treatment-related reduction in pup body weight was observed during the lactation periods of each generation. No data are available on the quality or quantity of the milk produced by the dams in this study, nor was the milk analysed for presence of trifloxystrobin or its metabolites. Studies in lactating ruminants, however, showed that trifloxystrobin is not excreted in the milk to any appreciable extent in cows or goats. This is not expected to be different in rats, and the DS considered it more likely that the reduced body weights in pups were partly due to the consumption of treated diet from PND12 (or avoidance of treated diet, on the basis of palatability). Reductions in body weight prior to PND12 were likely to be a non-specific secondary effect of maternal toxicity, as evidenced by reduced body weights, food consumption and slight kidney/liver toxicity in the mothers. Given that there is no clear evidence of an adverse effect due to transfer in the milk, or an adverse effect on the quality of the milk, the DS concluded that trifloxystrobin does not meet the criteria for classification for effects on or via lactation.

Comments received during public consultation

Two member state competent authorities (MSCAs) supported the 'no classification' proposal for effects on sexual function and fertility. One MSCA also supported the 'no classification' proposal for developmental toxicity, but two other MSCAs considered a classification in category 2 warranted, one on the basis of the sternebrae findings in rabbits, the other additionally also on the enlarged thymus findings in rats. The latter MSCA requested further details on the HCD for both findings. The DS, in response, provided the requested details, but remained of the opinion that enlarged thymus is a relatively frequent finding in the rat strain studied and that it is a

variation without postnatal consequences, as shown by the absence of thymus lesions in the 2-generation study conducted with trifloxystrobin in the same rat strain and in the same laboratory. Regarding the sternebrae findings in rabbits, the DS pointed to the additional information on the severity of the sternebrae fusions as provided by IND during the public consultation (see Additional key elements). This additional information concerned a re-evaluation of the sternebrae findings based on photographs recently taken from skeletal preparations from the original rabbit developmental toxicity study. Most sternebrae findings could be considered small deviations from the normal situation at the end of the gestation period without long-term postnatal consequences. According to the DS these can thus be downgraded to variations and would not support classification for developmental toxicity, particularly when the maternal toxicity (as evidenced by severe weight loss, resulting in a reduced body weight gain from GD7-20 of -130 % and -238 % of control at 250 and 500 mg/kg bw/d, respectively) and significantly reduced food consumption (by more than 50 %) during the treatment period) is taken into account.

The 'no classification' proposal for effects on or via lactation was supported by three MSCAs, agreeing with the DS that there is insufficient evidence directly linking the pup weight effects to lactation and that the criteria for classification are thus not considered fulfilled. One other MSCA however considered classification with Lact.; H362 warranted.

Assessment and comparison with the classification criteria

Sexual function and fertility

No treatment-related effects on fertility parameters were observed in the 1- and 2-generation studies in rats. The trifloxystrobin doses tested in these studies (up to 2 000 ppm and 1 500 ppm, respectively), however, resulted in only limited parental toxicity (no evidence of treatment-related mortality or clinical signs, only slightly reduced body weight at several time points throughout treatment, in association with reduced food consumption). Higher doses were not given in view of the pup toxicity seen (retarded weight development during lactation) at 2 000 ppm in the 1-generation study, as well as the (slight) parental toxicity in that study. RAC notes that this is not a proper argument and questions whether the top dose used in the 2-generation study (1 500 ppm; equal to 73.1-126.7 mg/kg bw/d for males and 98.0-242.0 mg/kg bw/d for females) was optimal. This raises the issue of whether the fertility endpoint was fully investigated or if the 2-generation study was truly OECD 416 test guideline compliant with regard to the selection criteria for determining the highest dose.

In addition to the 1- and 2-generation studies, the CLH report includes short summaries of a 90-d study (0/100/500/2 000 ppm in males and 0/100/500/2 000/8 000 ppm in females) and a 2-y study (0/50/250/750/1 500 ppm) in rats. In these studies no adverse effects on the reproductive organs were observed. It is noted that the DS considered the higher dose levels in these studies to have exceeded the maximum tolerated dose (MTD) (given mortality (90-d study) and large reductions in body weight gain). NOAELs were established at 500 and 250 ppm for the 90-d and 2-y study, respectively, as assessed by EFSA in their pesticides peer review report on trifloxystrobin. RAC agrees that 8 000 ppm for females in the 90-d study (equal to 618 mg/kg bw/d) exceeded the MTD with 20 % of the animals dying. However, 2 000 ppm tested in the 90-d study and 1 500 ppm in the 2-y study were tolerated without excessive toxicity.

On the basis of the data available, no classification for effects on fertility and sexual function is warranted. RAC, however, notes that the available 2-generation study may not fully inform on this endpoint.

