Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

dimethomorph (ISO); (*E*,*Z*)-4-(3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl)morpholine

EC Number: 404-200-2
CAS Number: 110488-70-5; (1135441-72-3)

CLH-O-0000001412-86-298/F

Adopted

20 September 2019

20 September 2019

CLH-O-0000001412-86-298/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: **dimethomorph (ISO); (*E,Z*)-4-(3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl)morpholine**

EC Number: **404-200-2**

CAS Number: **110488-70-5; (1135441-72-3)**

The proposal was submitted by **the Netherlands** and received by RAC on **20 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 Netherlands 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 **7 January 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **8 March 2019**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Ivan Dobrev**

Co-Rapporteur, appointed by RAC: **Anja Menard Srpcic**

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 **a simple majority of all members present and having the right to vote**.

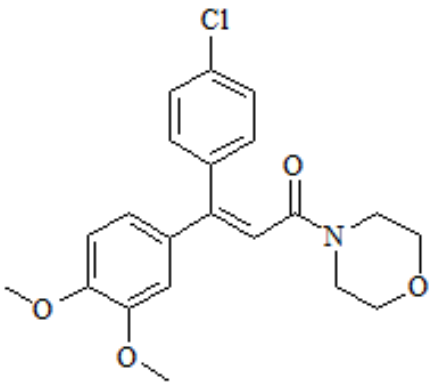
Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	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	613-102-00-0	dimethomorph (ISO); 4-(3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl)morpholine	404-200-2	110488-70-5; (113544 1-72-3)	Aquatic Chronic 2	H411	GHS09	H411			
Dossier submitters proposal	613-102-00-0	dimethomorph (ISO); (*E,Z*)-4-(3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl)morpholine	404-200-2	110488-70-5; (113544 1-72-3)	**Retain** Aquatic Chronic 2 **Add** Repr. 1B	**Retain** H411 **Add** H360FD	**Retain** GHS09 **Add** GHS08 Dgr	**Retain** H411 **Add** H360FD			
RAC opinion	613-102-00-0	dimethomorph (ISO); (*E,Z*)-4-(3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl)morpholine	404-200-2	110488-70-5; (113544 1-72-3)	**Retain** Aquatic Chronic 2 **Add** Repr. 1B	**Retain** H411 **Add** H360F	**Retain** GHS09 **Add** GHS08 Dgr	**Retain** H411 **Add** H360F			
Resulting Annex VI entry if agreed by COM	613-102-00-0	dimethomorph (ISO); (*E,Z*)-4-(3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl)morpholine	404-200-2	110488-70-5; (113544 1-72-3)	Repr. 1B Aquatic Chronic 2	H360F H411	GHS08 GHS09 Dgr	H360F H411			

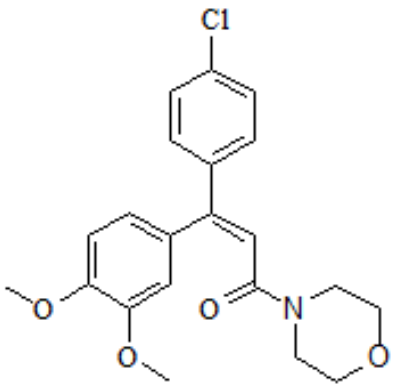
GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Dimethomorph is a cinnamic acid derivative and a member of the morpholine group of fungicides. Its mode of action is the disruption of the fungal cell wall formation. The active substance in plant protection products consists of two enantiomers, the E-isomer and Z-isomer with E/Z isomer ratio ranges from 40/60 to 50/50 % w/w. Fungicidal activity is primarily associated with the Z isomer.



E-Isomer



Z-Isomer

Dimethomorph is part of the AIR3 renewal programme for active substances (Commission Implementing Regulation (EU) No 844/2012) and has a harmonised classification in Annex VI as Aquatic Chronic 2 (H411).

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Reproductive toxicity of dimethomorph was evaluated in a two-generation reproduction toxicity study and an extended one-generation reproduction toxicity study (EOGRTS) in rats, as well as in pre-natal developmental toxicity studies in the rat and rabbit. In addition, adverse effects on the prostate and the testes observed in a 90-day and 1-year repeated dose toxicity studies in dogs have been considered with regard to classification of reproductive toxicity.

Sexual function and fertility

In a two-generation reproduction toxicity study (B.6.6.1.1), Sprague-Dawley rats were fed diets containing dimethomorph technical at dose levels of 0, 100, 300 and 1000 ppm (0, 6.9/8.0, 21/24 and 69/79 mg/kg bw/day for males/females, respectively). No treatment-related effects on mortality or clinical signs of toxicity were observed. Reduced body weight gains were observed during the pre-mating treatment period at 1000 ppm in the P0 (14.7%) and F1 females (6.8%, not statistically significant). A slight, but statistically significant (using ANOVA) reduction in the gestational length was reported at the top dose in both the P0 as well as F1A dams. A subsequent re-evaluation using the Dunnett test (two sided) revealed no statistical significance for this effect. Mating and fertility indices were not affected in this study. Sperm parameters, oestrous cycle, sexual organ weights and age of sexual maturation were not investigated in this study.

In an EOGRTS (B.6.6.1.2), dimethomorph was administered in the diet to groups of 25 male and 25 female Crl:WI(Han) Wistar rats at nominal dose levels of 0, 300, 800 and 1600 ppm corresponding to average doses of 0, 26, 70 and 144 mg/kg bw/day. No substance-related mortalities or adverse clinical observations were noted in any group. Adverse effects on liver weight were observed in P0 and cohort 1A animals at 800 and 1600 ppm, and the effect was associated with centrilobular hepatocellular hypertrophy in P0 and cohort 1A females at the high dose. Decreased absolute and relative seminal vesicle weight was observed in the males of cohort 1A (1600 ppm) and 1B (800 and 1600 ppm). Relative prostate weight was decreased in the cohort 1B males (800 and 1600 ppm). At 1600 ppm, the gestation length was significantly decreased and pup body weight development was affected (11% and 12% lower than in controls on PND 1 in males and females, respectively), but the effects did not influence the pup survival. A slight effect on anogenital distance/index in the mid and high dose males as well as a significant delay in vaginal opening (at 1600 ppm) and preputial separation (at 800 and 1600 ppm) were observed.

The DS considered the statistically significant reduction in gestation length (21.4 vs 22.3 days in the control group) observed in the EOGRTS as adverse and relevant for humans, and thus as clear evidence for an adverse effect on fertility or sexual function. This effect was slightly below the lower range of the historical control data (21.5 days). Further, in line with this finding, dimethomorph did shorten the gestational length at the top dose in P0 (21.8 vs 22.0 days in control group) as well as F1A dams (21.7 vs 21.9 days in control group) in the two-generation study (see the table below). However, the observed effect was not statistically significant using the Dunnett test.

***Table**: Summary of gestational lengths in the two-generation study and EOGRTS in rats*

	Gestation duration (days)					
Dose (ppm)	**0**	**100**	**300**	**800**	**1000**	**1600**
2-Gen P0	22.0 ± 0.3	22.1 ± 0.3	21.9 ± 0.4		**21.8 ± 0.4***#	
2-Gen F1A	21.9 ± 0.4	21.9 ± 0.3	22.1 ± 0.3		**21.7 ± 0.5***#	
2-Gen F1B	21.9 ± 0.2	22.2 ± 0.5	21.9 ± 0.3		21.8 ± 0.4	
EOGRTS	22.3		22.2	22.0		**21.4****
HCD	21.5 - 22.3					

*p<0.05 (ANOVA); **p<0.01 (Dunnett test); # upon re-evaluation using Dunnett test, statistical significance was not reached

The maternal effects in the EOGRTS at the highest dose consisted of decreased food consumption and body weight/body weight gain, as well as of changes in clinical chemistry parameters and pathological evidence of liver toxicity. The reduced gestation length was considered unlikely to be secondary to the reductions in food consumption and body weight gain. Based on the statistically significant reduction in gestation length observed in EOGRTS, the DS prosed to classify dimethomorph as Repr. 1B (H360F) for effects on sexual function and fertility.

