Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

dimoxystrobin (ISO); (2*E*)-2-{2-[(2,5-dimethylphenoxy)methyl]phenyl}-2-(methoxyimino)-*N*-methylacetamide; (*E*)-2-(methoxyimino)-*N*-methyl-2-[α-(2,5-xylyloxy)-o-tolyl]acetamide

EC Number: -
CAS Number: 149961-52-4

CLH-O-0000006865-62-01/F

Adopted

8 October 2020

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8 October 2020

CLH-O-0000006865-62-01/F

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

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

Chemical name: **dimoxystrobin (ISO); (2*E*)-2-{2-[(2,5-dimethylphenoxy)methyl]phenyl}-2-(methoxyimino)-*N*-methylacetamide; (*E*)-2-(methoxyimino)-*N*-methyl-2-[*a*-(2,5-xylyloxy)-o-tolyl]acetamide**

EC Number: **-**

CAS Number: **149961-52-4**

The proposal was submitted by **Hungary** and received by RAC on **7 May 2019.**

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

PROCESS FOR ADOPTION OF THE OPINION

Hungary 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 **1 July 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **30 August 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Miguel A. Sogorb**

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 **8 October 2020** by **consensus**.

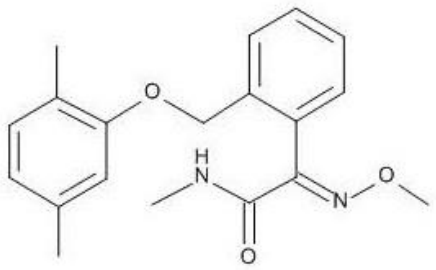
Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	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	616-164-00-7	dimoxystrobin (ISO); (2*E*)-2-{2-[(2,5-dimethylphenoxy)methyl]phenyl}-2-(methoxyimino)-*N*-methylacetamide; (*E*)-2-(methoxyimino)-*N*-methyl-2-[α-(2,5-xylyloxy)-*o*-tolyl]acetamide	-	149961-52-4	Carc. 2 Repr. 2 Acute Tox. 4* Aquatic Acute 1 Aquatic Chronic 1	H351 H361d*** H332 H400 H410	GHS07 GHS09 GHS08 Wng	H351 H361d*** H332 H410			
Dossier submitters proposal	616-164-00-7	dimoxystrobin (ISO); (2*E*)-2-{2-[(2,5-dimethylphenoxy)methyl]phenyl}-2-(methoxyimino)-*N*-methylacetamide; (*E*)-2-(methoxyimino)-*N*-methyl-2-[α-(2,5-xylyloxy)-*o*-tolyl]acetamide	-	149961-52-4	**Remove:** Repr. 2 **Add:** STOT RE 2 Lact. **Modify:** Acute Tox. 4	**Remove:** H361d*** **Add:** H373 (blood) H362	**Maintain**: GHS07 GHS09 GHS08 Wng	**Remove:** H361d*** **Add:** H373 (blood) H362		**Add:** inhalation: ATE=1.3 mg/L (dusts or mists) M = 100 M = 100	
RAC opinion	616-164-00-7	dimoxystrobin (ISO); (2*E*)-2-{2-[(2,5-dimethylphenoxy)methyl]phenyl}-2-(methoxyimino)-*N*-methylacetamide; (*E*)-2-(methoxyimino)-*N*-methyl-2-[α-(2,5-xylyloxy)-*o*-tolyl]acetamide	-	149961-52-4	Repr. 2 Acute Tox. 4 Aquatic Acute 1 Aquatic Chronic 1	H361d H332 H400 H410	GHS07 GHS09 GHS08 Wng	H361d H332 H410		inhalation: ATE=1.3 mg/L (dusts or mists) M = 100 M = 100	
Resulting Annex VI entry if agreed by COM	616-164-00-7	dimoxystrobin (ISO); (2*E*)-2-{2-[(2,5-dimethylphenoxy)methyl]phenyl}-2-(methoxyimino)-*N*-methylacetamide; (*E*)-2-(methoxyimino)-*N*-methyl-2-[α-(2,5-xylyloxy)-o-tolyl]acetamide	-	149961-52-4	Carc. 2 Repr. 2 Acute Tox. 4 Aquatic Acute 1 Aquatic Chronic 1	H351 H361d H332 H400 H410	GHS07 GHS09 GHS08 Wng	H351 H361d H332 H410		inhalation: ATE=1.3 mg/L (dusts or mists) M = 100 M = 100	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Dimoxystrobin is an existing fungicidal active substance for use in plant protection products. It is mainly used to control a range of fungal diseases on oilseed rape and sunflower. The chemical structure of dimoxystrobin is shown in the Figure below:



Dimoxystrobin has a current harmonized classification as Acute Tox. Cat. 4* (inhalation), H332; Carc. Cat. 2, H351; Repro. Cat. 2, H361d***, Aquatic Acute 1, H400 and Aquatic Chronic 1, H410 with an M-factor of 10; although there is no officially documented rationale for such classification.

Since the original harmonised classification of dimoxystrobin, new mechanistic data on reproductive toxicity were generated. These new data have been submitted according to Regulations (EC) 1107/2009 and 844/2012 within the supplementary dossier for the renewal of approval of dimoxystrobin as active substance in plant protection products. The dossier submitter (DS) concludes in the CLH-report that the classification with Repr. Cat. 2 is not justified. Instead, a classification for effects on or via lactation, H362 as well as STOT RE 2, H373 (blood) was proposed.

During the consultation, one member state competent authority (MSCA) requested clarification about whether the active substance contains relevant impurities. The DS replied that dimoxystrobin does not contain toxicologically relevant impurities at the specified limit.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

DS proposed no classification for acute oral toxicity based on an OECD TG 401 and GLP compliant test showing a LD_{50} higher than 5000 mg/kg bw. DS proposed no classification for acute dermal toxicity based on an OECD TG 402 and GLP compliant test showing a LD_{50} higher than 2000 mg/kg bw. DS proposed the classification of dimoxystrobin as Acute Tox. 4; H332 based on an OECD TG 403 and GLP compliant test showing a LC_{50} of 1.9 mg/L for males and 1.3 mg/L for females, with an ATE value of 1.3 mg/L (dusts or mists).

Comments received during consultation

One MSCA supported the proposal of classification as Acute Tox. 4; H332.

A manufacturer company provided a more detailed summary of the acute toxicity studies that had also been provided to EFSA during the pesticide peer review process.

Assessment and comparison with the classification criteria

The table below summarises the available studies for acute toxicity of dimoxystrobin.

***Table**: Summary of animal studies on acute toxicity with dimoxystrobin.*

Study	Dose level	Results	Reference
Acute oral toxicity Equivalent to OECD TG 401 (1987) GLP compliant Wistar rats 5 animals/sex N6 Lot 3004	Purity: 98.8% Vehicle: 0.5 % tylose 2000, 5000 mg/kg bw Single oral administration (gavage) 14-days post dose observation	No mortalities Clinical signs (both doses): impaired or poor general state, dyspnoea, apathy, staggering, and diarrhoea All animals appeared normal within six days after application No macroscopic pathological findings **LD_{50} > 5000 mg/kg bw**	Anonymous, 1998 1998/11002
Acute dermal toxicity Equivalent to OECD TG 402 (1987) GLP compliant Wistar rats 5 animals/sex N6 Lot 3004	Purity: 98.8% Vehicle: 0.5 % tylose 2000 mg/kg bw Single dose under a semiocclusive dressing, 24 h	No mortalities No clinical signs of toxicity No effects on the skin No pathological findings **LD_{50} > 2000 mg/kg bw**	Anonymous, 1998 1998/11001
Acute inhalation toxicity Equivalent to OECD TG 403 (1981) GLP compliant Wistar rats 5 animals/sex/dose N6 Lot 3004	Purity: 98.8% Dust aerosol MMAD (low and mid dose): 2.5 µm MMAD (high dose): 5.1 µm 0.51, 1.28, 5.9 mg/l Single head-nose inhalation 4-hour exposure	All animals exposed to 5.9 mg/L died during exposure. 1 male and 2 females died during or immediately after exposure to of 1.28 mg/l Low and mid dose: attempts to escape, irregular accelerated and intermittent respiration, as well as squatting posture and piloerection. No clinical signs could be detected from post exposure day 5 onward. No clinical signs were detected from day 8 onward. Necropsy of the decedent mid (1.28 mg/l) concentration animals showed agonal congestive hyperaemia. No macroscopic pathologic findings **Males: LC_{50} = 1.9 mg/l** **Females: LC_{50} = 1.3 mg/l**	Anonymous, 1997, 1998

Comparison with the criteria

According to Regulation EC No 1272/2008 a substance does not meet the classification criteria for acute oral and dermal toxicity when LD_{50} values by respective routes of exposure are higher than 2000 mg/kg bw. Dimoxystrobin at 5000 mg/kg bw did not cause mortality after dosage by oral route (table above) and therefore the classification for acute oral toxicity is not warranted. Dimoxystrobin at 2000 mg/kg bw did not cause mortality after dosage by dermal route (table above) and therefore the classification for acute dermal toxicity is not warranted. In conclusion, RAC supports the DS's proposal for **no classification of dimoxystrobin for acute and dermal toxicity.**

The CLP criteria for acute toxicity via inhalation warrant a classification in Category 4, if LC_{50} values between 1.0 and 5.0 mg/L are determined. Thus**, RAC agrees with the DS's proposal for classification of dimoxystrobin as Acute Tox. 4; H332 (Harmful if inhaled) with an ATE = 1.3 mg/L (dusts or mists).**

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

DS proposed no classification of dimoxystrobin based on an OECD TG 404 and GLP compliant study showing no oedema and erythema with the mean scores over 24, 48 and 72 hours being 0.0, 0.0, 0.0, 0.7, 1.0 and 2.0 in individual animals.

