Committee for Risk Assessment

RAC

Annex 1

Background document

to the 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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

20 September 2019

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

International Chemical Identification:

Dimethomorph (ISO) (E,Z) 4-(3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl)morpholine

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

CAS Number: **110488-70-5**

Index Number: **613-102-00-0**

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Version number: 3 **Date: November 2018**

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON DIMETHOMORPH (ISO); (E,Z)-4-(3-(4-CHLOROPHENYL)-3-(3,4-DIMETHOXYPHENYL)ACRYLOYL)MORPHOLINE

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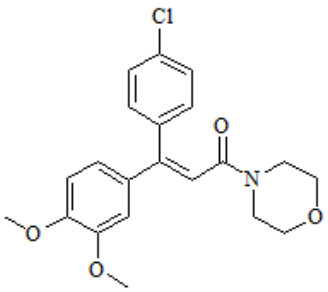
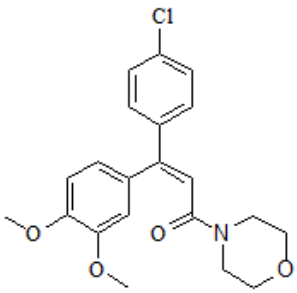
ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON DIMETHOMORPH (ISO); (E,Z)-4-(3-(4-CHLOROPHENYL)-3-(3,4-DIMETHOXYPHENYL)ACRYLOYL)MORPHOLINE

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	(E,Z) 4-[3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl]morpholine
Other names (usual name, trade name, abbreviation)	(E,Z) 4-[3-(4-chlorophenyl)-3-(3,4-dimethoxy-phenyl)-1-oxo-2-propenyl]-morpholine
ISO common name (if available and appropriate)	Dimethomorph (ISO)
EC number (if available and appropriate)	404-200-2
EC name (if available and appropriate)	(E,Z) 4-[3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl]morpholine
CAS number (if available)	110488-70-5
Other identity code (if available)	EINECS-No: 404-200-2 CIPAC-No: 483
Molecular formula	$C_{21}H_{22}ClNO_4$
Structural formula	 *E*-Isomer  *Z*-Isomer
SMILES notation (if available)	-
Molecular weight or molecular weight range	387.86
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	E/Z isomer ratio: ranges from 40/60 to 50/50 % w/w
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable
Degree of purity (%) (if relevant for the entry in Annex VI)	≥ 96.5%

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
Dimethomorph, CAS no 110488-70-5	96.5%	Aquatic Chronic 2; H411	Aquatic Chronic 2; H411

Besides the self-classification using EC number 404-200-2, there are also self-classifications notified under EC number 600-969-5. These notifiers mostly classify as Aquatic Chronic 2; H411 but some as Aquatic Chronic 1; H410.

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
No relevant impurities have been identified for dimethomorph				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
Confidential information					

Table 5: Test substances (non-confidential information)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
Dimethomorph, CAS no 110488-70-5			E/Z isomer ratio ranges from 40/60 to 50/50 % w/w In addition, acute oral and 28-day oral studies are available with the individual stereo-isomers.	

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6: Proposed harmonised classification and labelling of dimethomorph according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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	Aquatic Chronic 2	H411	GHS09	H411			
Dossier submitters proposal	613-102-00-0	Dimethomorph (ISO) 4-(3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl)morpholine	404-200-2	110488-70-5	**Add** Repr. 1B **Retain** Aquatic Chronic 2	**Add** H360FD **Retain** H411	**Add** GHS08 Dgr **Retain** GHS09	**Add** H360FD **Retain** H411			
Resulting Annex VI entry if agreed by RAC and COM	613-102-00-0	Dimethomorph (ISO) 4-(3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl)morpholine	404-200-2	110488-70-5	Repr. 1B Aquatic Chronic 2	H360FD H411	GHS08 GHS09 Dgr	H360FD H411			