Developmental toxicity

Rats

In a guideline-compliant rat developmental toxicity study (0, 10, 100, 1 000 mg /kg bw/d on GD6-15), the only possibly treatment-related effect observed was a statistically significant increase in the incidence of foetuses with enlarged thymus at the top dose group. The incidence was slightly outside the HCD range, both on a foetal and on a litter base (see table below). In the report presenting the laboratory HCD, it is stated that the in-life phase of the studies was within 3 years of the reference study (study number 943042; not included in the database). IND has confirmed that the reference study with number 943042 is indeed the rat study with trifloxystrobin and that this study was conducted in 1994.

***Table**: Incidences of enlarged thymus in the rat prenatal developmental toxicity study*

	Dose (mg/kg bw/d)				
	0	10	100	1 000	HCD# (mean; range)
Enlarged thymus					
No. foetuses affected/ total no. examined (foetal incidence)	3/149 (2.0 %)	3/135 (2.2 %)	3/139 (2.2 %)	11/146 (7.5 %)*	13/4 793 [anomaly] (0.3 %; 0.0-1.4 %) 32/4 793 [variation] (0.7 %; 0.0-6.0 %)
No. litters affected/ total no. examined (litter incidence)	3/23 13.0 %)	1/22 (4.5 %)	3/20 (15.0 %)	7/22 (31.8 %)	13/725 [anomaly] (1.8 %; 0.0-9.5 %) 29/725 [variation] (4.0 %; 0.0-29.2 %)

HCD: historical control data from 22 gavage studies with in total 31 control groups; studies conducted in 1988-1994, in same laboratory and rat strain. Database does not include study number 943042 (the trifloxystrobin study). Finding was first categorized as an anomaly but from mid-1992 as a variation, because in these later studies it was seen more often.
* Statistically significant ($p < 0.05$)

From the table above, it can be seen that the number of foetuses/litters with enlarged thymus at the low and mid dose groups was not different from that in the concurrent control group, whereas at the high dose group it was slightly higher and slightly outside the HCD ranges from the mid-1992 to 1994 studies. It is noted though that in all groups the incidences exceeded the mean incidence of the HCD.

RAC notes that the degree of enlargement is not given, making it difficult to discriminate between an anomaly and a variation. According to the DS, "enlarged thymus" is a descriptive finding of the technician/study director not based on exact size measurements. Furthermore, the laboratory where the study was conducted downgraded the finding from an anomaly to a variation ("Relatively frequent, transient structural deviation from normal development that is considered not to have any detrimental effect on foetal survival, development or function. Variations occur frequently in control foetuses."), given that from mid-1992 it occurred more regularly in the rat strain.

Considering that enlarged thymus is a relatively frequent finding in the rat strain studied, that the increase in incidence was relatively small and occurred only at the limit dose of 1 000 mg/kg bw/d which was maternally toxic (32 % lower net weight change over GD6-21 as compared to controls), that no thymus lesions were observed in the 2-generation study and that thymus was not a target organ in other repeated dose toxicity studies, RAC concludes that it does not provide sufficient evidence for classification.

Rabbits

In a guideline-compliant rabbit developmental toxicity study (0, 10, 50, 250, 500 mg/kg bw/d of trifloxystrobin on GD7-19), the only treatment-related finding was a slightly increased incidence of skeletal anomalies in foetuses in the two higher dose groups. These consisted mostly of fused sternebrae and asymmetrically shaped sternebrae, with the incidences for some sternal findings

slightly exceeding the HCD range (see table below). The laboratory HCD were from studies for which the in-life phase was reported to be within 3 years of the reference study (study number 943043; included in the database). IND has confirmed that the reference study with number 943043 is indeed the rabbit study with trifloxystrobin and that this study was conducted in 1994.

As can be seen from the table below, most foetal and litter incidences found for the skeletal anomalies in the treated groups exceeded the mean incidences of the HCD. Only occasionally though they (slightly) exceeded the HCD range. The increases in incidence were only small and mostly without dose response relation. There was only one statistically significant finding, for the occurrence of fused sternebrae 3-4 in the highest dose group.