Assessment and comparison with the classification criteria

The table below summarises the available study for skin corrosion/irritation by dimoxystrobin.

Table: *Summary of the available animal study on skin corrosion/irritation by dimoxystrobin.*

Study	Dose level	Results	Reference
Skin irritation OECD TG 404 (1992), GLP compliant New Zealand White rabbits 3 animals/sex N6 Lot 3004	Purity: 98.8% Vehicle: water 0.5 g moistened with water Single semiocclusive application 4 hours rinsed after removal of patch	Mean scores over 24, 48 and 72 hours: 0.0, 0.0, 0.0, 0.7, 1.0, 2.0 for erythema (mean average score: 0.6) 0.0 each for oedema Reversibility: yes (within 8 days) **Conclusion: Not irritating**	Anonymous, 1998

Comparison with the criteria

The mean individual scores (24, 48 and 72 h) for erythema and oedema (table above) were below the thresholds for warranting a classification, i.e. ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 (or 4 of 6) tested animals. Thus, the classification is not supported. In conclusion, RAC agrees with the DS's proposal for **no classification of dimoxystrobin for skin irritation or corrosion.**

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

DS proposed no classification of dimoxystrobin based on an OECD TG 405 and GLP-compliant study showing the average individual scores of corneal opacity, iritis, conjunctival redness and chemosis at 24, 48 and 72 hours after installation of the test substance below the thresholds for warranting a classification.

Comments received during consultation

No comments were received during the consultation.

Assessment and comparison with the classification criteria

The table below summarises the available study for serious eye damage/irritation by dimoxystrobin.

Table: Summary of the available animal study on serious eye damage/irritation by dimosxystrobin.

Study	Dose level	Results	Reference
Eye irritation OECD TG 405 (1987) GLP compliant New Zealand White rabbits 3 animals/sex N6 Lot 3004	Purity: 98.8% Vehicle: water 46 mg Single application the conjunctival sac of the right eye, washed out after 24 h	Mean scores over 24, 48 and 72 hours (corneal opacity): 0.0 (average score 0) Mean scores over 24, 48 and 72 hours (iris lesions): 0.0, 0.0, 0.0, 0.3, 0.0, 0.0 (average score 0.1) Mean scores over 24, 48 and 72 hours (redness of conjunctiva): 0.0, 0.3, 0.7, 1.7, 0.7, 0.3 (average score 0.6) Mean scores over 24, 48 and 72 hours (chemosis): 0.0, 0.0, 0.0, 0.7, 0.0, 0.0 (average score 0.1) **Conclusion: Not irritating**	Anonymous, 1998

Comparison with the criteria

The mean individual scores (at 24, 48 and 72 h) for corneal opacity, iritis, conjunctival redness and chemosis are below the thresholds for warranting a classification, i.e. ≥ 1 for corneal opacity and/or chemosis and/or ≥ 2 for conjunctival redness and/or oedema at least in 2 of 3 tested animals. In conclusion, RAC agrees with the DS's proposal for **no classification of dimoxystrobin for serious eye damage/irritation.**

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

DS proposed no classification of dimoxystrobin based on a skin sensitisation guinea pig maximisation test (GPMT) showing no positive response in any animal and on a skin sensitisation local lymph node assay (LLNA) showing a stimulation index lower than 3.

Comments received during consultation

No comments were received.

Assessment and comparison with the classification criteria

The table below summarises the available studies for skin sensitisation by dimoxystrobin.

***Table**: Summary of the animal studies on skin sensitisation by dimoxystrobin.*

Study	Dose level	Results	Reference
Skin sensitisation OECD TG 406 (1992) GLP compliant Pirbright White female Guinea pig 10 controls 20 treated groups N6 Lot 3004	Purity: 98.8% Vehicle: 1% tylose Intradermal induction: 5% in Freund's adjuvant /0.9% aq. NaCl (1:1) Percutaneous induction: 50% in 1% tylose Challenge: 50% in 1% tylose	0/20 animals showed a positive response Separate tests using alpha-hexylcinnamaldehyde as a positive control are conducted twice a year to determine the ability of the test to detect sensitising compounds. **No skin sensitisation**	Anonymous, 1998
Skin sensitisation, local lymph node assay OECD TG 429 (2010) GLP compliant CBA/CaOlaHsd female mice 5/group BAS 540 01 F	199.8 g dimoxystrobin/l Vehicle: Pluronic (1%v/v) Vehicle, 25%, 50%, 100% dilution in vehicle Topical application to the dorsal part of ear: 25 µl/day for 3 days At day 6: Injection of 19.5 µCi ^{3}H methyl thymidine Sacrifice after 5 h	<u>Results for vehicle/25%/50%/ 100% dose groups</u> Stimulation indices (SI) of cell count: 1.00/1.44/1.12/1.34* SI of ^{3}HTdR incorporation: 1.00/1.05/1.01/1.93* SI of lymph node weight: 1.00/1.11/1.09/1.34* SI of ear weight: 1.00/1.01/1.04/1.15 Positive control studies performed twice a year with the sensitizer alpha-hexylcinnamaldehyde proved the sensitivity of the method used **No skin sensitisation**	Anonymous, 2015a

Comparison with the criteria

None of the animals in the GPMT study showed a positive response after a challenge with dimoxystrobin and no tested concentration induced a stimulation index greater than the threshold of 3 in the LLNA conducted with a dimoxystrobin formulation containing 200 g/l dimoxystrobin. Therefore, classification is not warranted and RAC agrees with the DS's proposal for **no classification of dimoxystrobin as a skin sensitiser.**

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

Summary of the Dossier Submitter's proposal

DS proposed classification of dimoxystrobin as STOT RE 2; H373 (may cause damage to blood through prolonged or repeated exposure) based on reduction of iron levels and partially irreversible anaemia. In the modified one-generation reproduction toxicity study after 100 days of test substance administration in the dams of the mid dose group (57 mg/kg bw/day) decreases in mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) as well as increases in microcytosis were detected. The effective doses extrapolated for 90 days corresponded to 63 mg/kg bw/day.

Comments received during consultation

One MSCA highlighted that the comparison with guidance values was focused on doses that did not clearly evoke significant/severe effects and recommended to consider not only the doses of the modified one-generation reproduction toxicity study, but also those of other studies (e.g. short-term toxicity studies in rats, mice and dogs). DS replied that the results of the 90-day studies in rat, mouse and dog and 1-year study in dogs showed no effects or minor effects that were not sufficiently severe to warrant a classification for STOT RE.

Assessment and comparison with the classification criteria

Modified one-generation reproductive toxicity study (Anonymous, 2001, 2000/1016870)

A modified one-generation reproductive toxicity study was performed according to OECD TG 415 (1983) and GLP. Ten males and ten females Wistar rats were dosed with dimoxystrobin (purity 98.4%) at 1200, 500 and 150 ppm (equivalent to 130, 57 and 18 mg/kg bw/day; respectively). Males were treated during the 47-day premating period and 2-week mating period. Females were treated during the 47-day premating period, 2-week mating period and gestation period up to lactation day 21. The table below shows an overview on the haematological changes in parental animals and pups at PND 21.

After 4 weeks of test substance administration (before the mating period) decreased haemoglobin (HGB), mean corpuscular volume (MCV), MCH and mean corpuscular haemoglobin concentration (MCHC) were found in the peripheral blood of the high dose males (1200 ppm). Increased red blood cell counts (RBC), anisocytosis, microcytosis and hypochromasia were also detected in these males. Moreover, in the mid dose males (500 ppm) MCV and MCH were reduced and microcytosis was increased. In the females, decreased MCH and MCHC values and slightly increased microcytosis and hypochromasia were found in the high dose animals at this time interval (see table below). After 3 months of test substance administration (shortly before sacrifice), slightly increased microcytosis was seen in the high dose males (1200 ppm), only. In the peripheral blood of the high dose dams, decreased HGB, MCV, MCH and MCHC values and increased RBC, platelets (PNT), reticulocytes, microcytosis and hypochromasia were found. In the dams of the mid dose, group (500 ppm) decreases in MCH and MCHC as well as increases in microcytosis were detected. Slight effects were detected in the low dose group of 150 ppm. On day 21 after birth the following haematology changes were observed in the high dose male and female F1 pups (1200 ppm): decreases in RBC, HGB, haematocrit (HCT), MCV and MCH; increases in PNT, reticulocytes, microcytosis and anisochromasia. Moreover, in the high dose male pups MCHC was increased. In the male and female pups of the mid dose group (500 ppm)

HGB, HCT, MCV and MCH were decreased and reticulocytes, microcytosis, anisochromasia and normoblasts were increased. Significantly reduced erythrocytes were also measured in the blood of the mid dose male pups. In the low dose male pups (150 ppm) MCV was reduced and microcytosis and anisochromasia were increased. In the low dose female pups, reticulocytes and microcytosis were elevated.