The DS considered further a decrease in the prostate weight combined with prostatic interstitial fibrosis observed in the 90-day and 1-year repeated dose toxicity studies with dogs as well as an increase in testes weight in the 1-year dog study indicative for possible effects on the fertility and sexual function. Since these effects were observed in the presence of general toxicity, in the view of DS it was unclear whether they were direct effects of dimethomorph on the reproductive system or secondary to the general toxicity. Notably, no such effects were observed in the available repeated dose toxicity studies with rats and mice.

Development

The developmental toxicity of dimethomorph was investigated in GLP- and guideline-compliant oral developmental toxicity studies and their respective preliminary studies, conducted in Sprague-Dawley rats and in New Zealand White rabbits as well as in the two generation study and EOGRTS in rats. In the view of the DS, the oral developmental toxicity studies showed no evidence of teratogenic or other developmental effects in the absence of significant maternal toxicity.

In the rat developmental toxicity study (B.6.6.2.3), maternal toxicity was manifested as decreased body weights, body weight gains, and reduced food consumption at 160 mg/kg bw/day (the highest dose tested). A slight and statistically non-significant increase in the number of total litter losses was reported at 160 mg/kg bw/day.

In the rabbit developmental toxicity study, maternal toxicity was expressed as intermittently reduced food consumption and body weight gain in dams at 300 mg/kg bw/day. An increased rate of abortions was reported at 650 mg/kg bw/day.

For the assessment of developmental toxicity, the DS considered several findings observed in the EOGRTS (B.6.6.1.2, on Wistar rats) such as the reduced anogenital distance and the delayed sexual maturation as adverse and relevant for classification. These effects were considered to be related to the anti-androgenic effect of dimethomorph and not secondary to maternal toxicity. This mode of action was considered relevant to humans and therefore classification for developmental toxicity in category Repr. 1B (H360D) was considered justified.

Comments received during public consultation

Four MSCAs, 1 manufacturer and 1 academic institution provided comments during the public consultation.

With respect to the assessment of sexual function and fertility, 2 MSCA supported the DS proposal for classification as Repr. 1B (H360F) while 1 MSCA concluded that there was no clear evidence for an adverse effect and proposed no classification for effects on sexual function and fertility. One MSCA questioned whether the delayed sexual maturation and reduced anogenital distance were effects on sexual function and fertility or development, and suggested consideration of the effects on prostate weight in rats and dogs and reduced seminal vesicle weight in rats as a strong supportive evidence for classification as Repr. 1B (H360F).

Considering effects on development, 1 MSCA supported the proposed classification on development based on the decreased anogenital distance, delayed sexual maturation and decreased seminal vesicle, prostate, and pup weight observed in the EOGRTS. While supporting classification as Repr. 1B (H360D), 1 MSCA was of the opinion that effects such as decreased anogenital distance, delay in preputial separation and decreased absolute and relative seminal vesicle and prostate weight cannot be clearly assigned to either impairment of sexual function and fertility or to developmental toxicity. One MSCA was of the opinion that findings observed in the EOGRTS (reduced anogenital distance, delay in preputial separation, reduced pup weight and reduced seminal vesicle and prostate weight) were indicative of effects on development meeting best the criteria for category 2.

One MSCA indicated that the prostate findings in dogs might also trigger a classification for STOT RE 2 if not used to support the current proposal for reproductive toxicity, and 1 MSCA proposed to make it clear that other endpoints such as STOT RE had not been taken into consideration.

Industry strongly disagreed with the DS proposal for Repr. 1B (H360FD). In a "*Position paper on the proposed classification of Dimethomorph*", industry provided an analysis of the reproductive

effects observed in the studies with dimethomorph in relation to previous ECHA classifications arguing that, on a weight of evidence basis, this proposal was clearly disproportionate. The authors concluded that the effects on F1 offspring observed in the EOGRTS were limited to a decreased body weight, a slight decrease in anogenital distance/anogenital index (AGD/AGI), and a delay in preputial separation and were as such not severe enough to warrant classification in Cat. 1B for both fertility and development.

In addition, industry provided a second document titled "*Dimethomorph. Assessment of Potential Endocrine Disruption of the Active Substance"* analysing the potential endocrine disruption (ED) properties of dimethomorph following the ED criteria laid down in Commission Regulation (EU) No 2018/605. The report was prepared to address a request of EFSA for an updated ED assessment according to the new EFSA/ECHA Guidance for the evaluation of the active substance dimethomorph in the course of the AIR3 process. The report concluded that "*…following the ED guidance document, it is not possible to have a firm conclusion on the ED properties of dimethomorph for humans and (wild) mammals"*. A new extended one-generation reproduction toxicity study (EOGRTS) with a second-generation cohort was proposed with the aim to clarify some uncertainties related to possible anti-androgenic effects (i.e. changes in ano-genital distance/index of males, delayed sexual maturation, and decreased seminal vesicle weight) observed in males at the high dose in the present EOGRTS.

Assessment and comparison with the classification criteria

Sexual function and fertility

Potential adverse effects on sexual function and fertility of dimethomorph were investigated in two GLP and Guideline compliant studies; a two-generation reproductive toxicity study in the rat at dietary doses up to 1000 ppm (69/79 mg/kg bw/day for males/females) (B.6.6.1.1) and a more recent EOGRTS in the rat at dose levels up to 1600 ppm (144 mg/kg bw/day, B.6.6.1.2).

In the two-generation study performed according to the OECD TG 416 (B.6.6.1.1), groups of 30 male and 30 female Sprague-Dawley rats received diets containing dimethomorph (purity 96.6%) at nominal concentrations of 0, 100, 300 and 1000 ppm (0, 7/8, 21/24 and 69/79 mg/kg bw/day in males and females, respectively) starting 100 days before mating and continuing during the breeding, gestation and lactation period for each of the two generations. The F1 generation consisted of 25 pairs per group. The study provides information on mating performance, conception, gestation, parturition, lactation and weaning, as well as on survival, growth and development of the offspring. Deviations from the current OECD TG 416 include missing measurements on sperm parameters, oestrous cycle length, age of vaginal opening and preputial separation, ano-genital distance and organ weight changes.

No clinical signs of toxicity or treatment-related effects on mortality were observed in parental animals. Only slight maternal toxicity was observed at the top dose and it consisted of reduced body weight/ body weight gain as compared to controls during the pre-mating period in P0 females (14.7%) and F1 females (6.8%, not statistically significant) at 1000 ppm (Table below).