***Table**: Incidences of skeletal anomalies in the rabbit prenatal developmental toxicity study*

		Dose (mg/kg bw/d)					HCD# (mean; range)
		0	10	50	250	500	
Skeletal anomalies							
Sternebra 1, Fused 1-2	No. foetuses affected	1/116 (0.9 %)	1/130 (0.8 %)	1/90 (1.1 %)	2/97 (2.1 %)	1/97 (1.0 %)	8/2 562 (0.3 %; 0.0 %-2.5 %)
	No. litters affected	1/19 (5.3 %)	1/18 (5.6 %)	1/16 (6.3 %)	2/17 (**11.8 %**)	1/18 (5.6 %)	8/455 (1.8 %; 0.0 %-10.5 %)
Sternebra 1, asymmetrically shaped	No. foetuses affected	0/116 (0.0 %)	1/130 (0.8 %)	1/90 (1.1 %)	2/97 (2.1 %)	3/97 (**3.1 %**)	10/2 562 (0.4 %; 0.0 %-2.3 %)
	No. litters affected	0/19 (0.0 %)	1/18 (5.6 %)	1/16 (6.3 %)	1/17 (5.9 %)	1/18 (5.6 %)	10/455 (2.2 %; 0.0 %-13.3 %)
Sternebra 2, Fused 2-3	No. foetuses affected	1/116 (0.9 %)	1/130 (0.8 %)	1/90 (1.1 %)	4/97 (4.1 %)	4/97 (4.1 %)	25/2 562 (1.0 %; 0.0 %-5.7 %)
	No. litters affected	1/19 (5.3 %)	1/18 (5.6 %)	1/16 (6.3 %)	4/17 (**23.5 %**)	4/18 (**22.2 %**)	23/455 (5.1 %; 0.0 %-20.0 %)
Sternebra 2, asymmetrically shaped	No. foetuses affected	0/116 (0.0 %)	1/130 (0.8 %)	1/90 (1.1 %)	2/97 (2.1 %)	4/97 (4.1 %)	16/2 562 (0.6 %; 0.0 %-4.1 %)
	No. litters affected	0/19 (0.0 %)	1/18 (5.6 %)	1/16 (6.3 %)	2/17 (11.8 %)	3/18 (**16.7 %**)	15/455 (3.3 %; 0.0 %-13.3 %)
Sternebra 3, Fused 3-4	No. foetuses affected	2/116 (1.7 %)	2/130 (1.5 %)	1/90 (1.1 %)	5/97 (5.2 %)	10/97* (**10.3 %**)	68/2 562 (2.7 %; 0.0 %-9.2 %)
	No. litters affected	2/19 (10.5 %)	1/18 (5.6 %)	1/16 (6.3 %)	4/17 (23.5 %)	6/18 (33.3 %)	57/455 (12.5 %; 0.0 %-33.3 %)
Sternebra 3, asymmetrically shaped	No. foetuses affected	0/116 (0 %)	1/130 (0.8 %)	0/90 (0 %)	2/97 (2.1 %)	3/97 (**3.1 %**)	14/2 562 (0.5 %; 0.0 %-2.7 %)
	No. litters affected	0/19 (0 %)	1/18 (5.6 %)	0/16 (0 %)	2/17 (**11.8 %**)	3/18 (**16.7 %**)	13/455 (2.9 %; 0.0 %-10.5 %)
Sternebra 4, Fused 4-5	No. foetuses affected	4/116 (3.4 %)	2/130 (1.5 %)	4/90 (4.4 %)	7/97 (7.2 %)	8/97 (**8.2 %**)	68/2 562 (2.7 %; 0.0 %-8.0 %)
	No. litters affected	4/19 (21.1 %)	2/18 (11.1 %)	4/16 (25.0 %)	6/17 (**35.3 %**)	6/18 (**33.3 %**)	57/455 (12.5 %; 0.0 %-29.4 %)
Sternebra 4, asymmetrically shaped	No. foetuses affected	0/116 (0 %)	1/130 (0.8 %)	0/90 (0 %)	4/97 (**4.1 %**)	2/97 (2.1 %)	23/2 562 (0.9 %; 0.0 %-3.2 %)
	No. litters affected	0/19 (0 %)	1/18 (5.6 %)	0/16 (0 %)	4/17 (**23.5 %**)	2/18 (11.1 %)	22/455 (4.8 %; 0.0 %-17.6 %)
Sternebra 5, asymmetrically shaped	No. foetuses affected	0/116 (0 %)	0/130 (0 %)	0/90 (0 %)	0/97 (0 %)	1/97 (1.0 %)	18/2 562 (0.7 %; 0.0 %-2.7 %)
	No. litters affected	0/19 (0 %)	0/18 (0 %)	0/16 (0 %)	0/17 (0 %)	1/18 (5.6 %)	18/455 (4.0 %; 0.0 %-17.6 %)
Sternebra 6, asymmetrically shaped	No. foetuses affected	0/116 (0 %)	0/130 (0 %)	1/90 (1.1 %)	1/97 (1.0 %)	0/97 (0 %)	7/2 562 (0.3 %; 0.0 %-2.3 %)
	No. litters affected	0/19 (0 %)	0/18 (0 %)	1/16 (6.3 %)	1/17 (5.9 %)	0/18 (0 %)	7/455 (1.5 %; 0.0 %-13.3 %)

HCD: historical control data from 20 gavage studies with in total 24 control groups; studies conducted in 1989-1995, in same laboratory and rabbit strain. Database includes study number 943043 (the trifloxystrobin study). Values exceeding HCD range are **in bold**.
* Statistically significant ($p < 0.05$)

In the CLH report, the sternal findings were also presented on individual foetus basis (see table below), on the basis of which the DS concluded that severe sternebrae fusion, alignment of ribs with the sternebrae or abnormal curvature of the sternum, which could possibly impair postnatal development resulting in a shortened rib cage with consequently impairment of further pup development, did not occur. There was a slight increase in foetuses with fused sternebrae (2-1-1-3-3 at 0-10-50-250-500 mg/kg bw/d) and partially fused sternebrae (3-3-3-8-11 at 0-10-50-250-500 mg/kg bw/d) in the two highest dose groups, but the more severe finding of fusion of

all segments of the sternum (sternebrae 1 to 5) was not increased (1-0-1-1-1 at 0-10-50-250-500 mg/kg bw/d).