Table**: Summary of haematology parameters in the modified one-generation study. RBC = Red Blood Cells; HGB = Haemoglobin; HCT = Haematocrit; MCV = Mean Corpuscular Volume; MCH = Mean corpuscular haemoglobin; MCHC = Mean corpuscular haemoglobin concentration; PNT = Platelet *p ≤ 0.05; ** p ≤ 0.02; *** p ≤ 0.002

Dose [ppm]	RBC (TERA/L)	HGB (MMOL/L)	HCT (L/L)	MCV (FL)	MCH (FMOL)	MCHC (MMOL/L)	PLT (GIGA/L)
Males, day 29							
0	7.71	9.3	0.411	53.3	1.21	22.69	819
150	7.49	9.1	0.399	53.4	1.22	22.79	800
500	7.87	9.1	0.404	51.4**	1.16**	22.47	856
1200	8.2** (↑6%)	8.5*** (↓9%)	0.387	47.2*** (↓12%)	1.04*** (↓14%)	22.04** (↓3%)	896
Males, day 98							
0	8.84	9.5	0.484	54.7	1.08	19.68	709
150	8.6	9.5	0.474	55.2	1.11	20.09**	700
500	9.0	9.6	0.489	54.3	1.06	19.55	706
1200	8.97	9.4	0.479	53.4	1.05	19.63	723
Females, day 29							
0	7.68	9.4	0.409	53.3	1.22	22.94	740
150	7.58	9.3	0.403	53.1	1.22	22.59	768
500	7.72	9.2	0.403	52.2	1.19	22.78	728
1200	7.96	9.0	0.405	51.0	1.14** (↓7%)	22.28** (↓3%)	841
Females, day 100							
0	8.5	10.4	0.498	58.8	1.22	20.76	779
150	8.31	9.5**	0.471	56.7	1.14*	20.07*	763
500	9.09	10.0	0.505	55.7	1.11*	19.90***	793
1200	9.54* (↑12%)	9.4*** (↓10%)	0.491	52.0* (↓12%)	1.00** (↓18%)	19.21*** (↓8%)	981** (↑26%)
Male pups, PND 21							
0							
150	4.64	5.4	0.305	65.9	1.17	17.67	825
500	4.67	5.1	0.286	61.4**	1.08	17.62	821
1200	4.28*	3.9***	0.223***	52.0***	0.91***	17.48	1065
	3.10*** (↓33%)	3.0*** (↓44%)	0.152*** (↓50%)	47.1*** (↓29%)	0.97** (↓17%)	20.59* (↑16%)	1227** (↑49%)
Female pups, PND 21							
0	4.47	5.1	0.281	63	1.14	18.08	759
150	4.78	5.1	0.291	61	1.07	17.6	690
500	4.37	4.0***	0.230***	52.3***	0.91***	17.39	1084
1200	3.02** (↓35%)	2.7*** (↓47%)	0.139*** (↓51%)	44.5*** (↓29%)	0.91*** (↓20%)	20.65	1471* (↑94%)

Mechanistic study: Effect of dimoxystrobin on serum iron (2002a, 2002/1005354)

Dimoxystrobin (98.4% purity) was administered in the diet to 10-week old male Wistar rats at 0 (10 rats) and 4500 ppm (equivalent to 232 mg/kg bw/day) (5 rats) for 3 weeks and was followed by a 2-week recovery period. The effect of the treatment on serum iron levels and on

haematological parameters is shown in the tables below. Severe reductions in iron concentration were detected as early as 24 hours after beginning of the dimoxystrobin administration and this reduction was observed until day 36. The iron levels returned to normal and even higher levels than in control during the recovery period; however, no complete recovering of anaemia was noted during the recovery period.

Table: *Serum iron levels in a 5-week feeding study in rats (4500 ppm)* shown as mean of serum iron concentrations (µmol/l). The dose (4500 ppm) was equivalent to 264 mg/kg bw/day. D = day; D -5 = 5 days before administration; * = p<0.05; ** = p<0.01.

Dose [ppm]	D -5	D1	D2	D5	D15	D30	D36	D19 + recovery 11 D	D19 + recovery 17 D
Control	42.2	52.8	46.8	57.3	45.9	37.2	43.0	37.2	43.0
4500 ppm	48.5	**25.6**** ↓52%	**25.4**** ↓46%	**14.7**** ↓74%	**16.2**** ↓65%	**24.4*** ↓34%	**13.4**** ↓69%	55.9	54.9

Table: *Haematological parameters in a 5-week feeding study in rats (4500 ppm)* shown as means of respective parameters. The dose (4500 ppm) was equivalent to 264 mg/kg bw/day in the animals exposed for 30 days and 232 mg/kg bw/day in animals exposed for 19 days.
* = p<0.05; ** = p<0.01.

Dose [ppm]	HGB (mmol/l)	MCV (fl)	MCH (fmol)	MCHC (mmol/L)
Control (day 30)	9.4	56.3	1.17	20.79
4500 ppm (day 30)	**7.6**** ↓19%	**44.3**** ↓21%	**0.89**** ↓24%	**20.02**** ↓4%
4500 ppm (day 19 + 11 days recovery)	**8.7*** ↓7.4%	**48.7**** ↓13.5%	**1.01**** ↓13.7%	20.67

Mechanistic study: Determination of serum iron concentration in young and adult male Wistar rats after 7-day oral administration in the diet (2005a, 2005/1004845)

Dimoxystrobin (98.4% purity) was administered to groups of 10 young (3 weeks old) and adult (10 weeks old) male Wistar rats at dietary concentrations of 0 and 500 ppm over a period of 7 days. An additional group of young animals treated with 250 ppm was added. The dose of 500 ppm was equivalent to 65.3 and 33.8 mg dimoxystrobin/kg bw/day in young and adult animals, respectively. The dose of 250 ppm in young animals was equivalent to 33.8 mg/kg bw/day.

All animals showed significant reduction of iron concentration in serum after 2 and 7 days of dimoxystrobin treatment compared to control animals (table below). A thickening of the duodenum was observed during macroscopic examination in seven rats from group 3 (10- week old animals receiving 500 ppm of dimoxystrobin). This finding is considered as being related to treatment. No duodenum findings were observed in the other animal groups.

Table: *Serum iron concentration (µmol/l) of male rats (3 and 10 weeks old) after administration of dimoxystrobin for 2 and 7 days.* ** = p<0.01

		Dose (mg/kg bw/day)		
Animals	**Day**	**0**	**33.8**	**65.3**
3-weeks	2	92.6±7.5	56.0±27.8** (↓42%)	35.8±14.0** (↓61%)
	7	95.3±6.0	59.7±23.3** (↓38%)	33.6±13.1** (↓65%)
10-weeks	2	43.1±5.9	34.2±3.1** (↓21%)	
	7	44.0±3.5	36.0±3.5** (↓18%)	

Comparison with the criteria

The changes in haematological parameters observed (tables above) are indicative for an iron-deficiency microcytic hypochromic anaemia. Dimoxystrobin reduces iron levels in serum (tables above) and thus causes microcytic hypochromic anaemia, which is characterized by reduced HGB, MCH and MCV. The correlation of anaemia and reduced iron levels was clearly shown in a mechanistic study, where a reduction in serum iron levels was accompanied by changes in haematological parameters indicative for anaemia.

According to CLP criteria, any consistent and significant adverse change in clinical biochemistry or haematology shall be considered for classification. However, RAC notes that the severity of haematological effects in the parental animals in the modified one-generation reproductive toxicity study does not warrant a classification. The mechanistic study for testing the effects of dimoxystrobin on serum iron shows acute reductions in serum iron concentration that does not seem to progress over time. In this same study it was demonstrated that the large reduction in iron concentration was causing less than 20 % differences in HGB, MCV, MCH and MCHC values as compared to control animals. RAC concludes that these effects are not of sufficient severity to warrant classification. The second mechanistic study for the determination of serum iron concentration in adult male Wistar rats after 2 and 7-day oral administration in the diet did not show effects warranting classification.

The modified one-generation reproductive toxicity study suggests that pups might be more susceptible than adults to haematological alterations induced by dimoxystrobin. This higher sensitivity of young animals as compared to adults is also shown in the mechanistic study in which the magnitude of effects on serum iron concentrations is doubled in 3-week old rats as compared to 10-week old rats. RAC concludes that the effects in pups are relevant for the assessment of reproductive toxicity rather than for STOT RE.

RAC notes that DAR includes additional information on haematological effects of dimoxystrobin; this is considered further in the BD.

Overall, RAC concludes that the severity of anaemia observed in adult rats **does not warrant classification for STOT RE.**

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

DS proposed no classification of dimoxystrobin for fertility and sexual function based on the absence of treatment-related effects noted in a 2-generation reproductive toxicity study, a modified one-generation reproductive toxicity study and an enhanced one-generation reproductive toxicity study (all of them conducted according to OECD TG and GLP).

The DS proposed no classification of dimoxystrobin for development because they considered that there was no evidence for developmental toxicity in the rat and that in the developmental studies in rabbits the increased incidences of post-implantation losses and resorptions, the abortion and the increased incidences of fused sternebra and severely fused sternebra–bony plate, were considered non-specific developmental effects or the effects were within the HCD and were therefore considered not sufficient to warrant classification. The increased number of stillborn F1 pups and the increased number of dead F2 pups in the 2-generation toxicity study in rats were all within the historical control data range and were therefore considered not relevant for developmental toxicity classification. The other effects found in pups consisted of microcytic hypochromic anaemia, reduced body weights and cardiomegaly. Iron deficiency microcytic

hypochromic anemia was considered not a specific developmental effect as it was occurring also in parental animals. Classification due to cardiomegaly was considered not justified because this effect was considered not to be due to in utero exposure and was considered as a secondary non-specific consequence of anemia. Also the reduced pup body weight was considered to be secondary non-specific consequence of anemia.

The DS proposed classification of dimoxystrobin for effects on or via lactation because the observed body weight and cardiac effects on offspring were considered to be consequences of an iron-deficient anaemia, occurring after direct (via feed or milk) exposure with dimoxystrobin.

Comments received during consultation

Ona manufacturer provided comments supporting the DS's proposal for removing the current harmonised classification as Repro. 2 H361d.