Table 7: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	hazard class not assessed in this dossier	No
Oxidising gases	hazard class not assessed in this dossier	No
Gases under pressure	hazard class not assessed in this dossier	No
Flammable liquids	hazard class not assessed in this dossier	No
Flammable solids	hazard class not assessed in this dossier	No
Self-reactive substances	hazard class not assessed in this dossier	No
Pyrophoric liquids	hazard class not assessed in this dossier	No
Pyrophoric solids	hazard class not assessed in this dossier	No
Self-heating substances	hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	hazard class not assessed in this dossier	No
Oxidising liquids	hazard class not assessed in this dossier	No
Oxidising solids	hazard class not assessed in this dossier	No
Organic peroxides	hazard class not assessed in this dossier	No
Corrosive to metals	hazard class not assessed in this dossier	No
Acute toxicity via oral route	hazard class not assessed in this dossier	No
Acute toxicity via dermal route	hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	hazard class not assessed in this dossier	No
Skin corrosion/irritation	hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	hazard class not assessed in this dossier	No
Respiratory sensitisation	hazard class not assessed in this dossier	No
Skin sensitisation	hazard class not assessed in this dossier	No
Germ cell mutagenicity	hazard class not assessed in this dossier	No
Carcinogenicity	hazard class not assessed in this dossier	No
Reproductive toxicity	harmonised classification proposed	Yes
Specific target organ toxicity-single exposure	hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	hazard class not assessed in this dossier	No
Aspiration hazard	hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	harmonised classification proposed	Yes
Hazardous to the ozone layer	hazard class not assessed in this dossier	No

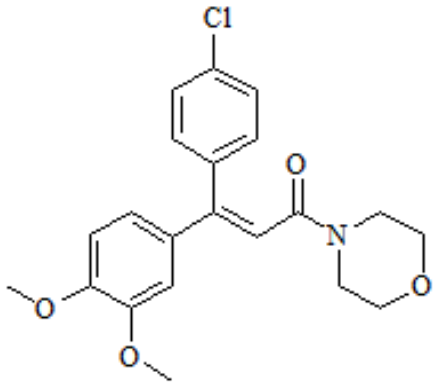
3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Dimethomorph has previously been assessed for harmonised classification by TC C&L. Dimethomorph has an Annex VI entry as Aquatic Chronic 2 (H411).

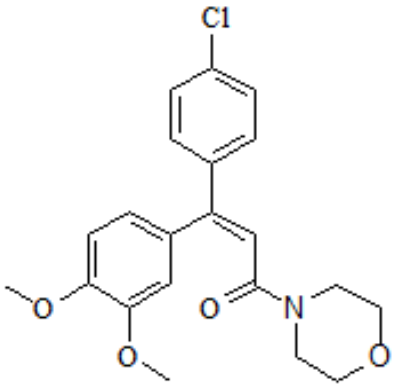
Dimethomorph has previously been evaluated and authorized within the plant protection products framework. Dimethomorph is part of the AIR3 renewal programme for active substances (Commission Implementing Regulation (EU) No 844/2012). For a renewal-application under Regulation (EC) 1107/2009, the compound is currently being re-evaluated with member state The Netherlands as rapporteur member state (RMS). The RAR was peer reviewed by the Co-Rapporteur Member State Germany. This process is currently ongoing. A draft assessment report (including a proposed decision) of the Netherlands has been published by EFSA for public consultation April 10th 2018.

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).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[B.] Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

- *Change in existing entry due to new data*

Further detail on need of action at Community level

New data is available for reproduction toxicity: an extended one-generation reproduction toxicity study in wistar rats following administration via the diet. Based on the effects observed in this study: delayed puberty (effect on fertility or development), shortened gestation length (effect on fertility) and reduced pup weight (effect on development) it is proposed to classify dimetomorph as reproductive toxicant category 1B; H360FD.

Dimethomorph is currently classified as Aquatic Chronic 2; H411. However, classification in category 1 was proposed in the RAR. This proposal was not taken over in this CLH proposal for the reasons described in Section 11.7.2. However, seen the discusion, inclusion of the environmental hazard class within the scope of the proposal is required.

5 IDENTIFIED USES

Dimethomorph is an active substance of a plant protection product and is used as a fungicide.

6 DATA SOURCES

This CLH report was based on the available data from the revised DAR as prepared during the renewal application of dimethomorph under Regulation (EC) 1107/2009 (published by EFSA for public consultation April 10th 2018). In addition , the data available in the registration dossier were considered. However, the level of detail of the summaries in the registration dossier (NONS) was limited.

7 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	white crystalline solid	RAR 2017	
Melting/freezing point	125.2-149.2°C	Registration dossier	E/Z mixture
Boiling point			Not applicable due to decomposition at 280 °C
Relative density	1.32 at 20°C	Registration dossier	
Vapour pressure	9.7 x 10-7 Pa for the E-isomer and 1.0 x 10-6 Pa for the Z-isomer	RAR 2017	
Surface tension	60.4 mN/m at 20 °C	Registration dossier	
Water solubility	49.2 mg/L at 20°C and pH 7 for the sum of isomers	RAR 2017	
Partition coefficient n-octanol/water	2.63 (E-isomer) and 2.73 (Z-isomer)	RAR 2017	measured, HPLC-method
Henrys law constant	5.4×10^{-6} Pa m^3/mol (E-isomer) and 2.5×10^{-5} Pa m^3/mol (Z-isomer)	RAR 2017	
Flash point			
Flammability	Negative	RAR 2017	
Explosive properties	Negative	RAR 2017	
Self-ignition temperature			