***Table**: Details of sternal findings in the rabbit prenatal developmental toxicity study*

		Dose (mg/kg bw/d)				
		0	10	50	250	500
No. foetuses examined		116	130	90	97	97
No. litters examined		19	18	16	17	18
Sternebra(e)		***identification number dam/identification number foetus***				
Sternebra 1 and 2	Fused	7/8	25/6		63/7	
	Partially fused			55/1	65/6	93/1
Sternebra 2 and 3	Fused				63/7	93/1
	Partially fused	7/8	25/6	55/1	65/4, 66/7, 74/4	84/1, 86/3, 87/5
Sternebra 3 and 4	Fused	7/8	25/6	55/1		93/5
	Partially fused	11/5	25/3		63/1, 63/7, 66/7, 67/7, 74/4	82/3, 84/2, 85/5, 86/3, 87/5, 93/1, 93/2, 93/6, 93/8
Sternebra 4 and 5	Fused	7/8, 9/1		55/1	66/7, 70/4	82/3, 93/1
	Partially fused	10/1, 17/2	32/7, 36/1	39/7, 48/2, 51/9	62/3, 63/7, 71/1, 71/7, 74/4	84/7, 85/4, 86/3, 86/7, 87/5, 93/6
Asymmetrically shaped			25/6	55/1	62/3, 63/1, 63/7, 63/8, 72/4, 74/4	86/3, 87/5, 93/1, 93/5, 93/6
No. of foetuses with						
Fused sternebra(e)		2	1	1	3	3
Partially fused sternebra(e)		3	3	3	8	11
Fusion of sternebrae 1-5		1	0	1	1	1

According to the DS, fused and asymmetric sternebrae are grey zone anomalies that, depending on their severity, can be upgraded (to malformations) or downgraded (to variations). The table above, however, gives no indication of the severity of the fusions, and therefore IND presented a re-evaluation of the sternebrae fusions during the public consultation, to better inform on the severity and toxicological significance of the findings (see the Background Document). The re-evaluation shows that at 250 and 500 mg/kg bw/d there were slight increases in the number of foetuses/litters with fused sternebrae 4-5, partially fused sternebrae and bridges of ossification. At 500 mg/kg bw/d there was additionally a small increase in the number of foetuses/litters with an abnormal sternum (two additional cases as compared to the other dose/control groups). However, except for one foetus at 250 mg/kg bw/d (number 74/4), none of the foetuses with sternebrae fusions appeared to have abnormalities of the rib cage and/or vertebral column. Hence, apparently postnatal and further pup development was not impaired in the foetuses with skeletal anomalies.

RAC notes that the sternal findings only occurred at doses where there was considerable maternal toxicity, even though this toxicity may not be responsible for the sternal findings. At 250 and 500 mg/kg bw/d, the dams had significant body weight losses compared to controls during the treatment period (-83 and -152 g over GD7-20, respectively, as compared to a body weight gain of 64 g for controls), associated with a decreased food consumption during these days, in particular during GD7-12 (reduction by above 50 % at 250 and 500 mg/kg bw/d). Since trifloxystrobin was administered by gavage, palatability could not have been the reason of the decreased food consumption.

RAC further notes that a higher dose of trifloxystrobin in rats (1 000 mg/kg bw/d) did not result in increases in skeletal anomalies. There was a statistically significant increase seen in the

occurrence of asymmetrically shaped sternebra 1, but only in foetuses of the low dose group (10 mg/kg bw/d), not in foetuses of the mid and high dose groups (100 and 1 000 mg/kg bw/d). Incidences of all other asymmetric and fused/partially fused findings of the sternebrae also showed no dose relation.

RAC finally notes that in rabbits, there were no other external, visceral or skeletal adverse findings and no increase in post-implantation loss that could have masked an increase in foetal abnormalities.

In conclusion, RAC agrees with the DS that most fused/partially fused and asymmetric sternal findings seen at 250 and 500 mg/kg bw/d are likely to represent small deviations from normal sternal development that have no effect on survival and do not persist postnatally. Fusion of all segments of the sternum (sternebrae 1 to 5), which is considered a more severe finding, was not increased by treatment. Another more severe finding, abnormal sternum, was increased at 500 mg/kg bw/d and could possibly warrant classification. However, as the increase was only small (two additional instances) and on GD29, the integrity of the rib cage and vertebral column did not appear to have been affected by the abnormal sterna, RAC considers this not to present sufficient evidence for classification, taking into account all the evidence as discussed in the paragraphs above.