One MSCA considered that there were insufficient mechanistic data to clearly demonstrate that the cardiomegaly in the 2-generation study in F1 and F2 offspring was due to iron deficiency in the lactating dams. The MSCA also noted that in the developmental toxicity studies in rabbits ventricular septal defects were described suggesting that the heart might be a target for developmental toxicity. It was also considered that impairment in quality of milk due to reduction of iron levels could also be plausible and that the reported effects on pup body weight during lactation justifies classification for on or via lactation. DS replied to the MSCA in the following terms:

- Cardiomegaly was determined at pup necropsy and was seen only in F1 and F2 pups sacrificed at PND21 and in none of the F0 or F1 pups that were sacrificed or died at PND < 1 (including stillborn) or at PND 4 at any dose group. All F1 parental animals were necropsied and the only finding related to heart was one isolated heart dilatation in one male of the 500 ppm dose group with no further effects in the heart observed in any other animals. All together, these observations, provide evidence that cardiomegaly is not an effect occurring after in utero exposure, but only after postnatal and/or lactational exposure to dimoxystrobin or to milk containing insufficient iron concentration.
- The ventral septum effects seen in rabbit development toxicity studies were clearly within historical control data ranges. The heart was a target organ in offspring rats only when young rats were directly dosed with dimoxystrobin or when offspring animals were exposed to milk with presumably lower iron content, as shown in rat generation toxicity study. In the rat prenatal developmental toxicity study with only in utero exposure, no effects on the heart were detected. It was thus concluded, that the heart was not a target organ after inutero exposure to dimoxystrobin.

Another MSCA supported no classification for fertility and sexual function but highlighted uncertainties regarding the removal of the Repr. 2 classification for adverse effects on development, especially because in the one-generation toxicity study relatively low doses were tested and because a difference in true NOAELs for anaemia between parental and offspring could not be excluded. Moreover, it was questioned whether the effects on pup body weight should be considered as direct or indirect effects (as it might affect the classification on lactation). DS replied that in the more recent enhanced one-generation toxicity study, no anaemia or decreased serum iron levels were detected in dams or offspring at the top dose of 50 ppm (the second highest dose of the original 2-generation toxicity study) and thus set the same NOAEL (50 ppm) for anaemia and serum iron level changes in adults and offspring.

One manufacturer/company provided confidential information (previously requested by EFSA during the pesticide peer review process since it was considered to be potentially relevant for classification purposes). This information contained the following items:

- Historical control data rabbit prenatal developmental toxicity studies April 1999 - November 2003;
- Historical control data rabbit prenatal developmental toxicity studies April 1997 - April 2002;
- Historical control data rabbit prenatal developmental toxicity studies May 1994 - October 2000;
- Historical control data rat prenatal developmental toxicity studies January 1994 - June 1999;
- Historical control data pup necropsy observations from reproduction toxicity studies January 2008 - December 2014;
- Benchmark Dose Calculations on body weight effects in dams and offspring of the 2-generation toxicity study;
- Benchmark Dose Calculations on body weight effects in dams and offspring of the 2-generation toxicity study (EPA BMDS Software 3.1.1);
- Graphical analysis of individual male entry into puberty (preputial separation - PPS) data correlated with body weight (1200 ppm dimoxystrobin dose vs control);
- Graphical analysis of individual male entry into puberty (preputial separation - PPS) data correlated with body weight (500 ppm dimoxystrobin dose vs control);
- Graphical analysis of individual female entry into puberty (Vaginal opening - VO) data correlated with body weight (1200 ppm dimoxystrobin dose vs controls);
- Graphical analysis of individual female entry into puberty (Vaginal opening - VO) data correlated with body weight (500 ppm dimoxystrobin dose vs controls);
- Five different publications of the open scientific literature.

This information, in particular the historical control data was noted by RAC.

Assessment and comparison with the classification criteria

The tables below summarise the relevant animal studies with dimoxystrobin for testing both sexual function and fertility and development.

***Table**: Summary table for animal studies on adverse effects on sexual function and fertility and development with dimoxystrobin.* Only statistically ($p<0.05$)/biologically significant toxic effects are shown. m=males; f=females. HCD = Historical Control Data.

Method	Results	Reference
Two-generation reproductive toxicity study OECD TG 416 (Draft 1996) Deviations: sexual maturation data did not include the body weight at the day of criterion; anogenital distance of F2 pups was not determined; thyroid weight of the parental animals was not determined GLP: yes Wistar rats 25 animals/sex/dose Purity: 98.4%	**Parental toxicity (F0)** *1200 ppm* ↓8% (m) and ↓7% (f) body weight ↓10% bodyweight gain (m) ↓4% (m) and ↓8-13% (f) food consumption ↓6% maternal bodyweight lactation day 21 **Developmental toxicity (F1 pups)** *1200 ppm* 11/24 pregnant F0 with stillborn pups (46% vs 8.3% in control dams) (HCD 3-13%) 17 stillborn/335 pups delivered (5.1% vs 0.6% in control) (HCD 4-35%) ↓41% (m) and ↓40% (f) pup body weight gain days 4-21 ↓15% pup bodyweight lactation day 21 ↓6.1% (absolute) and ↑45% (relative) brain weight ↓58% (absolute) and ↓37% (relative) thymus weight ↓52% (absolute) and ↓28% (relative) spleen weight	Anonymous, 2001 2000/1016869

Dose/concentration: 0, 50, 150, 500, 1200 ppm Route of administration: oral in feed <u>Duration of treatment:</u> <u>F0</u> ♂: 74 days prior mating, up to 2 weeks mating period ♀: 74 days prior mating, up to 2 weeks mating period, continuously exposed during gestation up to weaning (LD 21) <u>F1</u> ♂: from weaning for at least 76 days, up to 2 weeks mating period ♀: from weanling for at least 76 days, up to 2 weeks mating period, continuously exposed during gestation up to weaning (LD 21)	Cardiomegaly 19 % litter incidence (0 in control) Pale-yellowish liver 15% litter incidence (0 in control) Hypoplasia of thymus 13% litter incidence (0% in control) *500 ppm* ↓29% (absolute) and ↓16% (relative) thymus weight ↓26% (absolute) and ↓12% (relative) spleen weight **<u>Parental toxicity (F1)</u>** *1200 ppm* ↓18% (m) and ↓15% (f) body weight ↓16% (m) and ↓12-26% (f) food consumption ↓35% maternal bodyweight lactation day 21 *500 ppm* ↓9% (m) and ↓5% (f) body weight ↓8% (m) and ↓4-10% (f) food consumption ↓17% maternal bodyweight lactation day 21 **<u>Sexual function and fertility (only in F1 dams)</u>** *1200 ppm* Delay in sexual maturation (days to criterion 40.6 vs 34.9 in control in females, 47.8 vs 43.4 in males) Implantation sites per dams: 12.9 (HCD: 11.5-18.3%) Pups per F1 dam: 11.8 (HCD: 11.1-15.0%) *500 ppm* Delay in sexual maturation (days to criterion 36.4 vs 34.9 in control in females) **<u>Developmental toxicity (F2 pups)</u>** *1200 ppm* ↓42% (m) and ↓43% (f) pup body weight gain days 4-21 19 pups died/260 live born pups (HCD: 4-31) Viability index day 4: 92% (97% control; HCD range 83-99%) ↓36% pup bodyweight lactation day 21 ↓8.1% (absolute) and ↑46% (relative) brain weight ↓52% (absolute) and ↓25% (relative) thymus weight ↓55% (absolute) and ↓28% (relative) spleen weight Cardiomegaly 12% litter incidence (0 in control) Pale-yellowish liver 9% litter incidence (0 in control) *500 ppm* ↓14% pup bodyweight lactation day 21 ↓18% absolute thymus weight

	↓19% (absolute) and ↓8% (relative) spleen weight Cardiomegaly 5% litter incidence (0 in control)	
Modified one-generation reproductive toxicity study OECD TG 415 (1983) Deviations: only 10 animals/sex/generation were used; exposure before mating was shorter than 70 days GLP: yes Wistar rats 10 animals/sex/ dose Purity: 98.4% Dose/concentration: 0, 150, 500, 1200 ppm Route of administration: oral in feed Duration of treatment: ♂: 47 days prior mating, up to 2 weeks mating period ♀: 47 days prior mating, up to 2 weeks mating period, continuously exposed during gestation up to weaning (lactation day 21)	<u>Parental toxicity</u> *1200 ppm* ↓17% bodyweight (m) (week 13) ↓24% body weight gain (m) (week 13) ↓9% bodyweight (f) (*post coitum* day 20) ↓18% bodyweight gain (f) (*post coitum* day 20) ↓9% (m) and ↓12% (f) food consumption Haematological changes Mycrocytosis *500 ppm* ↓11% bodyweight (m) (week 13) ↓14% body weight gain (m) (week 13) ↓11% (m) food consumption Haematological changes Mycrocytosis <u>Developmental toxicity</u> *1200 ppm* ↓38% bodyweight (day 21) ↑57% relative heart weight (cardiomegaly) Haematological changes Pale discoloration of liver and kidney ↓20% (f) absolute liver weight ↑15% (m) relative liver weight ↑26% (f) relative liver weight Milky fluid in abdomen and/or thorax after organ evisceration *500 ppm* Haematological changes Pale discoloration of liver and kidney Milky fluid in abdomen and/or thorax after organ evisceration <u>No treatment related effects on sexual function and fertility at any dose</u>	Anonymous, 2001b 2000/1016870
Enhanced one-generation reproductive toxicity study OECD TG 416 (2001) GLP: Yes Route of administration: oral in feed Wistar rats 25 animals/sex/group Deviations: study design was limited to 1 generation; estrus cycle and sperm parameters	<u>No treatment related effects on sexual function and fertility or developmental or parental toxicity at any dose</u>	Anonymous, 2011 2011/1211676

were not determined; organ weight determination, gross necropsy and histopathology were not included; haematology and determination of iron and transferrin was included for blood samples of parental animals taken before sacrifice as well as of pups on PND 7, 14, 21

Purity: 98.5%

Dose/concentration: 0, 10, 20, 50 ppm

Duration of treatment:
♂: 73 days prior mating, up to 2 weeks mating period
♀: 73 days prior mating, up to 2 weeks mating period, continuously exposed during gestation up to weaning (LD 21), however, during lactation exposure levels were reduced by 50% due to increased food consumption during that phase

***Table**: Summary table for animal studies on developmental toxicity with dimoxystrobin*. Only statistically ($p<0.05$)/biologically significant toxic effects are shown. HCD = Historical Control Data.