***Table**: Mean body weight and mean body weight gain in females of P0 and F1 generations*

Dose level (ppm)		0	100	300	1000
P0	BW, week 15 (g)	292.3	291.2	280.8	**267.2***
	BW gain, week 1-15 (g)	138.0	137.5	128.3	**117.7***
	Food consumption week 1-14 (g)	18.3	18.5	18.3	17.5
F1	BW, week 15 (g)	292.4	285.2	281.0	277.4
	BW gain, week 1-15 (g)	183.4	178.2	174.4	171.0

* $p < 0.5$; analysis of variance with one factor treatment followed by Student Newman-Keuls test

No adverse effects were reported at any dose level for mating, fertility or gestation indices, or on the parturition for either generation. The length of gestation was slightly decreased in both the P0 and F1A generation at 1000 ppm as compared to the concurrent controls. The effect was statistically significant using ANOVA, but not by the Dunnett test. RAC considers the effect biologically non-significant due to the low magnitude of effect and as the mean lengths of gestation at the top dose of both generations are well within the historical control data range. No other effects relevant for the assessment of sexual function and fertility were observed in this study.

In the EOGRTS (B.6.6.1.2), dimethomorph (purity 99.7%) was administered in the diet to groups of 25 male and 25 female Crl:WI(Han) Wistar rats at nominal dose levels of 0, 300, 800 and 1600 ppm corresponding to average doses of 0, 26, 70 and 144 mg/kg bw/day. The premating treatment period lasted at least for 75 days. During lactation period, the dietary concentrations of dimethomorph were adjusted to 0, 150, 400, and 800 ppm in order to maintain constant dose levels despite of increased food intake.

There were no test substance-related clinical findings in P0 females during premating, gestation and lactation periods. Only limited maternal toxicity was observed at the top dose and it consisted of a decrease in body weight and body weight gain as compared to controls and reduced food consumption (Table below). An increase in liver weight and hypertrophy in combination with histopathological effects (lymphoid infiltration) was also reported at the high dose.

***Table**: Body weight development and change in food intake of P0 females during gestation and/or lactation phases*

Dose level [ppm]	**0**	**300**	**800**	**1600**
Body weight (as compared to controls on GD 20)		↓ (3%)	↓ (1%)	↓ **(6%)***
Body weight gain (as compared to controls on GD 0-20)		↓ (7%)	↓ (3%)	↓ **(11%)***
Body weight (as compared to controls on PND 21)		↓ (1%)	↓ (1%)	↓ **(4%)***
Food intake (as compared to controls on PND 1-21)		↓ (2%)		↓ **(6%)***

*p<0.05; (Dunnett test, two-sided)

The length of gestation was decreased slightly but dose-dependently when compared to the concurrent control group and reached a statistical significance at 1600 ppm ($p \leq 0.01$). The value of 21.4 days is slightly below the historical control range (21.5 to 22.3 days), while the concurrent control (22.3 days) is rather at the upper end of the historical control range.

The fertility index of 88% at 1600 ppm falls within the range of HCD for this strain of rats (HCD range: 84-100%, 36 studies, year 2000-2012).

A delayed onset of puberty was indicated by statistically significant delays in preputial separation at 800 ppm (males) and 1600 ppm (both sexes) in the study. The age at vaginal opening was delayed by two days which was statistically significant at 1600 ppm ($p<0.01$), exceeding also the range of the submitted historical control data (see Table below). According to the authors of the study, this delay was due to a decrease in body weight (i.e., delayed general development) at this dose level. The body weight on PND 21 was significantly reduced, by 8% as compared to controls, while there was no significant difference in the body weight on the day of vaginal opening. Reductions in body weight during post-natal development are known to cause delays in the onset of puberty. However, the reduced body weight of 8% during the initial post-natal period is considered by RAC not to fully explain the retarded onset of puberty since other chemicals (e.g.

fluxapyroxad) causing much larger body weight reduction on PND 21 have not shown similar effect on the age of puberty attainment. Thus, the delay of 2 days is considered by RAC as treatment related and adverse.

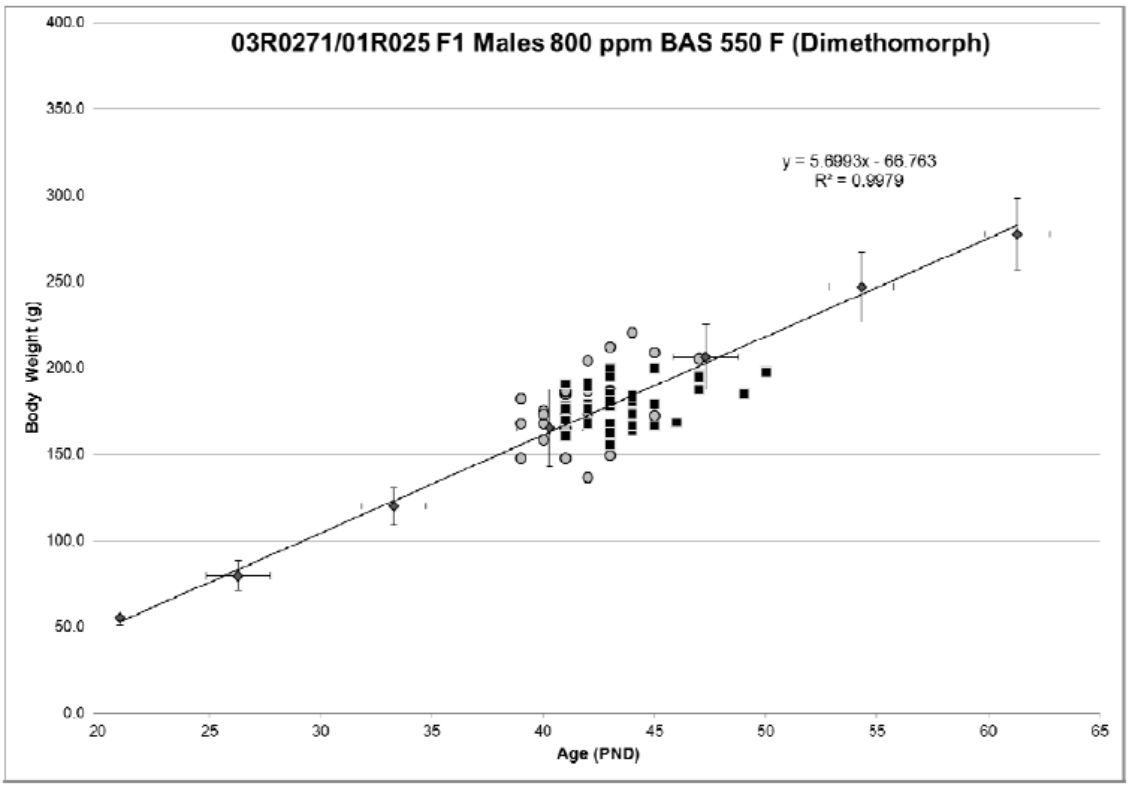
***Table**: Sexual maturation of F1 pups: age at vaginal opening in females*

Parameter	**Age at vaginal opening**			
Dose (ppm)	**0**	**300/150**	**800/400**	**1600/800**
Pups examined	40	40	40	40
Days to criterion	31.4	31.9	32.0	**33.4****
Historical control range (d)	30.0 - 32.1			
Additional historical control data (d)	29.5 - 31.9[#]			
Body weight at criterion (g)	96.4	96.9	95.9	96.9
Historical control range (g)	86.4 - 99.6			
Additional historical control data (g)	83.1 - 100.7[#]			

**p≤0.01 (Dunnett-test, two-sided); # additional historical control data (2010-2015) for vaginal opening as provided by the applicant upon request by EFSA during the renewal application

In males, preputial separation was dose-dependently and statistically significantly delayed at both 800 ppm and 1600 ppm dose levels (43.7 and 47.9 days versus 42.0 days in controls). Compared to controls, body weight of F1 males on PND 21 was slightly but statistically significantly (9%) reduced in the high dose group. However, an increase in body weight as compared to controls is noted at the day of achieving sexual maturation at 1600 ppm (13%, statistically significant). In order to evaluate whether the day of preputial separation might be secondary to alterations in body weight, the individual results of body weight and age at preputial separation were compared to the mean body weight development of the control animals.