Adverse effects on or via lactation

In the 2-generation study in rats, dietary treatment with 750 and 1 500 ppm trifloxystrobin resulted in a treatment-related reduction in male and female pup body weight during the lactation periods of each generation. At LD0, the mean weight of pups in all treated groups was equivalent to that of the controls. But from LD7 onwards it was statistically significantly decreased, see table below. A similar effect was seen in the 1-generation range-finding study at 2 000 ppm. For pups at 1 500 ppm, mean values for eye opening during the lactation period were statistically significantly delayed by 0.7 (F1a), 0.6 (F1b) or 0.7 (F2) days; this may have been secondary to the reduced body weight development.

***Table**: Body weight development (% of controls) in F1a, F1b and F2 pups (males and females combined) in the rat 2-generation study*

	Dose (ppm)		
	50	750	1 500
LD0			
F1a	100	100	102
F1b	105	102	107
F2	102	100	102
LD4 after reduction			
F1a	103	101	93
F1b	104	99	93
F2	103	97	93
LD7			
F1a	101	97	85**
F1b	103	94	84**
F2	101	91**	84**
LD14			
F1a	100	94*	79**
F1b	101	91**	78**
F2	101	89**	78**
LD21			
F1a	99	91**	72**
F1b	100	89**	73**
F2	100	86**	72**

* Statistically significant ($p < 0.05$)
** Statistically significant ($p < 0.01$)

As the effect at 750 and 1 500 ppm is statistically significant, dose-related and consistent over the sexes and generations, with effect sizes up to 14 and 28 %, respectively, it may be considered adverse. It is therefore important to consider whether it qualifies for classification for

developmental toxicity or for effects on or via lactation. When assessing the effect, the following observations are of note:

1. The F0/F1 parental generations also show a reduced body weight relative to controls with trifloxystrobin treatment, in the same order of magnitude.
2. It does not seem to be a specific developmental effect, as there was no effect on pup body weight at birth. There was also no *in utero* effect on mean foetal body weight at (gavage) doses up to 1 000 mg/kg bw/d in the rat developmental toxicity study.
3. There was no loss in body weight amongst pups. All pups continued to thrive throughout PND 1-21.
4. Although the 750/1 500 ppm F1 males and females selected to breed the F2 generation still had lower body weights when pre-mating started, there were no adverse effects on fertility (e.g. fertility index, duration of gestation, gestation index and litter size were not affected, and were not different from the F0 generation).
5. As the only developmental delay reported was a slight delay in eye opening in pups at 1 500 ppm, the onset of puberty/sexual maturation may be considered as not having been affected.
6. The survival of pups at 750 and 1 500 ppm was not affected, as viability and lactation indices were both in the range of 96.6-99.4 %.

From this it seems that classification for developmental toxicity is not warranted, as the significant adverse effect on rat F1 and F2 post-natal pup bodyweight does not appear to be a specific developmental effect and was without significant impact on later maturation and fertility.

For classification for effects on or via lactation, the CLP criteria require:

a) Human evidence indicating a hazard to babies during the lactation period

No such data from humans are available for trifloxystrobin.

b) Results of one- or two-generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk

There is no indication of behavioural changes in dams that could have affected weight gain development of the pups, as dams of all dose groups successfully reared their litters to weaning on day 21 post-partum. No information is available on the quantity or quality of the milk produced by the dams, nor was the rat milk analysed for the presence of trifloxystrobin or metabolites. The CLH report refers to three studies in ruminants (two in goats, one in cows) in which trifloxystrobin and its metabolites were not excreted in milk to an appreciable extent (in goats 0.06-0.08 % of the totally administered dose; in cows below the limit of quantification of 0.01 mg/kg). Given these results, the DS considered it highly unlikely that trifloxystrobin or its metabolites would be transferred into the milk of rats. RAC, however, notes that the doses in the ruminant studies were rather low (goats were administered 4.13-4.24 mg/kg bw trifloxystrobin for 4 days, cows received 0.065, 0.193 or 0.635 mg/kg bw/d trifloxystrobin for 28-30 days).

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

According to the DS, the available toxicokinetic data do not suggest likely transfer to milk, given rapid metabolism of trifloxystrobin to more polar, water-soluble molecules that are excreted primarily via urine and bile. In support, the studies with goats and cows showed no appreciable transfer to milk. Further, the unchanged parent compound was the major component in milk and fat of goats, for which the metabolic pathway of trifloxystrobin was similar to that in rats. Overall, the DS considered it highly unlikely that trifloxystrobin or its

metabolites would be transferred into the milk of rats. RAC, however, notes that the log P_{OW} of 4.5 indicates lipophilicity of the substance and thus some potential for transfer to milk. RAC further notes the low dosing in the studies with goats and cows.