Method	Results	Reference
Prenatal developmental toxicity study OECD TG 414 (Draft 1996) Gavage No deviations GLP: yes Wistar rats 25 females/dose Purity: 98.8% Dose/concentrations: 0, 60, 120, 300 mg/kg bw/day Treatment: GD 6 – 19 Vehicle: 0.5% tylose CB 30000 in doubly distilled water	<u>300 mg/kg bw/day</u> ↓8% food consumption ↓10% bodyweight gain <u>120 mg/kg bw</u> ↓12% bodyweight gain <u>No developmental toxicity at any dose</u>	Anonymous, 1999 1999/11680
Prenatal developmental toxicity study OECD TG 414 Gavage Deviations: only the head of those foetuses that showed severe abnormal findings were subject to the histopathological examinations. GLP: yes Himalayan rabbit Purity: 98.4% Dose/concentrations: 0, 25, 50, 100 mg/kg bw/day	<u>100 mg/kg bw/day</u> Maternal toxicity: Diarrhoea and further no defecation 1 doe found dead ↓ 15% food consumption (GD7-28) ↓ 40% bodyweight gain (GD7-28) Developmental toxicity: 1 abortion and further sacrifice 2.2 mean number of resorptions (control = 1) 2.0 mean number of early resorptions (control 0.8) Fused sternebrae litter incidence = 47% vs 8% in control (HCD = 0-50%) Fused sternebrae foetuses/litter = 15.2% vs 0.9% in control (11.1% at high dose if excluding a dam which had 100% affected foetuses (=1 affected pup)/litter) from the evaluation) (HCD = 0-13.5%) <u>50 mg/kg bw/day</u> Maternal toxicity: Diarrhoea (12 dams on day 8) and further no defecation (1 dam on day 9) ↓ 6% food consumption (GD7-28)	Anonymous, 2001 2001/1016351

Duration of treatment: GD 7 - 28 Vehicle: 0.5% tylose CB 30000 in doubly distilled water	Developmental toxicity: Fused sternebrae litter incidence = 35% Fused sternebrae foetuses/litter = 6.5% <u>25 mg/kg bw/day:</u> Maternal toxicity: Diarrhoea (2 dams on day 8) Developmental toxicity: Fused sternebrae litter incidence = 36% Fused sternebrae foetuses/litter = 5.1%	
Prenatal developmental toxicity study OECD TG 414 (2001) Gavage No deviations GLP: yes Himalayan rabbit 25 animals/dose Purity: 98.4% Dose/concentrations: 0, 5, 20, 75 mg/kg bw/day Duration of treatment: GD 7-28 Vehicle: 0.5% tylose CB 30000 in doubly distilled water	<u>75 mg/kg bw/day</u> Maternal toxicity: 16/25 diarrhoea 10/25 no defecation (most of them with previous diarrhoea) 2 does found dead ↓18 % food consumption (GD7-28) ↓55% body weight gain (GD7-28) Developmental toxicity Total skeletal malformations: litter incidences: 41% (control 13%); foetuses/litter: 9.4±14 (control 2.2±6.16) Bony plate (sternebra severely fused-malformation): Litter incidence 14 % vs 0 % in control; foetuses/litter: 2.2±6.16 (control 0) <u>20 mg/kg bw/day</u> Maternal toxicity: 6/25 diarrhoea	Anonymous, 2001 2001/1016351

Comparison with the criteria

<u>Sexual function and fertility</u>

In the rat 2-generation reproduction toxicity study, there were no treatment-related significant effects on sexual function or fertility. Treatment with dimoxystrobin up to the concentration of 1200 ppm had no effects on the oestrous cycle, the number, morphology and motility of sperm as well as on male or female fertility. Male and female fertility indices ranged between 80 and 100% without relation to dose. Dimoxystrobin treatment did not affect the reproductive performance as was evident from the absence of effects on the pre-coital interval or gestation lengths as well as gestation (96 to 100%) or live birth indices (95 to 99%).

A reduction on the implantation sites and pups per F1 dams were noted. However, these effects were within the historical control data range. In addition, a delay in sexual maturation of both males and females was noted in F1 generation at the highest dose. However, RAC notes that the delayed onset of puberty is likely secondary to lower offspring body weights.

The enhanced one-generation toxicity study conducted according to OECD TG 416 (2001) and the modified one-generation toxicity study conducted according to OECD TG 415 (1983) showed no effects on sexual function and fertility; although the first of these two studies was performed

using very low dosing and therefore the information provided in this study is not conclusive enough. RAC agrees with the DS's proposal for **no classification of dimoxystrobin for sexual function and fertility.**

Development: Prenatal toxicity studies in rats and rabbits

No developmental toxicity was observed at the highest dose tested (300 mg/kg bw/day) in the prenatal toxicity study in rats. In rabbits, different effects were reported in two prenatal toxicity studies where doses of dimoxystrobin were 0, 25, 50 and 100 mg/kg bw/day in the first study and 0, 5, 20 and 75 mg/kg bw/day in the second study.

In the first study maternal toxicity was seen at 100 mg/kg bw/day, indicated by maternal mortality (1 female was found dead), diarrhoea, no defecation, 15% decrease in food consumption and 40% decrease in body weight gain between GD7 and GD28. At 50 mg/kg bw/day, one dam had no defecation on day 9 and 12 dams had diarrhea on day 8. Transient drop in food consumption and effects on body weight were observed at all dose levels. At 100 mg/kg bw/day the significant maternal toxicity was considered to result in increased resorptions (mainly early resorptions) and post implantation loss (due to an increased number of early resorptions). As a consequence gravid uterus weights were lower at this dose level without attaining statistical significance. One dam was sacrificed due to abortion. The effects on sternebrae are assessed below.

In the second study severe maternal toxicity was seen at 75 mg/kg bw/day, indicated by maternal deaths (2 females died), diarrhoea and no defecation. Mean body weight gain during treatment was significantly decreased at the high dose of 75 mg/kg bw/day (about 55%) and non-statistically significant at the mid dose of 20 mg/kg bw/day (about 19%). At 75 mg/kg bw/day this maternal toxicity was considered to result in increased non-statistically significant resorptions (mainly early resorptions) and post implantation loss. As a consequence, gravid uterus weights were lower at this dose level but without attaining statistical significance.

Thus, increased incidences of post-implantation losses and mean numbers of resorptions co-occurred with severe maternal toxicity (including mortalities, clinical signs and reductions in body weight gain between 40 and 55%) and were therefore not considered by RAC as indicative of developmental toxicity.

The incidence of total skeletal malformations was statistically significantly increased in the second rabbit study at the 75 mg/kg bw/day dose. However, there were no treatment-related malformations seen in the first rabbit study, which had been dosed up to 100 mg/kg bw/day. In the table below, the incidences for total skeletal malformations are summarized for both rabbit studies, which clearly demonstrates the absence of a dose-response. In consequence, RAC considers the effects on total skeletal malformations at 75 mg/kg bw/day as incidental.

***Table**: Incidences of total skeletal malformations in both rabbit studies (Anonymous 2001a, 2000/1016867 and 2001/1016351).* * = p < 0.05

	Dose (mg/kg bw/day)							
Parameter	**Control 1**	**Control 2**	**5**	**20**	**25**	**50**	**75**	**100**
Fetal incidence [N (%)]	4 (2.6)	3 (1.8)	6 (3.6)	3 (2.0)	2 (1.2)	3 (1.9)	11 (8.1)	5 (4.8)
Litter incidence [N (%)]	3 (12)	3 (13)	6 (25)	2 (8.0)	2 (8.0)	3 (13)	9* (41)	4 (21)
Affected fetuses/litter (Mean ± SD) [%]	3.4± 9.9	2.2± 6.2	3.4± 6.1	1.6± 5.7	2.4± 7.5	2.4± 7.5	9.5*± 14	6.9± 17

The increased incidences of fused sternebrae was seen above the concurrent controls at all doses in the first study and at the top dose in the second study and within or slightly above the historical

control data range in both studies. RAC considers that the fused sternebrae raises a concern for developmental toxicity. The finding *"severely fused sternebra (bony plate)"* was slightly but statistically significantly increased in the second study with a litter incidence of 3. This finding was also observed in the control group of the first rabbit study, with the same incidence (3) and is therefore considered an incidental finding.