Analysis of the individual data indicates that for the mid dose group the effect is less pronounced than the clear shift to the right (i.e., later maturation times) observed for the top dose males (Figure). Thus, the delay in preputial separation in the mid dose males is considered by RAC minimal and possibly related to the overall growth development. For the high dose males, the data indicate a clear effect on preputial separation that cannot be explained with delay in body weight development.



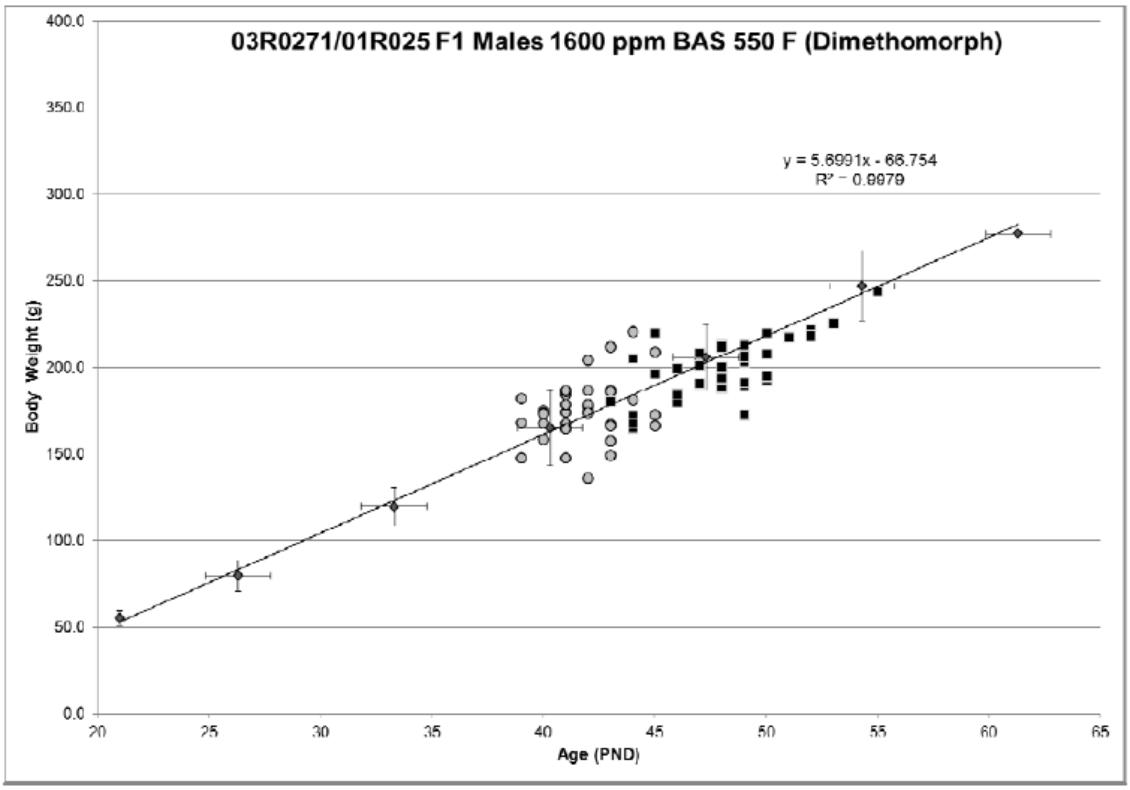


Figure: Age at sexual maturation of males exposed to dimethomorph at 800 ppm (upper panel) and 1600 ppm (lower panel) compared to body weight development. Round points: controls; square points: treated animals.

***Table**: Sexual maturation of F1 pups: age of preputial separation in males*

parameter	**Age of preputial separation**			
Dose (ppm)	**0**	**300/150**	**800/400**	**1600/800**
pups examined	38	40	39	39
Days to criterion	42.0	41.8	**43.7****	**47.9****
Historical control range (d)	39.7 - 42.5			
Additional historical control data (d)	40.5 - 45.2##			
Body weight at criterion (g)	176.6	174.0	180.5	**199.5****
Historical control range (g)	156.5 - 181.0			
Additional historical control data (g)	168.1 - 195.3##			

**p≤0.01 (Dunnett-test, two-sided); ## additional historical control data (2010-2015) for preputial separation as provided by the applicant upon request by EFSA during the renewal application

The delayed sexual maturation in rats appears to reflect the anti-androgenic effects of dimethomorph demonstrated in several *in vitro* assays. Dimethomorph tested positive for anti-androgenic activity in the Yeast Androgen Screening (YAS) assay using test systems with the hAR yeast strain and the MDA-kb2 cell line. No androgenic, estrogenic or anti-estrogenic effects were observed. Other anti-androgens such as vinclozolin, prochloraz, and flutamide cause also significant delay in puberty onset occurring together with changes in several other reproductive parameters.

In addition to strong evidence on effects on the sexual maturation and weak evidence on the effect on gestation length, reduction in seminal vesicle and prostate weights as well as increased testes weight without corresponding histopathological changes were observed in the adult F1A and F1B animals at 300, 800 and/or 1600 ppm (Table below). For F1A males, the study author attributed effects on seminal vesicle and prostate weights to the significantly decreased terminal body weight (11% lower than in controls) in this group. However, since both absolute and relative seminal vesicle weights were reduced at the high dose in F1A males, and as the effects are outside the historical control range for the F0 generation (0.905 – 1.426 g, no HCD for F1 generation), the effect is considered by RAC as treatment-related. Furthermore, the decreased absolute and relative weights of prostate and seminal vesicle in the mid and high dose groups of F1B are regarded by RAC as treatment-related.

***Table**: Prostate, testes and seminal vesicle weights in males of cohort 1A/1B rearing animals*

	Dose [ppm]	**Cohort F1A**		**Cohort F1B**	
		Abs. weight (% of control)	Rel. weight (% of control)	Abs. weight (% of control)	Rel. weight (% of control)
Prostate (g)	0	0.752	0.227	0.737	0.232
	300	**0.669*** (89)	0.212 (93)	**0.665*** (90)	0.217 (93)
	800	**0.643**** (86)	0.213 (94)	**0.625**** (85)	**0.203**** (87)
	1600	**0.576**** (77)	0.194 (85)	**0.542**** (74)	**0.176**** (76)
Testes (g)	0	3.637	1.096	3.554	1.124
	300	3.564 (98)	1.123 (102)	3.569 (100)	1.159 (103)
	800	3.766 (104)	**1.244**** **(113)**	3.709 (103)	**1.203*** **(107)**
	1600	3.746 (103)	**1.269**** **(116)**	**3.847**** **(108)**	**1.248**** **(111)**
Seminal vesicle (g)	0	1.004	0.304	0.949	0.300
	300	0.958 (95)	0.302 (99)	0.899 (95)	0.293 (98)
	800	**0.831**** (83)	0.275 (91)	**0.812**** (86)	**0.265*** (88)
	1600	**0.708**** (71)	**0.239**** (79)	**0.721**** (76)	**0.234**** (78)
HCD for F0		0.905 - 1.426			

**p≤0.05, **p ≤0.01 (Kruskal-Wallis and Wilcoxon-test, two-sided)*

The testes weights were significantly increased in F1A at 800 and 1600 ppm (relative) and in F1B at 1600 ppm (absolute) and, at 800 and 1600 ppm (relative). There was no comparable effect in F0 generation parental males. In F1A males, the increased relative testes weights are considered to be related to reduced terminal body weights (11% lower than in controls) since no effects on absolute testes weights were observed. However, the effect in F1B males is considered by RAC to be treatment-related. It is also noted that an increased incidence of benign testicular lesions (i.e., focal interstitial cell hyperplasia and adenoma) was observed at 2000 ppm (approx. 97 mg/kg bw/day) in two chronic/carcinogenicity studies with Sprague Dawley rats (B.6.5.1.1, study 1 and 2). The effect was not statistically significant and just at the upper boundary/slightly above HCD (4-20%, Table below). According to the study report, a conservative size criterion was used to diagnose testicular interstitial cell adenomas. Thus, some of these benign tumours could possibly be downgraded to interstitial cell hyperplasia using the contemporary less conservative size criterion. Nevertheless, the two studies show a clear adverse effect on the testes of rats at chronic doses of ca. 97 mg/kg bw/day.