In absence of data on transfer into milk or on quality of the milk, the available data unfortunately do not allow directly linking the effect to lactation. Other possibilities include a direct effect of pups consuming treated diet (or avoiding it, because of palatability reasons), as solid food intake starts from around LD14. Whereas this may contribute to the reduced body weight development during the later phase of the lactation period, it does not explain the effect seen at LD7 when the pups are still mostly breast-fed only. Another possibility is that the retarded body weight development is a secondary effect of maternal toxicity (i.e., reduced food consumption and lower body weights during lactation in the parental females). However, this maternal toxicity was also seen during gestation, where it did not result in an effect on body weight of the pups at birth (LD0). Thus, discarding these possibilities, the most plausible explanation is that the effect is caused through the milk, given the log P_{ow} and the fact that it partly occurred during a time period where milk is the only nutrition source for pups.

With consistency seen over two generations, two studies and two sexes, RAC considers **classification for effects on or via lactation (Lact.; H362) justified.**

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Summary

Trifloxystrobin has an existing entry in Annex VI of the CLP regulation as Aquatic Acute 1; H400 and Aquatic Chronic 1; H410. This proposal seeks to confirm the existing entry and assign M-factors.

The proposal from the DS concluded that trifloxystrobin is not rapidly degradable for hazard classification based on the absence of degradation in a valid OECD TG 301B study. Under aerobic conditions, trifloxystrobin was also shown to hydrolyse rapidly.

Trifloxystrobin has a lipid normalised (5 %) bioconcentration factor (BCF) of 370 L/kg and a Log P_{OW} of 4.5 at 25 °C, indicating a low potential for bioaccumulation.

Valid aquatic acute- and long-term studies for all trophic levels were available. All studies presented in the CLH report were conducted according to GLP. Regarding the acute tests included in the report, all trophic groups showed similar sensitivity to the test substance, with the lowest endpoints in the range of 0.015 to 0.0174 mg/L. Based on these endpoints, the DS concluded that trifloxystrobin should be classified as Aquatic Acute 1, with an acute M-factor of 10 as the data falls in the range 0.01 to 0.1 mg/L. However, during the public consultation, a comment was received relating to the presence of a study, evaluated during the pesticidal active-substance renewal program for trifloxystrobin, on *Mysidopsis bahia*. As the study was deemed valid by the DS and derived a more conservative toxicity value (96h LC_{50} of 0.00862 mg/L) this value was used by the DS to change the proposed acute M-factor from 10 to 100.

Chronic toxicity data for trifloxystrobin were available for fish, invertebrates, algae and aquatic plants. The lowest endpoint is a 72h E_rC_{10} = 0.0025 mg/L for green algae (*Desmodesmus subspicatus*). Therefore, as trifloxystrobin is considered as not rapidly degradable, the DS proposed to classify the trifloxystrobin as Aquatic Chronic 1 with an M-factor of 10.

Degradation

Two valid aqueous hydrolysis studies performed under GLP were available. Both studies illustrated that trifloxystrobin rapidly hydrolyses to form the metabolite CGA 321113 and that the hydrolytic degradation of trifloxystrobin is pH-dependent. Rates of degradation increased as the pH increased from pH 5 to pH 13, where the fastest hydrolytic degradation rates were observed.

Four valid photolysis studies performed under GLP are available. Under photolytic conditions in the laboratory in sterile buffers at pH 5 and pH 7 and in sterile natural water, both trifloxystrobin and its major metabolite CGA 321113 were shown to rapidly degrade.

A valid, GLP-compliant study on rapid degradability is available, according to OECD TG 301B (1992). Evolved CO_2 concentrations from the trifloxystrobin (CGA 279202 tech.) samples were identical to that of the untreated inoculum at 28 days and thus no rapid degradability could be concluded.

In a valid, GLP-compliant, water simulation study, performed following the OECD TG 309, trifloxystrobin hydrolysed rapidly to form the metabolite CGA 321113. Degradation in surface waters appears to occur only via abiotic processes. The DT_{50} was calculated to be 3.4 and 3.3 days at 12 °C for high and low concentrations, respectively. Two valid, GLP-compliant aerobic sediment/water studies were available. For trifloxystrobin, the DT_{50} (12 °C) values were calculated to be around 2.1 days, 6.3-7.4 days and 5.3-6.1 days for river water, river sediment and total river system, respectively. For the metabolite CGA 321113, DT_{50} (12 °C) values were calculated as 560-588 days, 872 to > 1 000 days and 7 210 to > 1 000 days for river water, river sediment and total river system, respectively. A third study is available that offers a re-evaluation of the validated data from previous studies. The DT_{50} (12 °C) values for trifloxystrobin were calculated as 1.44 days, 4.65 days and 3.21 days for water, sediment and total system compartments, respectively. For the metabolite CGA 321113, DT_{50} (12 °C) the values were calculated as 398 days, > 1 000 days and 736 days for water, sediment, and total system compartments, respectively.