***Table**: Incidences of fused sternebra, severely fused sternebra and septum ventricular defects in the first (Anonymous, 2001, 2001/1016351) and the second (Anonymous, 2001 2001/1016351) rabbit prenatal toxicity study.* HCD = Historical control data covering a time span of roughly ± 5 years around the experimental date. [1]when excluding dam #87 (which had 100% affected foetuses (=1 affected pup)/litter) from the evaluation the incidence decreases to 11.1%. [2]comparable incidence as the control group of the first study

Finding	Control	Low dose	Mid Dose	High Dose
Fused sternebra - First study				
Fetal incidence [N (%)] (HCD 0.0-10.7)	2 (1.3)	9 (5.5)	10 (6.2)	11 (10)
Litter incidence [N (%)] (HCD 0.0-50.0%)	2 (8.0)	**9* (36)**	**8* (35)**	**9** (47)**
Affected fetuses/litter (Mean) [%] (HCD 0.0-13.5%)	0.9	**5.1****	**6.5****	**15.2**[1]**
Fused sternebra - Second study				
Fetal incidence [N (%)] (HCD 0.0-10.7)	5 (3.0)	8 (4.8)	3 (2.0)	16 (12)
Litter incidence [N (%)] (HCD 0.0-50.0%)	4 (17)	5 (21)	2 (8.0)	8 (36)
Affected fetuses/litter (Mean) [%] (HCD 0.0-13.5%)	2.7	4.6	2.5	11.2
Membranous ventricular septum defect – Second study (not seen in first study)				
Fetal incidence [N (%)]	1 (0.6)	0 (0.0)	1 (0.7)	3 (2.2)
Litter incidence [N (%)] (HCD: 0 – 17.6%)	1 (4.2)	0 (0.0)	1 (4.0)	3 (14)
Affected fetuses/litter (Mean) [%]	0.5	0.0	0.5	2.4
Sternebrae severely fused (bony plate) – First study				
Fetal incidence [N (%)]	3 (2.0)	0 (0.0)	0 (0.0)	1 (1.0)
Litter incidence [N (%)]	3 (12.0)	0 (0.0)	0 (0.0)	1 (5.3)
Affected fetuses/litter (Mean) [%]	2.6	0.0	0.0	1.8
Sternebrae severely fused (bony plate) – Second study				
Fetal incidence [N (%)]	0 (0.0)	0 (0.0)	1 (0.7)	3 (2.2)
Litter incidence [N (%)]	0 (0.0)	0 (0.0)	1 (4.0)	3 (14)
Affected fetuses/litter (Mean) [%]	0.0	0.0	0.5	**2.2*[2]**

Development: Developmental toxicity investigated in generation toxicity studies

Stillborn and reductions in viability

An increased litter (11 (46%) vs 2 (8.3%) in control) and foetal (17 (5.1%) vs 2 (0.6%) in control) incidence in the number of stillborn F1 pups and a decreased viability index of F2 pups between PND 0-4 (92% vs 97% in control) were reported at the top dose in the 2-generation reproduction toxicity study in rats. These incidences were within the historical control data range. However, RAC notes that the concurrent control is the most relevant control and that these effects show a dose-response with some effects at 500 ppm and no effects at 0, 50 and 150 ppm. Thus, RAC considers that effects on stillborn index and reductions in viability index raise a concern for developmental toxicity.

Pup body weight

Significant effects on body weight were essentially absent at birth in the offspring animals. Mean pup body weights of F1 pups in the 500 and 1200 ppm dose test groups were statistically significantly reduced compared to controls from PND 4 onwards. Maternal body weights were between 4 and 7% lower than controls in the 500 ppm dose group and between 6 and 9% lower in the 1200 ppm dose group. In the F1 pups the body weights were 3-17% lower than in controls at 500 ppm and 5–35% lower than in controls at 1200 ppm (the table below).

***Table**: Maternal (F0) and pup (F1) body weights during lactation in the 2-generation reproductive toxicity study (Anonymous, 2001, 2000/1016869).* * = p < 0.05; ** P < 0.01.

	ppm				
Day	**0**	**50**	**150**	**500**	**1200**
F0 MATERNAL					
1	298.5	301.7	300.9	**277.6* (-7%)**	**278.9* (-7%)**
4	315.3	309	312.8	**294.4** (-7%)**	**287.2** (-9%)**
7	323.6	320.6	322.1	308.9 (-5%)	**299.2** (-8%)**
14	334.9	333.6	332	**315.2* (-6%)**	**305.2** (-9%)**
21	325.7	327.3	324	312.7 (-4%)	**307.7* (-6%)**
F1 LITTERS					
1	6.4	6.4	6.4	6.2 (-3%)	6.1 (-5%)
4 preculling	9.2	9.1	9.3	8.2 (-11%)	**8.1* (-12%)**
4 postculling	9.3	9.2	9.3	**8.2* (-12%)**	**8.1* (-13%)**
7	14.9	14.8	15.1	13.1* (-12%)	**11.9** (-20%)**
14	32	31.8	31.7	**27.7** (-13%)**	**23.4** (-27%)**
21	52.6	52.9	51.8	**43.8** (-17%)**	**34.0** (-35%)**

A similar picture with regard to pup body weights is seen in the second generation of this 2-generation toxicity study (the table below). Body weight effects are seen in the F2 pups from 150 ppm. As in F1 generation, no effects on pup body weight were observed at birth but the effect was statistically significant from PND 7 onwards.

***Table**: Maternal (F1) and pup body weights (F2 litters) during lactation in the 2-generation reproductive toxicity study (Anonymous, 2001, 2000/1016869).* * = p < 0.05; ** P < 0.01.

	ppm				
Day	**0**	**50**	**150**	**500**	**1200**
F1 MATERNAL					
1	308.7	306.0	299.9	**275.8** ** **(-11%)**	**248.7** ** **(-20%)**
4	317.9	320.3	309.6	**288.4** ** **(-9%)**	**256.2** ** **(-19%)**
7	327	328.9	319.4	**299.5** ** **(-8%)**	**265.7** ** **(-19%)**
14	347.2	345.9	342	**314.9** ** **(-9%)**	**276.6** ** **(-20%)**
21	330	330.6	330.2	313.4	**280.7** ** **(-15)**
F2 LITTERS					
1	6.4	6.4	6	6.2	6.2
4 preculling	9.2	9.5	8.4	9.2	8.5
4 postculling	9.2	9.6	8.5	9.2	8.5
7	14.8	15.3	**13.2*** **(-11%)**	14.2 (-4%)	**11.8** ** **(-20%)**
14	31.9	32.7	**29.2*** **(-9%)**	**28.8** ** **(-10%)**	**22.3** ** **(-30%)**
21	51.2	52.3	**47.1*** **(-8%)**	**44.3** ** **(-14%)**	**32.7** ** **(-36%)**

It was expected by the DS that pups showed more severe effects on body weights on PND 14 and PND 21 since they were estimated to receive higher daily doses of dimoxystrobin compared to the dams at the same dietary doses during the last week of lactation. The dietary exposure was continuous throughout the 2-generation study (and the supplementary modified one-generation study, see below), and dietary concentrations were not reduced during lactation. A comparison of the actually measured maternal (F0 and F1) dimoxystrobin doses is shown in the table below. When comparing the measured substance intakes between the first and the second generation of this study, it is evident, that F1 parents during premating and F2 pups (during the last week of lactation) had considerably higher daily substance intakes compared to the respective values of the F0/F1 generation. The estimated daily values are considerably higher in pups during the last week of lactation compared to female adults (a dose of 227.7 mg/kg bw/day is estimated for F1 pups, while females consume only 168.2 mg/kg bw/day over the lactation period in the 1200 ppm dose group). This difference is even more pronounced in the F2 pups of the 1200 ppm dose group with an estimated daily test substance intake of 315.4 mg/kg bw/day during the last week of lactation compared to 168 mg/kg bw/day in the respective high dose females (table below).

***Table**: Approximate daily compound exposure (mg/kg bw/day) to parental (F0 and F1) animals and estimated daily exposure (mg/kg bw/day) to F1 and F2 pups during the last week of lactation (excluding amount transferred in milk) in the 2-generation study.*

	Compound exposure (ppm)				
ppm in diet	**0**	**50**	**150**	**500**	**1200**
F0 male (premating)	0	4.7	14.1	46.4	108.8
F0 female (premating)	0	5.1	15.6	49.9	118.9
F0 Female (gestation)	0	4.5	13.6	43.6	102.5
F0 Female (lactation)	0	7.6	22.1	74.5	168.2

F1 pups	0	9.8	29.7	96.3	227.7
F1 pups (not corrected)	0	6.1	17.9	59.1	135.4
F1 Male (premating)	0	5.9	18.2	61.8	156.4
F1 Female (premating)	0	6.2	18.6	63.7	159
F1 Female (gestation)	0	4.6	13.6	46.1	107.8
F1 Female (lactation)	0	7.4	22.4	75.4	168
F2 pups	0	12.1	36.8	125.5	315.4
F2 pups (not corrected)	0	6	18	60.8	138

RAC notes that a higher daily compound intake by pups is a plausible (although not conclusive) explanation for the difference in magnitude of effects between dams and pups during the last week of lactation. However, this is not considered by RAC as a justification for disregarding the effects on pup body weight. Pups were severely affected already before they started self-feeding. In addition, even though for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure, developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. These effects can be also manifested at any point in the life span of the organism (CLP Annex I: 3.7.1.4.). The effects on pup body weight were consistently reported in all generations and in all available generational studies. Thus, RAC considers that the severe reductions in pup body weight raise a concern for developmental toxicity.

Microcytic hypochromic anaemia

The modified one-generation reproductive toxicity study shows significant reductions in several haematological parameters in exposed pups as compared to controls on PND 21, especially in RBC (33 and 35%), HGB (44 and 47%) and HCT (50 and 51%) (at top dose in males and females, respectively). In parental animals the slight effects on RBC pointed to the opposite direction than in pups (i.e. the values were higher in treated parental animals as compared to controls) and the effects on the other haematological parameters were of lower severity than in pups. The daily doses after pups start self-feeding may have been higher than those in adults, but as discussed above, this is not considered by RAC as a reason for discounting the effects observed in pups. There is also no information allowing to conclude that the exposure of the pups via parental animals did not play a role in the manifestation of the effects in pups. Thus, RAC notes that the severe anaemia in pups induced by dimoxystrobin exposure raises a concern for developmental toxicity.