***Table**: Incidence of testicular hyperplasia and adenoma in dietary chronic toxicity and carcinogenicity studies with male rats*

Dose /Group (ppm)	**0**	**200**	**750**	**2000**
Chronic toxicity study				
Number of animals	19	20	20	20
Interstitial cell adenoma	2	5	4	6
Carcinogenicity study				
Number of animals	50	49	50	50
Focal interstitial cell hyperplasia	6	6	10	10
Interstitial cell adenoma	5	7	8	10
Adenoma and focal hyperplasia	8	12	12	15

Effects on prostate weight were also observed in dogs exposed orally to dimethomorph in 13- and 52-week repeated dose toxicity studies. Reduction in the absolute and relative prostate weights (up to 60% of controls) and an increased incidence of prostatic interstitial fibrosis were observed at dose levels of approx. 43-47 mg/kg bw/d in both studies (Table below). An increase in interstitial fibrosis is understood as a change in the ratio between glandular and connective tissue of the prostate. Lower prostate weight and higher proportion of connective tissue is expected to result in a reduction of functionally active glandular tissue, thus having an impact on the production of prostate secretion which is needed to ensure sperm motility. Such effects are considered adverse and to support classification for sexual function and fertility. In addition, statistically significant increases in the adjusted testes weights were observed in males at the mid and high dose in the 52-week study.

***Table**: Absolute and adjusted prostate/testes weights observed in 90-day and 52-week dietary toxicity studies in male dogs (4 animals/dose group)*

52-week dietary toxicity study in dogs				
Dose (mg/kg bw/day)	**0**	**4.9**	**14.7**	**44.6**
Prostate–absolute (g)	8.25	8.97 (+9%)	5.55 (-33%)	**4.27* (-48%)**
#Prostate–adjusted (g)	7.40	9.04 (+22%)	6.23 (-16%)	4.36 (-41%)
#Testes–adjusted (g)	25.44	27.56 (+8%)	**31.49* (+24%)**	**32.73* (+29%)**
90-day dietary toxicity study in dogs				
Dose (mg/kg bw/day)	**0**	**5**	**15**	**43**
Prostate–absolute (g)	8.56±3.67	6.63±1.18	6.49±2.08	**3.27±1.31****
Relative to control (%)		-23%	-24%	**-62%**
Prostate–relative (as % BW)	0.070±0.026	0.060±0.008	0.057±0.023	**0.027±0.010****
Relative to control (%)		-14%	-19%	-61%

* p<0.05 (analysis of covariance); ** p<0.01 ("F-max" test; parametric ANOVA; Student`s t-test); # values adjusted using body weight as covariate

In summary, the key evidence for the adverse effects on sexual function and fertility was the clear and significant delay in the onset of puberty in males at a rather low top dose in the EOGRTS. Also a marked decrease in prostate and seminal vesicle weight was observed. Although to a lesser degree, testes weights were also affected in this study. The slightly delayed length of gestation and the delay in vaginal opening are considered as supporting evidence for adverse effects on sexual function and fertility.

In the two-generation study (B.6.6.1.1), only a slightly reduced gestation duration was reported in P0 and F1A parents. This effect was within HCD and it is considered statistically and biologically non-significant due to its low magnitude. No impairment in mating behaviour, reproductive performance or physiology was observed. It is noted, however, that the top dose level in the two-generation study is considerably lower (1000 ppm) than the high dose in the EOGRTS (1600 ppm). Furthermore, important parameters such as sperm parameters, oestrous cyclicity, age at puberty onset, AGD and sexual organ weights were not reported.

Additional supporting evidence on adverse effects on sexual function and fertility was received from a 90-day and one-year repeated dose toxicity studies with dogs (B.6.3.2.2 and B.6.3.2.3, respectively) and chronic and carcinogenicity studies with rats (B.6.5.1.1). The studies in dogs showed significant prostate weight reduction (absolute and relative) associated with interstitial prostatic fibrosis of dose-dependent severity (histopathological findings were graded as mild to moderate). It is recognized that prostatic interstitial fibrosis is a common finding in ageing dogs, however the animals used in these studies were 5-7.5 months old at the start of the study (B.6.3.2.2). A slight decrease in the absolute prostate weight was also observed in the parental animals at the high dose in the EOGRTS, but this change was within HCD. Statistically significant increases in adjusted testes weights but without any corresponding histopathology were reported in dogs at mid and high dose in the 1-year study. These effects were not observed in the 90-day study in dogs. An increased incidence in testicular interstitial cell adenomas was reported in the chronic and carcinogenicity studies with rats. The increase in the benign testicular tumours appears dose-dependent and at the upper range of the HCD from the performing laboratory.

With respect to the application of classification criteria, due to the lack of human studies on sexual function and fertility, classification in Repr. 1A is not justified. Classification in Category 1B is largely based on data from animal studies that provide clear evidence of an adverse effect on sexual function and fertility that are considered not to be solely secondary non-specific consequences of other toxic effects. Under CLP (Annex I: 3.7.1.3) it is stated that adverse effects on sexual function and fertility include effects on the onset of puberty and therefore RAC

considers the delay in preputial separation and vaginal opening covered by sexual function and fertility rather than by development. Considering the overall data, there is clear evidence of adverse effects on sexual function and fertility parameters. These effects were observed at dose levels causing only mild or moderate maternal toxicity manifested as slightly reduced food consumption, reduced maternal body weight/body weight gain, and signs of liver toxicity. Thus, the effects discussed above are not regarded as secondary non-specific consequences of maternal systemic toxicity and they are considered as relevant to humans. Altogether, RAC considers delayed puberty onset in combination with pronounced effects on male reproductive organs/systems as adverse and relevant for humans, and concludes that **classification as Repr. 1B (H360F) for adverse effects on sexual function and fertility** is warranted.

Development

Developmental toxicity of dimethomorph was investigated in an GLP- and OECD TG 414-compliant PNDT study with Sprague-Dawley rats and New Zealand White rabbits, two dose range finder studies in rats, one dose-range finder study in rabbits and the EOGRTS and two-generation study in rats.