Property	Value	Reference	Comment (e.g. measured or estimated)
Oxidising properties	Negative	RAR 2017	
Granulometry			
Stability in organic solvents and identity of relevant degradation products			
Dissociation constant	-1.3	RAR 2017	calculated
Viscosity			

8 EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

Not evaluated in this dossier

8.2 Flammable gases (including chemically unstable gases)

Not evaluated in this dossier

8.3 Oxidising gases

Not evaluated in this dossier

8.4 Gases under pressure

Not evaluated in this dossier

8.5 Flammable liquids

Not evaluated in this dossier

8.6 Flammable solids

Not evaluated in this dossier

8.7 Self-reactive substances

Not evaluated in this dossier

8.8 Pyrophoric liquids

Not evaluated in this dossier

8.9 Pyrophoric solids

Not evaluated in this dossier

8.10 Self-heating substances

Not evaluated in this dossier

8.11 Substances which in contact with water emit flammable gases

Not evaluated in this dossier

8.12 Oxidising liquids

Not evaluated in this dossier

8.13 Oxidising solids

Not evaluated in this dossier

8.14 Organic peroxides

Not evaluated in this dossier

8.15 Corrosive to metals

Not evaluated in this dossier

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 9: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
ADME by oral route Directive 96/54/EC B 36; OECD Guideline 417 (EPA Pesticide Assessment Guidelines, subdivision F: Hazard Evaluation: Human and Domestic Animal, § 85-1 (October 1982) claimed by the author)	Dimethomorph is rapidly absorbed in the gastrointestinal tract following oral administration to rats. The amount absorbed is limited at high dose levels. Absorbed dimethomorph is efficiently metabolised and rapidly excreted mainly via the feces. Accumulation of dimethomorph in organs and tissues did not occur. The main degradation pathway was found to be the demethylation of the dimethoxyphenyl ring. To a smaller extent, degradation also occurred by oxidation of the morpholine ring.		B.6.1.1.1a/b
ADME by oral route Directive 96/54/EC B 36; OECD Guideline 417 (EPA Guidelines, 40 CFR, Part 158,85-1 (October 1982) claimed by the author)	Dimethomorph is efficiently absorbed and metabolised in the rat. Dimethomorph is mainly excreted via the bile after conjugation to glucuronides. The main aglycone was Z67 and/or Z69.		B.6.1.1.2
ADME by oral route Directive 96/54/EC B 36; OECD Guideline 417 (USEPA Pesticide Assessment Guideline 85-1 claimed	The rate and route of degradation is similar for male and female rat with about 95 % and > 80 % excretion of administered dose in 48 hours, respectively.		B.6.1.1.3

Method	Results	Remarks	Reference
by the author)	Feces was the major route of excretion in both sexes and both labelled compounds (chlorophenyl-ring labelled and morpholine-ring labeled). There was no difference between metabolic profile for rats treated with the 14C-chlorophenyl and 14C-morpholine ring		
ADME by oral route Directive 96/54/EC B 36; OECD Guideline 417 (EPA Pesticide Assessment Guideline 85-1 (October 1982) claimed by the author). Mass spectroscopic investigations were not conducted in compliance with GLP.	Similar urine and feces excretion patterns were found in male and female rats after single oral administration of dimethomorph at 50 mg/kg bw. The demethylation of one of the methoxy groups of the dimethoxyphenyl ring is the major metabolism pathway of dimethomorph. The presence of Z98 and Z93 confirmed also the fact that there is a second minor metabolism pathway resulting in a degradation of the morpholine ring.		B.6.1.1.4
ADME by oral route Directive 96/54/EC B 36; OECD Guideline 417 (JMAFF Testing Guidelines for Toxicology Studies: Metabolism Study (59 NohSan No. 4200, Jan. 28, 1985) claimed by the author) Feed and water analyses were not conducted under GLP. 0.1 % Tween 80 served as a control substance and was not characterised under GLP	At low dose absorption is quicker than at high dose. At both dose levels, the elimination occurred within 72 hours post-dosing.		B.6.1.1.5
ADME by oral route JMAFF Testing Guideline for Toxicity Studies: Metabolism Study (59 NohSan No. 4200, Jan. 28, 1985) claimed by the author Minor alterations were described in the protocol.	Dimethomorph is rapidly absorbed in the gastrointestinal tract following oral administration to rats. Absorbed dimethomorph is rapidly excreted. Accumulation of dimethomorph in organs and tissues did not occur.		B.6.1.1.6
ADME by oral route OECD 417, 2004/10/EC of 11 February 2004, EPA 870.7485	The metabolism of Dimethomorph in rat is very extensive. The main metabolic steps were identified as: * hydroxylation of either the dimethoxy or chlorophenyl ring and subsequent glucuronidation * demethylation of the dimethoxy ring and subsequent glucuronidation * hydroxylation and oxidative opening of the morpholine ring		B.6.1.1.7