Cardiomegaly

Cardiomegaly was determined at pup necropsy and was seen in F1 (2-generation study and modified one-generation reproductive toxicity study) and F2 (2-generation study) pups sacrificed at PND21 and in none of the pups sacrificed or that died at PND < 1 (including stillborn pups) or at PND 4 at any dose group. All F1 parental animals were necropsied and the only finding in heart was one isolated heart dilatation in one male at 500 ppm. No findings in the hearts of the offspring were either observed in the rat prenatal developmental toxicity study (Anonymous 1999 a, 1999/11680). There is information in the literature indicating that young animals can undergo cardiac remodelling secondary to nutritional anaemia (Tanne *et al.*, 1994) supporting the link between anaemia and cardiac effects in pups. After dimoxystrobin exposure, cardiomegaly was

observed in pups only at PND21 and correlated with the severe anaemia present in offspring animals. Thus, considering that cardiomegaly is an effect of concern and even if it would be secondary to anaemia, anaemia would be considered by RAC as a specific mechanism that does not reduce the level of concern for cardiomegaly. RAC considers that cardiomegaly raises a concern for developmental toxicity.

Other gross necropsy observations

Reductions in absolute and/or relative weight of different organs (brain, thymus, spleen and liver) were reported at the top and mid dose of F1 and F2 generations of the 2-generation toxicity study and at the top dose in pups of the modified one-generation reproductive toxicity study. These effects can be partly, but not completely, explained by the reductions in the pup body weight. Anaemia can be the explanation for the organ discoloration found mainly in liver and kidney. Hypoplasia of thymus was also detected at the top dose of the F1 and F2 generation, although statistical significance was reached only in the F1 generation. This hypoplasia of thymus at the high dose may be related to anaemia, which is supported by finding in open scientific literature showing lesions in spleens and thymuses of the iron-deficient rats (Rothenbacher and Sherman, 1980). However, the mechanism(s) of the observed effects were not investigated. The milky fluids reported in the abdomen and the breast cavity of pups in the modified one-generation reproductive toxicity study are considered to be secondary to the heart-insufficiency (cardiomegaly).

Overall, RAC notes that the effects observed especially in the thymus and spleen raise concern for developmental toxicity.

Conclusion

RAC concludes that dimoxystrobin meets the CLP criteria for Repr. 2, H361d because of anaemia, cardiomegaly and severe reductions in body weight in rat pups. The co-occurring maternal toxicity was not severe and therefore the developmental effects are considered not to be secondary non-specific consequences of maternal toxicity. RAC concludes that the increased incidences in fused sternebrae in rabbits and the increased number of stillborn F1 pups and a decreased viability index of F2 pups between PND 0-4, hypoplasia of thymus and decreases in organ weights (especially in thymus and spleen) in the two-generation study in rats increase the level of concern and these effects are considered as supportive evidence for classification for developmental toxicity. Themode of action of the developmental effects have not been demonstrated, but RAC concludes that even if the effects in developing animals were secondary to anaemia, anaemia would be considered by RAC as a specific mechanism that does not reduce the concern for the adverse effects in development. As in the two-generation studies, exposure is continuous from the prenatal period, the role of exposure via the mother cannot be excluded even if effects would appear only postnatally. However, according to CLP, developmental toxicity is not limited only to effects via parental animals as it includes any effect which interferes with normal development of the conceptus resulting also from exposure of the developing offspring postnatally to the time of sexual maturation.

RAC concludes that dimoxystrobin warrants **classification as Repr. 2, H361d.**

Lactation

There is no data on dimoxystrobin contents in rat milk, however, from livestock studies there is no evidence indicating the existence of considerable amounts of dimoxystrobin or metabolite contents in milk (especially at lower concentrations). In lactating goats after 5 consecutive daily oral administration of ^{14}C-dimoxystrobin, the test item was rapidly absorbed and almost completely excreted. There was no indication of accumulation of ^{14}C-dimoxystrobin in goat milk. The parent compound was detected in milk at maximum levels of 0.1% of administered doses of 288 ppm (10.3 mg/kg bw/day). At lower concentrations, the radioactive residue in milk was even

below 0.1% (7-day study in lactating goats that received up to 11.8 ppm ^{14}C-dimoxystrobin in feed (0.19 mg/kg bw/day)). In a livestock feeding study, lactating cows were dosed with up to 25 ppm dimoxystrobin for 30 days (up to 0.64 mg/kg bw/day) and detected residues of ^{14}C-dimoxystrobin were below the limit of quantification of 0.010 ppm.

Milk is generally a poor source of iron. In addition, according to published literature, milk of dams suffering from iron deficiency anaemia contains less iron than usual (e.g. 34 µg/g dry wet in controls vs. 22 µg/g dry wet in treated dams), so that these dams are even less able to transfer sufficient iron to the young via the milk in the early postpartum period.

Substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned based on:

a) human evidence indicating a hazard to babies during the lactation period; and/or
b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or
c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

No human data is available for dimoxystrobin with regard to potential hazards via lactation. In ADME / residue studies on lactating ruminants (dosed up to 25 ppm), no detectable levels of dimoxystrobin in milk were determined. In rat reproduction studies, which were dosed up to 1200 ppm, no analytical determination of the rat milk had been conducted. Roth and Smith (1988) documented that mother rats with nitrite-induced iron deficiency produced milk of reduced iron content. However, there are no data about the iron content in milk generated by dimoxystrobin-exposed females.

In conclusion, there is no clear evidence of adverse effect in the offspring due to transfer of dimoxystrobin in the milk or adverse effect on the quality of the milk. Moreover, there is no toxicokinetic evidence indicating that the substance is present in potentially toxic levels in breast milk. Thus, overall, **RAC does not support the DS's proposal for classification of dimoxystrobin for effects on or via lactation H362 (may cause harm to breast-fed children).**

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Dimoxystrobin has a current entry in Annex VI of CLP as Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410) with an M-factor of 10.

Dimoxystrobin, being a fungicidal active substance, has gone through the following regulatory processes:

(i) an initial risk assessment provided by the Rapporteur Member State United Kingdom (DAR published in 2005)
(ii) the current CLH process

(iii) a renewal of the approval of the active substance (RAR prepared according to the Commission Regulation (EC) No 1107/2009 by Hungary and Ireland on August 2017)

Additional information was provided by the PPP Applicant during the renewal of the approval of the active substance dimoxystrobin that included updates of already reviewed studies. These studies have already been evaluated within the Annex I inclusion of dimoxystrobin and were provided in the EU Review documents of dimoxystrobin (Draft Assessment Report (DAR), Vol. 3, B.9, 2005; EFSA Scientific Report (2005) 46, 1-82; Renewal Assessment Report (2017), Volume 3–B.8 (AS) & B.9 (AS)). The information included statistical re-evaluations, elaborations on study validity and missing analytical tables, update of endpoints and the inclusion of ECx re-calculations and relevant study summaries. These data were assessed by RAC for the preparation of this opinion.

Biodegradation

One ready biodegradability test following OECD TG 301F (biochemical oxygen demand) (Werner, 1999) was available. The degree of biodegradation (% biological oxygen demand/theoretical oxygen demand) over the 28-day test duration was in the range 0-10%. In a surface water simulation biodegradation test (OECD TG 309), the mineralisation of dimoxystrobin was below 1% after 59 days of incubation (Yeomans, 2014). Two water/sediment studies were available. In the laboratory aerobic water/sediment study investigating two systems (A=pond and B=pond-like side arm river), the DT_{50} was calculated after kinetic evaluation from Budde (2015) to be 298 and 835 days, respectively (Ebert, 2000). An outdoor aerobic sediment/water study was also reported and the resulting calculated DT_{50} after the kinetic evaluation from Budde (2015) was 27 days (Fendt, 2001).

Hydrolysis

The hydrolytic stability of dimoxystrobin was studied at 25°C (pH 5,7 and 9) and 50°C (pH 4,7 and 9). The results of the hydrolysis study indicate that dimoxystrobin was stable at all pH-values (McKenna & Baucom, 1997).

Photolysis

The aqueous photolysis of dimoxystrobin was investigated in two studies using sterile buffer and natural surface water. Dimoxystrobin photodegraded slowly in the sterile water with DT_{50}s of 62 and 64 days (2 radiolabels) (Singh, 1998, kinetic evaluation Budde, 2014). Faster photolysis was observed in the natural water study with a DT_{50} of 14 days (Goetz & Moss, 1998, kinetic evaluation Budde, 2014).

Conclusion on degradation

Dimoxystrobin was not considered rapidly degradable for the purpose of classification and labelling by the DS, namely biotic and abiotic degradation in the aquatic environment did not exceed a level of 70% or above. This was based on the available ready biodegradability test, the data from the hydrolysis studies and the data from water/sediment studies showing limited degradation.

Bioaccumulation

The bioaccumulation potential of dimoxystrobin was considered to be low based on a measured $BCF_{whole\ fish}$ of 84 L/kg for *Oncorhynchus mykiss* (Anonymous, 1999a) and a Log P_{OW} of Dimoxystrobin which is 3.59. The lipid normalised kinetic bioconcentration factor BCF_{KL} was re-calculated to be BCF_{KL} = 91 L/kg and it was presented in additional information provided by the PPP Applicant during the renewal of the approval of the active substance dimoxystrobin. The BCF was normalised to 6% lipid content, as a worst-case value. The mean lipid content in whole fish was reported to be 5.1%. This is a GLP study and fulfils all the validity criteria of OECD TG 305.

The DS considers dimoxystrobin to have low potential for bioaccumulation based on available data, as the experimental BCF value did not exceed the cut-off value of 500 L/kg and the log K_{OW} was below 4.

Aquatic Toxicity

Aquatic toxicity tests for both acute and chronic aquatic toxicity are available for all three trophic levels. Only reliable studies from each trophic level with the most conservative endpoint are summarised in the table below for acute and chronic aquatic toxicity. Based on the additional data provided by the PPP Applicant, some endpoint values may have been re-calculated and these updated values are shown in the table 1 below, where relevant. The re-calculation of toxicity values has no impact on the proposed classification. Dimoxystrobin's major metabolites and formulations are shown to be of lesser toxicity based on data provided in the RAR (2017), DAR (2005), and additional information provided by the PPP Applicant and, thus, were not evaluated further for classification purposes.