Bioaccumulation

A GLP-study is available that determined the BCF of trifloxystrobin for bluegill sunfish (*Lepomis macrochirus*). The study was performed following the EPA 165-4 guideline and was considered comparable to OECD TG 305. Steady state BCF for whole fish was calculated to be 431 L/kg and the corresponding lipid normalised (5 %) BCF was reported to be 370 L/kg.

In a GLP-study performed according to OECD TG 107, the 1-octanol/water partition coefficient of trifloxystrobin was determined in pH 7.51 (average pH of aqueous phase) as Log P_{OW} of 4.5 ± 0.0094 at 25 °C.

Therefore, the DS concluded that trifloxystrobin has low bioaccumulation potential.

Acute Aquatic Toxicity

There are several, GLP-compliant, acute studies for all trophic levels available. Four studies are available for fish and aquatic invertebrates respectively and one study for algae. The data for all the studies are summarised in the table below. Trifloxystrobin metabolites as reported by the DS are not considered more toxic than the parent substance and thus they are not considered further for classification purposes.

***Table**: Summary of the relevant acute toxicity data on fish, aquatic invertebrates and algae/aquatic plants (key data are highlighted in bold)*

Guideline	Species	Endpoint data	Exposure		Results		Reference
			Design	Duration	Endpoint	Toxicity (mg/L)	
Fish and amphibians							
OECD TG 203	*Oncorhynchus mykiss*	Mortality	Flow through	96h	LC_{50}	**0.015 mm**	Anonymous (1997f) M-032048-01-1
OECD TG 203	*Lepomis macrochirus*	Mortality	Flow through	96h	LC_{50}	0.054 mm	Anonymous (1997g) M-032068-01-1
OECD TG 203	*Cyprinodon variegatus*	Mortality	Flow through	96h	LC_{50}	0.078 mm	Anonymous (1996a) M-032072-01-1
No formal TG	*Xenopus laevis*	Mortality	Flow through	48h	LC_{50}	0.038 mm	Anonymous (2009) M-358069-01-1
Aquatic invertebrates							
FIFRA 72-2	*Daphnia magna*	Immobilisation	Flow through	48h	EC_{50}	**0.016 mm**	Neumann (1997) M-051484-01-1
FIFRA 72-2	*Daphnia magna*	Mortality	Flow through	48h	LC_{50}	0.0253 mm	Boeri (1997) M-032084-01-1
EPA 72-2(a)	*Procambarus acutus*	Mortality	Flow through	96h	LC_{50}	>0.31 mm	Ward (1998) M-052687-01-1
EPA 72-3(b)	*Crassostrea virginica*	Mortality	Flow through	96h	EC_{50} LC_{50}	0.0349 mm (shell deposition) > 0.0748 mm	Boeri (1996) M-032088-01-1
Algae							
OECD TG 201	*Desmodesmus subspicatus* (formerly *Scenedesmus subspicatus*)	Cell number	Static	72h	E_rC_{50}	**0.0174 mm**	Grade (1995) M-032098-01-1 Recalculation by: Herno (2017) M-032098-01-1

mm = mean measured

All trophic groups showed similar sensitivity to the substance. The lowest endpoints for fish, aquatic invertebrates and algae, based on mean measured concentrations, were 96h 0.015 mg/L, 48h 0.016 mg/L and 72h 0.0174 mg/L, respectively. Based on the above-mentioned endpoints, the DS concluded that trifloxystrobin should be classified as Aquatic Acute 1 with an acute M-factor of 10 based on acute endpoints, which fall in the range 0.01 to 0.1 mg/L.

However, during the public consultation, a comment was received relating to the presence of a study, evaluated during the pesticidal active-substance renewal program for trifloxystrobin, on *Mysidopsis bahia*. As the study was deemed valid by the DS and derived a more conservative toxicity value (96h LC_{50} of 0.00862 mg/L), this value was used by the DS to change the proposed acute M-factor from 10 to 100. More details on the study can be found in the section below that summarises the comments received during the public consultation.

Chronic Aquatic Toxicity

One long-term study for each trophic level is available. The data for all the studies are summarised in the table below. As mentioned above, trifloxystrobin metabolites as reported by the DS are not considered more toxic than the parent substance and, thus, they are not considered further for classification purposes.