Method	Results	Remarks	Reference
	and subsequent conjugation * cleavage and release of the intact morpholine ring		
In vitro metabolism study No guideline available	All the components identified in human hepatocytes were also detected in rat and dog hepatocyte samples		Birks V. 2015

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Short summary, as presented in the RAR:

Dimethomorph following a single oral dose to both sexes at the low dose level is rapidly and almost completely absorbed (urine, bile and residual carcass). The excretion balance of dimethomorph demonstrates that approximately 3-17% of the applied radioactivity is excreted via the urine at 10, 50 and 500 mg/kg bw (B.6.1.1.1a, B.6.1.1.3, B.6.1.1.4, B.6.1.1.7). Excretion via the feces accounts for 80 – 90 % of the dose for non-cannulated rats (B.6.1.1.1a, B.6.1.1.2, B.6.1.1.3, B.6.1.1.4, B.6.1.1.7).

In a study with bile cannulated rats, more than 90 % of the administered dose at 10 mg/kg bw was eliminated via the bile within 24 hours with a short half-life of about 3 hours (B.6.1.1.2). At higher dose levels (500 mg/kg bw), absorbed dimethomorph in both sexes was limited as indicated by lower amounts elimanted via the bile (31-49%).

In a new study biliary excretion amounted to 61-88% of the administered dose at 10 mg/kg bw and 46-60% for the 250 mg/kg bw dose group (B.6.1.1.7). Urinary excretion in this study amounted to 3-5 % dose in males and 10-23 % of the dose in females. Based on the this study the total absorbed dose is considered to be 80-90% for the low dose group and approximately 60% for the high dose group.

Dimethomorph was found to be primarily metabolised by demethylation of one of the methoxy groups. Further conjugation of the resulting metabolites could be identified as the major radioactive residues in the urine as well as in the bile of rats. Oxidation of the morpholine ring was found as a second minor degradation pathway in the rat. This step was considered to be the first in the pathway resulting in the cleavage and further degradation of the morpholine ring. This assumption was further substantiated by the identification of metabolite CUR 7117, and characterisation of traces of CUR 7586, CUR 7216 as well as Z43.

In addition to the previously peer-reviewed data, a new rat study focussing on the identification and quantification of metabolites in urine, faeces, bile, plasma and tissues after administration of dimethomorph (in two radiolabeled forms: chlorophenyl and morpholine ring label) was submitted for the purpose of the renewal, which confirms and extends the knowledge obtained from previous investigations.

The new study shows an extensive metabolism of dimethomorph with over 100 identified structures. The observed metabolic pathway is in good agreement with the information coming from the already peer reviewed studies. Metabolite CUR 7586 (=M550F010), depicted in the pathway based on

previous data, was found in its other isomeric form as M550F051. Metabolite Z43 (=M550F005) from the previous pathway was observed in its single or double demethylated form as M550F039, M550F040 and M550F037, respectively. All other previously identified metabolites from the rat were detected in the new study as well. This confirms that all metabolic steps observed in the previous studies (with the chlorophenyl radiolabel) are observed in the new study (with chlorophenyl and morpholine label) as well.

The following main transformation steps were observed in rats:

- hydroxylation of either the dimethoxy or chlorophenyl ring and subsequent glucuronidation (Metabolic steps 1 and 2)
- demethylation of the dimethoxy ring and subsequent hydroxylation and/or glucuronidation (Metabolic step 3)
- hydroxylation of the morpholine ring and subsequent modification (further hydroxylation, ring opening, degradation, conjugation) (Metabolic step 5)
- cleavage and release of the intact morpholine ring (Metabolic step 4)

The combination of these reactions followed by conjugation steps results in a huge number of metabolites.

The proposed metabolic pathway is provided in Annex 1 (Figure 1).