In the rat OECD TG 414 study (B.6.6.2.3), groups of 30 female Sprague-Dawley rats were treated with dimethomorph (purity 96.6%) during gestation days 6 to 15 at dose levels of 0, 20, 60, or 160 mg/kg bw/day by gavage. Decreased maternal body weights, body weight gains, and food consumption were observed at 160 mg/kg bw/day. Two total litter losses at the top dose of 160 mg/kg bw/ day and one at 60 mg/kg bw/day were reported. All post implantation losses were described as early resorptions. The high dose dams with total litter losses had markedly reduced food consumption being more than 50% compared to controls (mean being 77% in the high dose group as compared to controls) as well as body weight loss of 15 and 20g, respectively. This severe maternal toxicity was considered by the study authors to be the likely cause of the early resorptions in these dams, and RAC agrees with this conclusion. While corrected body weight gains were not reported, the food consumption was reduced more than 50% and an overall body weight loss during pregnancy can be considered as a clear sign of poor maternal health. Effects of such magnitude were not reported for the remaining animals in the same dose group. RAC notes that no association between marked maternal effects and the one total litter loss in the mid dose group can be established. However, a single incidence in this group is likely to be a chance finding.

The above study was preceded by a range-finding study in which female Sprague-Dawley rats (8 per dose group) received dimethomorph (purity 98.7%) by oral gavage at doses of 0, 50, 120, or 300 mg/kg bw/day on days 6 to 15 of gestation (B.6.6.2.1). No treatment related effects indicating maternal and/or developmental toxicity were reported. In a second dose-range finding study, female Sprague-Dawley rats received dimethomorph by oral gavage at doses of 150 mg/kg bw/day (4 animals) and 300 mg/kg bw/day (3 animals) on days 6 to 15 of gestation (B.6.6.2.2). At the low dose, 100% intra-uterine deaths in one female and one to three early resorptions in each of the remaining females were observed. At the high dose, two out of three females showed 100% intra-uterine deaths. Both studies are very poorly reported (Klimisch score 3) and not useful for classification purposes.

In the OECD TG 414 rabbit study (B.6.6.2.5), female New Zealand White rabbits (22/group) received dimethomorph (purity 96.6%) at dose levels of 0, 135, 300, or 650 mg/kg bw/day by gavage from day 6 until day 18 of gestation. Signs of maternal toxicity were expressed as significantly reduced food consumption and decreased body weight at 650 mg/kg bw/day. During the study, 1, 0, 2 and 4 animals were found dead at dose levels of 0, 135, 300 and 650 mg/ kg bw/day, respectively. According to the report, these were accidental deaths due to gavaging errors, and no mortalities were attributed to the test material. The numbers of females with 100%

intra-uterine deaths or post-implantation loss were not significantly affected and did not show a dose dependency (Table below).

***Table**: Summary data on reproductive parameters from the oral teratogenicity study in the rabbit (B.6.6.2.5)*

Group/dose (mg/kg bw/day)	**0**	**135**	**300**	**650**
Number of inseminated females	22	22	22	22
Number of pregnant females	20	17	18	20
Number of pregnant females which were found dead	1	0	2	4
Number of females which aborted and were killed	1	1	0	3
Number of females with 100 % intra-uterine deaths	1	2	0	1
Number of females with live foetuses at necropsy	17	14	16	12
Post-implantation loss (%)	10.0	4.6	5.3	11.3

An increased incidence of pregnant dams with abortions was observed at the top dose (3 out of 20 pregnant, 15%). Historical control data on abortion incidence is not available from the performing laboratory. However, HCD on mean abortion rate in New Zealand White rabbits of 2% (range: not specified, performed from 1980 to 1989), 2.8% (range: 0 – 28.6%, performed from 1994 to 2000) and 1.4% (range: 0 – 28.6%, performed 2001–2010) are reviewed by Nitzsche (2017). Mean body weight and food consumption were statistically significantly reduced at the high dose in relation to controls on gestation days 12-18. According to the original study records, the 3 animals with abortions showed body weight loss and some of these dams showed additionally severe diarrhoea, blood in the excrement tray, and/or changes in liver and spleen morphology/colour. RAC concludes that the abortions are likely to be secondary non-specific consequences of severe maternal toxicity in the aborting dams. No treatment-related malformations or variations were evident from the foetal external, visceral or skeletal examination data.

High abortion rates were also noted in a preceding dose-range finding study (B.6.6.2.4) with female New Zealand White rabbits (8 or 9 per group) treated with dimethomorph (purity 96.6%) at dose levels of 0, 300, 600, or 1000 mg/kg bw/day by gavage on days 6 to 18 of gestation. In the high dose group, 6 out of 8 live dams aborted and were terminated pre-term and one further animal showed 100% intra-uterine deaths at necropsy. Review of the individual data shows that animals with abortions or intra-uterine deaths at the top dose displayed reduced food and water consumption and severe body weight loss during GD 6-18 (-0.5 to -1.0 kg vs. mean of +0.3 kg in controls). In addition, three of these dams had also effects in the liver and/or spleen. Altogether, RAC concludes that the abortions and intrauterine deaths are likely to be secondary non-specific consequences of severe maternal toxicity in these dams. One female aborted in the low dose group, but no abortions were reported at the mid dose level and therefore the single incidence in the low dose group is considered a chance finding.

In the EOGRTS (B.6.6.1.2), there were no indications for substance-induced intrauterine embryo-/foetolethality, malformations or effects on pup survival, sex ratio or other developmental landmarks in the Wistar rats exposed to dimethomorph at dose levels of up to 144 mg/kg bw/day. Anogenital distance (AGD) of male and female pups was statistically significantly reduced at all dose levels (pup-based analysis). When corrected for body weight (AGI), the reduction was below the HCD in high dose males only, while in females only the low and mid-dose pups were significantly below the control, and without a dose response. A subsequent analysis of the same data based on litter (as provided by the applicant during the pesticide renewal application) showed that only the changes in AGI in the mid and top dose males were statistically significant,

the high dose males being also slightly below the historical control range (Table below). For females, no treatment-related effects were observed on litter-based data.

***Table**: AGD and AGI of pups on PND 1 -litter based analysis#*

Dose level (ppm)	**0**	**300**	**800**	**1600**
	mean (SD)	mean (SD)	mean (SD)	mean (SD)
male pup (N)	24	23	25	22
AGD (mm)	3.16 (0.13)	3.10 (0.19)	**2.99** (0.16)**	**2.87** (0.21)**
HCD (mm)	2.99 – 3.15 (mean 3.06, SD 0.04)			
AGI	1.65 (0.04)	1.62 (0.09)	**1.59** (0.05)**	**1.57** (0.09)**
HCD (mm)	1.58 – 1.67 (mean 1.62, SD 0.03)			
female pup (N)	24	23	25	22
AGD (mm)	1.53 (0.10)	1.50 (0.06)	1.49 (0.09)	**1.45**** (0.10)
HCD (mm)	1.48 - 1.67 (mean 1.52, SD 0.04)			
AGI	0.82 (0.05)	0.80 (0.03)	0.80 (0.05)	0.81 (0.05)
historical control	0.79 - 0.86 (mean 0.82, SD 0.02)			

*p<0.05; **p<0.01; (Dunnett test, two-sided); # additional analysis based on litter-data as provided by the applicant upon request by EFSA during the renewal application

In the 2-generation study, a decreased percentage of pups with erupted incisors was reported in the F1, F2A and F2B pups at 1000 ppm. However, since the incisors eruption was complete at PND 15 in all groups and did not interfere with the feeding ability, the effect is not considered adverse. Other markers for pre- or postnatal development of the pups were not affected.