***Table**: Reliable studies from each trophic level with the most conservative endpoint for acute and chronic toxicity. Endpoints in bold are the key critical endpoints for classification purposes*.

Acute toxicity				
Species	**Method**	**Endpoint (Effect Observed)**	**Toxicity value (mg a.s./L)**	**Reference (as in CLH Report unless otherwise stated)**
Fish				
Oncorhynchus mykiss	EPA 72-1	LC_{50} (96h), (Mortality)	0.0434 mm	Anonymous, 1998a
Oncorhynchus mykiss	EPA 72-3(a), EPA 850.1075	LC_{50} (96h) , (Mortality)	0.0465 (1) nm	Anonymous, 2000
Invertebrates				
Daphnia magna	OECD TG 202	EC_{50} (48h) (Immobility)	0.0394 nm	Dohmen P., 1999a
Americamysis bahia	EPA 72-3(b), EPA 850.1035	LC_{50} (48h) , (Mortality) EC_{50} (96h), (Mortality)	0.0429 mm 0.0272 mm	Wyskiel D.C. *et al.*, 2000b
Algae				
Navicula pelliculosa	EPA 123-2, EPA 850.5400	E_rC_{50} (72h), (Growth rate)	**0.0078 mm**	Wyskiel D.C. *et al.*, 2000d
Pseudokirchneriella subcapitata	OECD TG 201	E_rC_{50} (72h), (Growth rate)	0.1526 nm	Kubitza J. 1999
Chronic toxicity				
Species	**Method**	**Endpoint (Effect Observed)**	**Toxicity value (mg a.s./L)**	**Reference (as in CLH Report unless otherwise stated)**
Fish				
Oncorhynchus mykiss	OECD TG 210, EPA 72-4 (a)	NOEC, (Growth, sublethal effects)	**0.001 (1) nm**	Anonymous, 1999a
Pimephales promelas	OECD TG 210, EPA 72-4 (a)	NOEC, (Mortality)	0.016 nm	Anonymous, 2000
Oncorhynchus mykiss (2)		NOEC, (Growth, sub-lethal effects)	0.012 nm (Peak Conc)	Anonymous, 2008a (as in RAR 2017)

	OECD TG 210, EPA 72-4, EPA 850.1400			
Invertebrates				
Daphnia magna	EEC XI/691/86, DIN 38412 (Entwurf 1981), OECD TG 202, EPA 660/3-75-009	NOEC, (Reproduction)	0.0125 nm	Jatzek H.-J., 2000 a
Algae				
Navicula pelliculosa	EPA 123-2, EPA 850.5400	NOE_rC (120h) (Growth rate)	0.00122 (3) mm	Wyskiel D.C. *et al.*, 2000 d
Pseudokirchneriella subcapitata	OECD TG 201	E_rC_{10} (72h) (Growth rate)	**0.0035 (1) nm**	Kubitza J. 1999

(1) Data presented as the re-calculated values provided by the applicant as part of a recent Request for Additional Information, the Applicant submitted new information to EFSA.

(2) The study was available in RAR 2017 but was not included in CLH Report. Study results do not impact classification, detailed explanation is provided in the Supplemental Information, below. It is shown in the table for completeness.

(3) The OECD TG 201 guideline validity criteria for the study were confirmed to for the 72h duration alone thus this NOE_rC (120h) value cannot be used for classification purposes.

nm= nominal concentrations

mm=measured concentrations

Acute aquatic toxicity

Data is available for all three trophic levels (fish, crustacean, algae/aquatic plants). Five fish studies, three invertebrate studies, and four algae studies were evaluated in the CLH report as reliable and valid for classification purposes. Reliable studies for each trophic level with the most conservative endpoints are shown in the Table above. The lowest effects endpoint is a 72h E_rC_{50} value of 0.0078 mg/L (measured concentration) derived from a study on the algae, *Navicula pelliculosa*. Based on this endpoint, the DS proposes a classification of Aquatic Acute 1 (H400) with an acute M factor of 100.

Chronic aquatic toxicity

Data is also available for all three trophic levels (fish, crustacean, algae/aquatic plants). Three fish studies, one invertebrate study and four algae studies were evaluated in the CLH report as reliable and valid for classification purposes. Reliable studies for each trophic level with the most conservative endpoints are shown in the Table. A study by Anonymous (2008a) that was available in the RAR (2017) but was not included in the CLH Report is also shown in the Table above. The study results do not impact classification. The executive summary of the study and detailed explanation on the assessment of the study is provided in the Supplemental Information, below. It is shown in the Table for completeness purposes.

The lowest chronic fish toxicity endpoint is a NOEC = 0.001 mg a.s./L, (nominal concentration) from a ELS study on *Oncorhynchus mykiss*. Based on this endpoint and taking into account that dimoxystrobin is not rapidly degradable (and has low potential for bioaccumulation), the DS proposes a classification of Aquatic Chronic 1 (H410) with an M factor of 100.

Comments received during consultation

Comments were received from four MSs. Three of the MSs explicitly supported the DS on the classification proposal, while requesting some clarifications on certain studies. The fourth member state requested clarification on the two key studies leading to classification, without commenting on the classification proposal. Clarifications were given by the DS in the RCOM document. The clarification/statement given by the DS regarding the key study by Anonymous (1999b), 1999/10521 (*Oncorhynchus mykiss*, NOEC = 0.001 mg a.s./L) lead to the conclusion by the DS that the study is invalid and should not be used for classification purposes. More explicitly the DS stated that the calculated hatching success in the control replicates as well as the mean hatching success were below the control survival validity criterion stipulated in the OECD TG 210.

Assessment and comparison with the classification criteria

Degradation

Dimoxystrobin is not considered by the DS to be readily biodegradable based on data from a valid study performed under OECD TG 301 F (Manometric Respirometry) (Werner, 1999). The degree of biodegradation (% biological oxygen demand/theoretical oxygen demand) over the 28-day test duration was in the range 0-10%, which is below the 60% of the theoretical maximum criterion for readily degradable substances. This is also supported by limited mineralisation in an aerobic surface water-simulation biodegradation test (OECD TG 309) and long DT_{50}s in two water/sediment studies. Also, dimosystrobin was shown to be hydrolytically stable under high pH and temperatures. RAC agrees with the DS in concluding that dimoxystrobin is considered not rapidly degradable for the purpose of classification and labelling.

Bioaccumulation

Dimoxystrobin has a lipid-normalised kinetic bioconcentration factor BCF_{KL} = 91 L/kg which is below the criterion of BCF of ≥ 500 L/kg. It also has a log P_{OW} = 3.59, which is below the Log P_{OW} ≥ 4 criterion for substances with bioaccumulation potential. Thus, RAC agrees that dimoxystrobin is not bioaccumulative under CLP.

Aquatic Toxicity

The most sensitive species for acute aquatic toxicity is *Navicula pelliculosa* with an E_rC_{50} (72h) value of 0.0078 mg a.s./L, based measured concentrations. Acute toxicity for fish and invertebrates were reported for *Oncorhynchus mykiss* as LC_{50} (96h) = 0.0434 mg a.s./L (measured concentrations) and for *Daphnia magna* EC_{50} (48h) = 0.0394 mg a.s./L (nominal concentration). RAC supports the DS on the use of the *Navicula pelliculosa*, E_rC_{50} (72h) of 0.0078 mg a.s./L, based on measured concentrations, as the basis for the aquatic acute classification.

The most sensitive species for chronic aquatic toxicity is *Oncorhynchus mykiss* with a NOEC (97d) of 0.001 mg a.s./L, based on nominal concentrations. The lowest chronic toxicity endpoint for invertebrates was a *Daphnia magna* NOEC (21d) of 0.0125 mg a.s./L (nominal concentrations) and for algae an E_rC10 (72h) of 0.0035 mg a.s./L from the *Pseudokirchneriella subcapitata* study. The use of nominal concentration for the above-mentioned endpoints is valid as concentrations were maintained with in the acceptable range throughout the testing periods as stated in the respective guidelines. RAC considers the *Oncorhynchus mykiss* study as valid (more in-depth analysis is presented in a subsequent section) and agrees to use the derived NOEC value (=0.001 mg a.s./L) as the basis for the chronic classification.

Conclusion on classification

Based on an E_rC_{50} (72h) of 0.0078 mg a.s./L (*Navicula pelliculosa*), which is ≤1 mg/L, RAC agrees that dimoxystrobin warrants classification as:

Aquatic Acute 1 (H400), M=100 (0.001 < L(E)C_{50} ⩽ 0.01 mg/L).

Dimoxystrobin is not rapidly degradable and is not bioaccumulative in the aquatic environment. Based on the chronic endpoint NOEC (97d) of 0.001 mg a.s./L (*Oncorhynchus mykiss*), which is below 0.1 mg/L, RAC agrees that dimoxystrobin warrants classification as:

Aquatic Chronic 1 (H410), M=100 (0.0001 < NOEC ⩽ 0.001 mg/L).

Additional references

Request for Additional Information (EFSA). BASF DocID 2019/2045936. Version 2, 25/Aug/2019

Amendment No1 to the report BAS 505 F, Early Life-Stage Toxicity Test on the Rainbow Trout (Oncorhynchus mykiss WALBAUM 1792). BASF DocID 2019/2047112, 21/08/2019.

Addendum to study BASF DocID: 2000/5128. Growth and Reproduction Toxicity Test with BAS 505 F and the Freshwater Alga, Navicula pelliculosa. BASF DocID 2019/1006413. 10/01/2019

Renewal Assessment Report (RAR) Dimoxystrobin, July 2017.

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).