In a comparative *in vitro* metabolism study of dimethomorph, incubation of dimethomorph with liver hepatocytes of humans, rats and dogs showed similar metabolite patterns and MS analysis demonstrated that all components formed by human hepatocytes were also observed with rat and dog hepatocytes. Thus, there have not been found any human specific metabolites which were not also observed in the tested animal species.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Not evaluated in this dossier

10.2 Skin corrosion/irritation

Not evaluated in this dossier

10.3 Serious eye damage/eye irritation

Not evaluated in this dossier

10.4 Respiratory sensitisation

Not evaluated in this dossier

10.5 Skin sensitisation

Not evaluated in this dossier

10.6 Germ cell mutagenicity

Not evaluated in this dossier

10.7 Carcinogenicity

Not evaluated in this dossier

10.8 Reproductive toxicity

10.8.1 Adverse effects on sexual function and fertility

Table 10: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Dietary two generation reproductive study Directive 96/54/EC B 34, OECD Guideline 416; (US EPA Guideline 83-4; Japanese MAFF 59 NohSan 4200 claimed by the author) Sprague Dawley rats, P1: 30/sex/dose; F1: 25/sex/dose	Dimethomorph (SAG 151); Batch No. DW 11/86; purity 96.6 % 0, 100, 300 and 1000 ppm (Males: 6.9, 21 and 69 mg/kg bw/day; Females: 8.0, 24 and 79 mg/kg bw/day) 100 days pre-mating-sacrifice	<u>Parental toxicity:</u> 1000 ppm: reductions in pre-mating body weight gains for P1 and F1 females. <u>Sexual function/fertility:</u> 1000 ppm: shortened pregnancy duration for P1 and F1 females (not statistically significant) NOAEL for parental toxicity: 300 ppm (equivalent to 21 mg/kg bw/day) NOAEL for fertility/sexual function: 1000 ppm (equivalent to 69/79 mg/kg bw/day)	B.6.6.1.1 Reliability 1
Dietary extended one-generation reproduction toxicity study OECD 443 Crl:WI(Han) Wistar rats, 25/sex/dose	Dimethomorph (BAS 550 F; Batch: COD-001646; Purity 99.7%) 0, 300, 800 and 1600 ppm (26, 70, 144 mg/kg bw/day) 75 days pre-mating-sacrifice	<u>Parental toxicity:</u> ≥ 800 ppm: decreased food consumption and body weight/body weight gain, decreased seminal vesicle weight, clinical-chemical changes and pathological evidence of liver toxicity <u>Sexual function/fertility:</u> 1600 ppm: reduced gestational length NOAEL for parental toxicity: 300 ppm (equivalent to 26 mg/kg	B.6.6.1.2 Reliability 1

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		bw/day) NOAEL for fertility/sexual function: 800 ppm (equivalent to 70 mg/kg bw/day)	

10.8.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

In a two-generation reproduction toxicity study conducted with Sprague-Dawley rats, dimethomorph technical was administered via the diet at doses of 100, 300 and 1000 ppm (6.9, 21 and 69 mg/kg bw/day for males; 8.0, 24 and 79 mg/kg bw/day for females). No treatment related effects on mortality or clinical signs of toxicity were observed. Body weight gains during the pre-mating treatment period for P1 females in the 1000 ppm group were reduced 14.7 % as compared to controls. Although not statistically significant, a decrease in body weight gain of 6.8 % was observed during the pre-mating treatment period for F1 females in the 1000 ppm group as compared to controls. Dimethomorph did shorten the gestational length at the top dose in P0 as well as F1 dams for the generation of the F2a offspring (statistically significant using ANOVA). However, this effect was only slight and, based on a re-evaluation using the Dunnett test, not statistically significant. No other effects on fertility parameters were observed. The NOAEL for parental toxicity was 300 ppm (equivalent to 21 mg/kg bw/day), based on reductions in pre-mating body weight gains for P1 and F1 females in the 1000 ppm group. The NOAEL for fertility and reproductive function, was 1000 ppm (highest dose tested).

In an extended one generation study, the NOAEL (no observed adverse effect level) for general systemic toxicity is 300 ppm (approx. 26 mg/kg bw/day), based on decreased food consumption and body weight/body weight gain, decreased seminal vesicle weight, as well as clinical-chemical changes and pathological evidence of liver toxicity at 800 and/or 1600 ppm (approx. 70 and 144 mg/kg bw/day), in the F0 parental animals and adult F1 offspring. The NOAEL for fertility and reproductive performance for the parental rats is 800 ppm (approx. 70 mg/kg bw/day), based on a significantly reduced duration of gestation (outside historical control range) (Table 11).