Classification as Repr. 1B for effects on development was proposed by the DS based on reduced AGD, delayed puberty, reduced pup weight, reduced seminal vesicle and prostate weight. The DS considered these effects as clear evidence for an adverse effect on development, which are relevant for humans and not secondary to maternal toxicity. As indicated under the RAC assessment of sexual function and fertility, effects on the onset of puberty are considered as effects on sexual function and fertility in line with CLP (annex I: 3.7.1.3). The effect on AGD is a marker reflecting in utero anti-androgenicity and it is an effect on development, but as such not sufficient for classification. Mean pup body weight in the high dose group of the EOGRTS was 13% below control at PND 1 and 9% below controls at PND 21. The effect on pup weight can be at least partly related to the moderate maternal toxicity (reduced body weight gain of 10.7% and signs of liver toxicity) as well as to shortened gestation length, and on its own does not justify classification for developmental toxicity. The effects observed in the rat and rabbit prenatal studies do not provide sufficient evidence supporting classification for developmental toxicity.

RAC concludes that **no classification** for effects on development is warranted.

Adverse effects on or via lactation

There are no effects meeting the CLP criteria, therefore, **no classification for effects on or via lactation** is warranted.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Dimethomorph is currently listed in Annex VI of the CLP Regulation (EC) No 1272/2008 with a classification for environmental hazards Aquatic Chronic 2 (H411). The DS proposed to retain the classification as Aquatic Chronic 2 (H411) based on lack of rapid degradation and a 34d NOEC value of 0.107 mg/L for fish *Pimephales promelas*.

Degradation

The hydrolysis of dimethomorph was tested according to OECD TG 111 following GLP principles. The substance was hydrolytically stable in buffer solutions at pH 4, 7, and 9 at both test temperatures (70 and 90°C).

There are three aqueous photolysis studies available on dimethomorph. In two studies with radiolabelled dimethomorph in sterile buffer solution at pH 5 and 25°C, the half-lives were calculated to be 25-28 days in the first study and 107 (chlorophenyl label) and 86 days (morpholine label) in the second study. In a third study with unlabelled dimethomorph in sterile buffer solution at pH 7 and 25°C, the half-lives were determined to be 303 hours (under test conditions) and 29.2 hours (normalized to sunlight).

There are two ready biodegradability tests available for dimethomorph, following OECD TG 301D (Closed Bottle Test; based on oxygen consumption) and OECD TG 301B (Modified Sturm Test; based on carbon dioxide consumption). In both tests, no degradation was observed after 28 days. Dimethomorph was not inhibitory to microorganisms at the test concentrations. The substance is therefore not readily biodegradable.

In an inherent biodegradation test following OECD TG 302C (Modified MITI (II) Test) and GLP, maximum biodegradation of 27% ThOD was observed after 28 days.

The rate of degradation of radiolabelled dimethomorph in aquatic systems was assessed using two water-sediment studies. The total recovery was in the range of 93 – 106% for both systems in both tests. In both systems, dimethomorph rapidly partitioned to the sediment and was retained as bound residues. In the first study, the complete mineralisation was 14 - 22% of the applied radiation (RA) after 105 days, while in the second test the complete mineralisation was 3.2 - 8.6% of RA after 100 days. No metabolites were observed at levels above 10% in either test. In the first study, 57 to 69% of RA was reported as non-extractable radiation in the sediment after 105 days. Dissipation half-lives for the total systems were determined to be 3.6 and 2.6 days in the first test and 15.4 and 58.4 days in the second test.

No significant degradation of dimethomorph was observed in an aerobic mineralisation study (OECD TG 309). After 59 days, at least 86.2 and 91.6% of total RA was recovered as the unchanged active substance for the morpholine and chlorophenyl label, respectively. Several minor metabolites were observed during the study in small amounts of up to 4.0% AR. At the end of the study, the radioactivity in the water accounted for 92.4 to 96.5% of RA for the viable test vessels and for 95.3 to 96.0% of RA for the sterilized vessels. Radioactivity in the volatile traps did not exceed 2.1 or 0.7% of AR for the morpholine and chlorophenyl label respectively, indicating a low rate of mineralization. Overall, the compound was considered to be stable in the test systems.

Based on available data, the DS concluded that dimethomorph is considered as not rapidly degradable.

Bioaccumulation

A fish bioaccumulation study (OECD TG 305) was available for dimethomorph. Bluegill Sunfish (*Lepomis macrochirus*) were exposed to mean measured concentrations (0.021 mg/L and 0.210 mg/L) of radiolabelled dimethomorph for 28 days, followed by a 14 days depuration period. Kinetic BCF (based on total radioactive residues and lipid-normalised) values were 10 at the low exposure and 13 at the high exposure, while kinetic BCF (based on the parent concentration and lipid-normalised) values were 1.4 for the low exposure and 2.0 for the high exposure. The measured octanol-water partition coefficient (log K_{ow}) was 2.63 (E-isomer) and 2.73 (Z-isomer) (HPLC method).

The DS concluded that dimethomorph has a low potential to bioaccumulate in aquatic organisms.

Aquatic toxicity

Reliable aquatic toxicity data are available for all three trophic levels, and a summary of the relevant information on aquatic toxicity is provided in the following table (the key endpoints used in hazard classification are highlighted in bold). Studies that were considered unreliable by the DS were not provided in the Table. The dimethomorph used in the aquatic toxicity studies was of technical grade, the E/Z ratio was not specified in the RAR.

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

Method/Exposure	Test organism	Endpoint	Toxicity values in mg a.s./L	Reference/Remarks
Short-term toxicity to fish				
OECD TG 203 static	*Oncorhynchus mykiss*	96h LC_{50} mortality	6.1 mm	B.9.2.1.1 (1986) B.9.2.1.4 (2010)
OECD TG 203 flow through	*Oncorhynchus mykiss*	96h LC_{50} mortality	6.8 mm	B.9.2.1.7 (2001)
OECD TG 203 flow through	*Cyprinodon variegatus*	96h LC_{50} mortality	11.3 mm	B.9.2.1.8 (1997)
OECD TG 203 static	*Cyprinus carpio*	96h LC_{50} mortality	16.6 mm	B.9.2.1.3 (1986) B.9.2.1.2 (2010)
OECD TG 203 static	*Lepomis macrochirus*	96h LC_{50} mortality	>13.7 mm	B.9.2.1.5 (1988) B.9.2.1.6 (2010)
OECD TG 203 flow through	*Lepomis macrochirus*	96h LC_{50} mortality	>9.5 mm	B.9.2.1.9 (2001)
OECD TG 203 flow through	*Pimephales promelas*	96h LC_{50} mortality	>8.4 mm	B.9.2.1.10 (2014)
Long-term toxicity to fish				
OECD TG 210 flow through	*Oncorhynchus mykiss*	96d NOEC Weight 96d EC_{10} weight 96d EC_{10} length	0.056 mm 0.116 mm >0.897 mm	B.9.2.2.2 (2015) B.9.2.2.1 (1997) B.9.2.2.2 (2015)
EPA guideline 850.1400 static	*Cyprinodon variegatus*	40d NOEC hatching, weight, length 40d EC_{10} weight 40d EC_{10} length	0.136 mm 0.150 mm 0.759 mm	B.9.2.2.2 (2015) B.9.2.2.6 (2010) B.9.2.2.2 (2015)