***Table**: Summary of the relevant chronic toxicity data on fish, aquatic invertebrates and algae/aquatic plants (key data are highlighted in bold).*

Guideline	Species	Endpoint data		Exposure		Results Toxicity (mg/L)	Reference
		Effects endpoint	Design	Duration	Endpoint		
Fish							
EPA 72-4(a)	*Oncorhynchus mykiss*	Survival and development	Flow through	ELS, 95d	NOEC EC_{10}	0.0043 mm (time to swim-up) 0.0075 mm (survival at the end of the test)	Anonymous (1997h) M-032080-02-1
Aquatic invertebrates							
EPA 72-4(b)	*Daphnia magna*	Reproduction	Flow through	21d	NOEC EC_{10}	0.00276 mm 0.00328 mm	Boeri (1996) M-032097-01-1 recalculation by Herno (2017) M-582256-01-1
Algae							
OECD TG 201	*Desmodesmus subspicatus (formerly Scenedesmus subspicatus)*	Cell number	Static	72h	NOEC E_rC_{10}	0.00192 mm **0.0025 mm**	Grade (1995) M-032098-01-1 recalculation by Herno (2017) M-582093-01-1

mm = mean measured

Based on trifloxystrobin being non-rapidly degradable and based on the toxicity value for algae (*Desmodesmus subspicatus*), the DS proposed that trifloxystrobin should be classified as Aquatic Chronic 1 with an acute M-factor of 10, based on the chronic endpoint of 72h E_rC_{10} = 0.0025 mg/L, which falls in the range 0.001 to 0.01 mg/L.

Comments received during public consultation

One MSCA commented and agreed with the initial environmental classification as it was proposed by the DS. A second MSCA also agreed with the proposed environmental classification but drew attention to an additional acute toxicity study (Boeri, 1996) that would lead to an acute M-factor of 100 instead of the proposed value of 10. As mentioned by the commenting MS, during the Annex I renewal process for trifloxystrobin, the Rapporteur Member State (RMS) concluded that a reliable toxicity endpoint could not be derived for this study, therefore the RMS considered that it was not suitable for use in the risk assessment (page 113 of dRAR Vol 3 B.9 (AS), July 2017). However, upon further consideration from the DS, the study (Boeri, 1996) was concluded to be reliable for the purpose of hazard classification. The DS based its decision to consider the study for classification purposes on the fact that the study was conducted according to GLP, follows the US FIFRA guideline 72-3 with the validity criteria being met. The study reported a 96h LC_{50} of 0.00862 mg/L (based on mean measured concentrations).

The DS agreed that the additional acute study could be used for classification purposes. The use of these data would change the M-factor of the proposed acute classification from 10 to 100.

Assessment and comparison with the classification criteria

Degradation

Trifloxystrobin was shown to degrade rapidly through hydrolysis and photolysis. No significant concentrations of CO_2 were measured in a valid, GLP-compliant study on rapid degradability study (OECD TG 301B (1992)) during 28 days of incubation. Trifloxystrobin does not fulfil the criterion for carbon dioxide generation of 60 % of the theoretical maximum. Consequently, RAC agrees that trifloxystrobin is not rapidly degradable for the purpose of classification and labelling. It should be noted that the main metabolite (CGA 321113) is not considered more toxic than the parent molecule and thus is not considered further for classification purposes.

Bioaccumulation

Trifloxystrobin has a reliable, lipid normalised BCF of 370 L/kg, which is below the CLP criterion of ≥ 500 L/Kg. Although the Log P_{ow} is above the CLP criterion for Log P_{ow} of ≥ 4, the high quality BCF is given preference. Consequently, RAC agrees with the DS that trifloxystrobin is not bioaccumulative.

Aquatic Toxicity

Acute toxicity

The critical acute endpoint is a 96h LC_{50} of 0.00862 mg/L for aquatic invertebrates (*Mysidopsis bahia*) from the Boeri (1996) study. This study, as mentioned by the DS, was performed under GLP and following US FIFRA guideline 72-3 with the validity criteria being met. Small derogations from the above-mentioned guideline on the testing temperature and the testing photoperiod exist, although RAC considers this study to be reliable and relevant for hazard classification.

This value is below the 1 mg/L criterion and thus the classification of trifloxystrobin as Aquatic Acute 1 should be retained. Also, the value is in the range of 0,001 < $L(E)C_{50}$ ≤ 0,01 which justifies an acute M-factor of 100. Thus, RAC agrees that trifloxystrobin should be classified as Aquatic Acute 1 with an M-factor of 100.

Chronic toxicity

The critical chronic endpoint is the 72h E_rC_{10} = 0.0025 mg/L for algae (*Desmodesmus subspicatus*). This value is in the range of below 0.1 mg/L which is the classification threshold for Aquatic Chronic 1 for not rapidly degradable substances, and justifies a chronic M-factor of 10 (0.001 < NOEC ≤ 0.01 mg/L). Thus, RAC agrees that trifloxystrobin should be classified as Aquatic Chronic 1 with an M-factor of 10.

Conclusion on classification

Trifloxystrobin is considered not rapidly biodegradable and is not bioaccumulative.

RAC agrees with the DS that Trifloxystrobin warrants **classification as Aquatic Acute 1; H400 with an M-factor of 100, and Aquatic Chronic 1; H410 with an M-factor of 10.**

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).