Table 11. Gestational length in the 2 generation and extended one generation study in rats

Gestation length	Dose level (ppm)						HC
	0	100	300	800	1000	1600	
2 gen F1	22.0 +/- 0.3	22.1 +/- 0.3	21.9 +/- 0.4		**21.8 +/- 0.4*#**		
2 gen F2a	21.9 +/1- 0.4	21.9 +/- 0.3	22.1 +/- 0.3		**21.7 +/- 0.5*#**		
2 gen F2b	21.9 +/- 0.2	22.2 +/- 0.5	21.9 +/- 0.3		21.8 +/- 0.4		
EOGRT	22.3		22.2	22.0		**21.4****	21.5-22.3

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

In addition, in the 90-day and 1-year dog repeated dose toxicity studies (see 10.10), an increase in prostate weight and fibrosis was observed. In addition, there was an increase in testes weight in the 1-year dog study. This could be considered as indicative for possible effects on the fertility and reproductive function possibly requiring classification. These effects were observed in presence of other general toxicity and it is unclear whether the effects on the male reproductive organs were a direct effect of dimethomorph or secondary to the general toxicity. No such effects were observed in the available repeated dose studies with rats and mice.

10.8.3 Comparison with the CLP criteria

Since no human studies are available for effects on fertility, classification in Repr. 1A is not appropriate.

The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide 'clear evidence of an adverse effect on sexual function and fertility in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate'.

According to the guidance on the application of the CLP criteria 'Effects on sexual function and fertility include, but are not limited to, **alterations to the female and male reproductive system**, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, **parturition**, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems'.

In the dog 90-day and 1-year study increased prostate weight combined with prostatic interstitial fibrosis was observed. Since these effects were observed in presence of other general toxicity, but it cannot be excluded that they are primary effects on the reproductive system, they would warrant classification in Category 2. This is further justified as no such effects were observed in the repeated dose studies with rats and mice.

In the reproductive toxicity studies no effect on the mating index, fertility index, gestation index, live birth index and sperm parameters was observed. However, in the 2 generation study, dimethomorph did shorten the gestational length at the top dose in P0 (21.8 days vs 22.0 days in control group) as well as F1 dams for the generation of the F2a offspring (21.7 days vs 21.9 days in control group) (statistically significant using ANOVA). It is noted that this effect was only slight and, based on a re-evaluation using the Dunnett test, not statistically significant. A statistically significant (Dunnett test) reduction in gestation length was however observed in the high dose group of the extended one generation study (21.4 days vs 22.3 days in control group) which was below the lower range of the historical control data (21.5 days). A shortened gestation length can result in adverse effects such as decreased fetal weight (as shown in the extended generation study). In addition, the effect is also relevant for humans. Since there is evidence for a statistically significantly reduced gestation length in the extended one generation study (supported by a slight, though not significantly, reduced gestation length in the 2-generation study), we conclude that there is clear evidence for an adverse effect on sexual function or fertility, which is relevant for humans. The reduced gestation length was observed in the presence of maternal toxicity. The maternal effects in the EOGRT at the highest dose consisted of decreased food consumption and body weight/body weight gain, as well as clinical-chemical changes and pathological evidence of liver toxicity. The reduced gestation length is unlikely to be secondary to the reductions in food consumption, body weight and body weight gain as food restriction in rats results in an increase in the gestation length (Chernoff, 2009 table 2). As the reduced gestation length could have resulted in the observed reduced pup weight and development, this is considered an adverse and severe effect as in humans it is known that reduced birth weight is related to other adverse effects. Therefore, dimethomorph should be classified as **Repr 1B for effects on sexual function and fertility**.

10.8.4 Adverse effects on development

Table 12: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Dietary two generation reproductive study Directive 96/54/EC B 34, OECD Guideline 416; (US EPA Guideline 83-4; Japanese MAFF 59 NohSan 4200 claimed by the author) Sprague Dawley rats, P1: 30/sex/dose; F1: 25/sex/dose	Dimethomorph (SAG 151); Batch No. DW 11/86; purity 96.6 % 0, 100, 300 and 1000 ppm (Males: 6.9, 21 and 69 mg/kg bw/day; Females: 8.0, 24 and 79 mg/kg bw/day) 100 days pre-mating-sacrifice	<u>Parental toxicity:</u> 1000 ppm: reductions in pre-mating body weight gains for P1 and F1 females. <u>Development:</u> No adverse effects observed NOAEL for parental toxicity: 300 ppm (equivalent to 21 mg/kg bw/day) NOAEL for development: 1000 ppm (equivalent to 69 mg/kg bw/day)	B.6.6.1.1 Reliability 1
Dietary extended one-generation reproduction toxicity study OECD 443 Crl:WI(Han) Wistar rats, 25/sex/dose	Dimethomorph (BAS 550 F; Batch: COD-001646; Purity 99.7%) 0, 300, 800 and 1600 ppm (26, 70, 144 mg/kg bw/day) 75 days pre-mating-sacrifice	<u>Parental toxicity:</u> ≥ 800 ppm: decreased food consumption and body weight/body weight gain, decreased seminal vesicle weight, clinical-chemical changes and pathological evidence of liver toxicity <u>Development:</u> ≥ 800 ppm: decreased anogenital distance/index in males (pup-based data), reduced seminal vesicle and prostate weight 1600 ppm: decrease in preweaning pup body weight, delay of puberty in males NOAEL for parental toxicity: 300 ppm (equivalent to 26 mg/kg bw/day) NOAEL for development: 300 ppm (equivalent to 26 mg/kg bw/day)	B.6.6.1.2 Reliability 1
Preliminary Oral Developmental toxicity Study	Dimethomorph; ZTH 236Z50; Batch No. T2/85; purity 98.7 %	No treatment-related effects observed	B.6.6.2.1 Reliability 3