OECD TG 210 static	*Pimephales promelas*	34d NOEC hatching	**0.107 mm**	B.9.2.2.5 (2002) B.9.2.2.2 (2015)
21 day Short term reproduction assay flow-through study	*Pimephales promelas*	21d NOEC survival, weight, length, behaviour	≥ 0.488 mm	B.9.2.4.1 (2014)
Short-term toxicity to aquatic invertebrates				
OECD TG 202 static	*Daphnia magna*	48h EC_{50} mobility	20.1 mm	Ellgehausen (1986a) Habekost (2010)
OECD TG 202 static	*Daphnia magna*	48h EC_{50} mobility	>10.6 mm	Mitchell *et al*. (2001)
EPA guideline 72-3 flow through	*Americamysis bahia*	48h EC_{50} mobility	7.92 mm	Mitchell *et al*. (1997a)
EPA guideline 72-3 flow through	*Crassostrea virginica*	96h EC_{50} shell growth	**4.42 mm**	Mitchell *et al*. (1997b)
Long-term toxicity to aquatic invertebrates				
OECD TG 202 static renewal	*Daphnia magna*	22d NOEC survival, reproduction 22d EC_{10} reproduction	0.1 nom 0.152 nom	Anonymous (1993) Brausch (2015) Memmert and Knoch (1993)
EPA guideline 72-4 flow-through	*Daphnia magna*	21d NOEC length 21d EC_{10} reproduction 21d EC_{10} length 21d EC_{10} weight	0.22 mm 0.42 mm >2.0 mm 1.343 mm	Brausch (2015) Murrell *et al*. (1997)
EPA guideline 72-4 flow-through	*Americamysis bahia*	28d NOEC reproduction 28d EC_{10} reproduction	0.24 mm 0.24 nom	Hicks (2010)
ASTM 1992 static	*Chironomus riparius*	24d NOEC emergence and weight 24d EC_{10} weight 24d EC_{10} emergence	4.11 im 3.02 nom >15.6 nom	Brausch (2015) England *et al*. (1997)
Toxicity to algae and aquatic plants				
OECD TG 201 Static (initially considered unreliable by the DS but was considered reliable after assessment of additional information received during PC)	*Pseudokirchneriella subcapitata*	72h E_rC_{50} growth rate 72h $NOEC_r$ growth rate 72h E_yC_{50} yield 72h $NOEC_y$ yield	65.6 mm* 5.4 mm* 26.5 mm* 5.4 mm*	Jatzek (2001)

Notes: mm-mean measured concentration; nom-nominal concentration; im-initial mean measured concentration; * - the value were reported in the latest version of the RAR (January 2019) and are not included in the CLH report;

In the CLH report, only adequate toxicity data are reported for fish and invertebrates, while adequate data for algae and aquatic plants are lacking. During the public consultation additional information were presented in relation to the acute toxicity study carried out on algae *Pseudokirchneriella subcapitata* (Jatzek, 2001). Due to a lack of adequate acute and chronic toxicity data for algae at the time of submitting the proposal for acute and chronic aquatic classification, the DS based their proposal on the results of acute and chronic data for fish and invertebrates.

Acute toxicity

For dimethomorph, there are reliable aquatic acute toxicity data for fish and invertebrates. The lowest endpoint for fish is the 96h LC_{50} value of 6.1 mg/L for *Oncorhynchus mykiss* and for invertebrates is 96h EC_{50} value of 4.42 mg/L for *Crassostrea virginica*. The lowest acute toxicity value of 4.42 mg/L is above the classification threshold value of 1 mg/L. Therefore, the DS proposed that classification of dimethomorph as Aquatic Acute 1 is not warranted.

Chronic toxicity

Reliable long-term aquatic toxicity data on dimethomorph are available for fish and invertebrates. The most sensitive chronic endpoint for fish is the 34d NOEC value of 0.107 mg/L (*Pimephales promelas*) and for invertebrates is the 22d NOEC of 0.15 mg/L (*Daphnia magna*). The chronic aquatic classification proposed by the DS (Aquatic Chronic 2) was based on fish (*Pimephales promelas*) (34d NOEC = 0.107 mg/L) along with the understanding that the substance is not rapidly degradable. Due to the lack of both adequate acute and chronic toxicity data for algae, the surrogate approach could not be applied.

Comments received during public consultation

Three MSCA and one company-manufacturer submitted comments on the environmental part of the DS's proposal during the public consultation. All commenting MSCAs agreed with the proposed classification for environmental hazards. One commenting MSCA asked for clarification regarding the NOEC in the key study for chronic classification carried out with fish *Pimephales promelas*. The same MSCA asked if the EC_{10} (reproduction) based on mean measured concentrations is available for the chronic toxicity study performed with *Americamysis bahia*. The commenting company-manufacturer pointed out that the acute algae toxicity study (Jatzek, 2001) in the CLH report is considered unreliable by the DS although this study was considered acceptable by the RMS in the revised RAR from January 2019. The commenting company-manufacturer presented information on the measured concentrations and the validity criteria to demonstrate that the study could be considered as reliable for classification purposes. The DS considered the additional information on the algae study and agreed that the study could be considered as reliable, completing the data set for both acute and chronic aquatic hazards.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the DS proposal to consider dimethomorph as not rapidly degradable. The substance is hydrolytically stable at environmentally relevant pHs (pH 4-9) and is not readily biodegradable. No significant degradation in the aerobic mineralisation study was observed and limited mineralisation was observed in two water-sediment simulation studies (8.6% after 100 days and 22% after 105 days).

Bioaccumulation

RAC agrees with DS that dimethomorph has no potential to bioaccumulate in aquatic organisms. The basis for this is that measured BCF values of 1.4 and 2.0 are below the decisive CLP Regulation criterion of 500. This is supported by log K_{ow} values ranging from 2.63 to 2.73, which are below the CLP criterion of 4.

Aquatic toxicity

In the CLH report, no adequate toxicity data were reported for algae and aquatic plants. During the opinion development process, additional information for the Jatzek (2001) algae study from the revised RAR (January 2019) were provided by the DS. E_rC_{50} and NOE_rC values based on mean measured concentrations were reported for acute toxicity study carried out on the algae *P. subcapitata* (Jatzek, 2001). The algae study meets all validity criteria according to the current version of OECD TG 201 and is considered acceptable by the RMS and DS. RAC is of the opinion that it is appropriate to consider this data relevant for classification of the substance. According to current CLP Guidance (Version 5.0, July 2017), the endpoint based on growth rate reduction is preferred for algae. Therefore, the 72h E_rC_{50} of 65.6 mg/L and 72h NOE_rC of 5.4 mg/L were selected as the lowest values for this trophic level by RAC.

Acute toxicity

RAC is of the opinion that adequate acute toxicity data are available for all three trophic levels. Invertebrates are the most sensitive group and the lowest result is a 96h EC_{50} value of 4.42 mg/L for *Crassostrea virginica*. RAC notes that all $L(E)C_{50}$s for fish, invertebrates and algae (see Table) are above the CLP criterion of 1 mg/L. Consequently, RAC agrees with the DS that dimethomorph does not warrant classification for acute aquatic hazards.

Chronic toxicity

RAC is of the opinion that adequate chronic toxicity data are available for all three trophic levels. Fish are the most sensitive group and the lowest result is a 34d NOEC value of 0.107 mg/L for *P. promelas*. The chronic fish test using O. mykiss provides a lower NOEC (0.056 mg/L) but this is not taken for comparison with the criteria as an EC_{10} of 0.116 mg/L is the preferred value for comparison with the CLP criteria. No EC_{10} is available for the *P. promelas* study. Based on the fish NOEC of 0.107 mg/L and the lack of rapid degradability, RAC agrees with the DS that dimethomorph warrants classification as Aquatic Chronic 2.

In summary, RAC agrees with the Dossier Submitter's proposal that dimethomorph warrants **classification as Aquatic Chronic 2 (H411).**

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).