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Guideline not specified female Sprague-Dawley rats, 8/dose group	50, 120 or 300 mg/kg bw/day GD 6 to 15	NOAEL for maternal toxicity: 300 mg/kg bw/day NOAEL for development: 300 mg/kg bw/day	
Preliminary Oral Developmental toxicity Study Guideline not specified female Sprague-Dawley rats, 4/dose group	Dimethomorph; CME151, Batch No. not specified; purity not specified 150 or 300 mg/kg bw/day GD 6 to 15	≥ 150 mg/kg bw: Intra-uterine death, early resorptions, 300 mg/kg bw: reduced fetal weight NOAEL for maternal toxicity: not determined NOAEL for development: < 150 mg/kg bw/day	B.6.6.2.2 Reliability 3
Oral teratogenicity study Directive 96/54/EC B 31; OECD Guideline 414; (US EPA Guideline 83-3 claimed by the author) Female Sprague-Dawley rats, 30 /group	Dimethomorph (SAG 151); Batch No. DW 11/86; purity 96.6 % 0, 20, 60 and 160 mg/kg bw/day GD 6 to 15	<u>Maternal toxicity:</u> 160 mg/kg bw/day: reduced food consumption, reduced body weight and body weight gain <u>Development:</u> 160 mg/kg bw/day: total litter loss in two animals NOAEL for maternal toxicity: 60 mg/kg bw/day NOAEL for development: 60 mg/kg bw/day NOAEL for teratogenicity: > 160 mg/kg bw/day	B.6.6.2.3 Reliability 1
Preliminary Oral Developmental toxicity Study The author claimed that the study was conducted according to guideline No. 83-3 of the "U.S. EPA Pesticide Assessment Guidelines, Subdivision F	Dimethomorph; CME 151; ZTH 236Z50; purity 98.7 % 0, 300, 600 or 1000 mg/kg bw/day GD6-18	<u>Maternal toxicity:</u> ≥ 300 mg/kg bw/day: reduced body weight gain ≥ 600 mg/kg bw/day: reduced food consumption <u>Development:</u> ≥ 600 mg/kg bw/day: reduced fetal weight 1000 mg/kg bw/day: high rate of abortions and increased number of intra-uterine deaths NOAEL for maternal toxicity: < 300 mg/kg bw/day	B.6.6.2.4 Reliability 3

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
(November 1982)" Female New Zealand White rabbits, 8 or 9/group		NOAEL for development: 300 mg/kg bw/day NOAEL for teratogenicity: > 600 mg/kg bw/day	
Oral Developmental toxicity Study Directive 96/54/EC B31, OECD Guideline 414, (US EPA Guideline 83-3 claimed by the author) Female New Zealand White rabbits, 22/dose	Dimethomorph (SAG 151); Batch No. DW 11/86; purity 96.6 % 0, 135, 300 or 650 mg/kg bw/day GD6-18	<u>Maternal toxicity:</u> 650 mg/kg bw/day: reduced food consumption, reduced body weight gain <u>Development:</u> 650 mg/kg bw/day: slightly increased abortion rate NOAEL for maternal toxicity: 300 mg/kg bw/day NOAEL for development: 300 mg/kg bw/day NOAEL for teratogenicity: > 650 mg/kg bw/day	B.6.6.2.5 Reliability 1

10.8.5 Short summary and overall relevance of the provided information on adverse effects on development

In a two-generation reproduction toxicity study conducted with Sprague-Dawley rats, dimethomorph technical was administered via the diet at doses of 100, 300 and 1000 ppm (6.9, 21 and 69 mg/kg bw/day for males; 8.0, 24 and 79 mg/kg bw/day for females). No treatment related effects on mortality or clinical signs of toxicity were observed. Body weight gains during the pre-mating treatment period for P1 females in the 1000 ppm group were reduced 14.7 % as compared to controls. Although not statistically significant, a decrease in body weight gain of 6.8 % was observed during the pre-mating treatment period for F1 females in the 1000 ppm group as compared to controls. No effects were observed on pup survival or mean pup weight. In the 1000 ppm group, the percentage of pups in the F1, F2a and F2b generations which achieved incisor eruption was reduced on one or more days from postnatal days 9 - 11 when compared to controls and the differences were statistically significant. However, the delay in incisor eruption did not interfere with the development of feeding ability and is therefore not considered an adverse finding. There were no other treatment-related developmental effects observed. The NOAEL for parental toxicity was 300 ppm (equivalent to 21 mg/kg bw/day), based on reductions in pre-mating body weight gains for P1 and F1 females in the 1000 ppm group. The NOAEL for development was 1000 ppm (equivalent to 69 mg/kg bw/day), the highest dose administered.

In an extended one generation study, the NOAEL (no observed adverse effect level) for general systemic toxicity is 300 ppm (approx. 26 mg/kg bw/day), based on decreased food consumption and body weight/body weight gain, decreased seminal vesicle weight, as well as clinical-chemical changes and pathological evidence of liver toxicity at 800 and/or 1600 ppm (approx. 70 and 144 mg/kg bw/day),

in the F0 parental animals and adult F1 offspring. No effects were observed on pup survival. At 1600 ppm, mean pup body weight was 13% below control at PND 1 and stil 9% below controls at PND 21. Anogenital (AG) distance of male pups (pup-based data) was statistically significantly reduced at all dose levels; 2, 6 and 10% below control, respectively (below historical control values in mid and high dose). When corrected for body weight (AG index) the reduction was 2, 4 and 5%, respectively (below historical control values in high dose only). AG distance of all female treated pups was also statistically significantly decreased, by 2, 3 and 6%, respectively. When corrected for body weight (AG index) only the low and mid-dose pups were significantly below control, and without dose response. An additional evaluation of these data, based on litter data (as provided by the applicant upon a request by EFSA during the renewal application), showed that for males only the changes at the top dose are statistically significant and slightly outside the historical controls. For females, the analysis based on litter data confirmed that no treatment-related effects are noticed. Furthermore, a delay of puberty onset at 800 ppm (males) and 1600 ppm (both sexes) was observed. However, the delay in vaginal opening was concluded to be due to a decrease in body weight. The same was concluded for the delay in preputial separation in mid dose males. However, for the high dose group a specific effect on preputial separation could not be excluded. In addition, reductions in absolute and relative seminal vesicle and prostate weight were observed in the adult F1 at 800 and 1600 ppm without histopathological changes. The NOAEL for developmental toxicity in the F1 progeny is 300 ppm (approx. 26 mg/kg bw/day), due to the decreased anogenital distance/index at 800 ppm (approx. 70 mg/kg bw/day) based on pup-based data.

Developmental toxicity studies with dimethomorph, conducted in Sprague-Dawley rats (day 6 to 15 of gestation) and in New Zealand White rabbits (day 6 to 18 of gestation), showed no evidence of teratogenic effects for fetuses, and no evidence of developmental toxicity in the absence of maternal toxicity. In the rat developmental toxicity study, the NOAEL for maternal toxicity was 60 mg/kg bw/day based on decreased body weights, body weight gains, and food consumption at 160 mg/kg bw/day (highest dose tested). The NOAEL for developmental toxicity was also 60 mg/kg bw/day, based on a slightly increased number of total litter losses at 160 mg/kg bw/day. In the rabbit developmental toxicity study, the NOAEL for maternal toxicity was 300 mg/kg bw/day based on decreased body weight gains and food consumption at 300 mg/kg bw/d and a slightly increased abortion rate at 650 mg/kg bw/day. The NOAEL for developmental toxicity was 300 mg/kg bw/day based on a slightly increased embryolethality presenting as abortion. As important parts of the development of the reproductive organs happens after gestation day 15, these effects were not fully studied in these tests.

Dimethomorph was anti-androgenic in the Yeast Androgen Screening (YAS) assay using the hAR yeast strain (Woitkowiak, 2011d). No androgenic effects were observed. In a Yeast Estrogenic Screening (YES) assay using the hERα yeast strain no estrogenic nor anti-estrogenic effects were observed (Woitkowiak, 2011e). These results are supported by public literature studies where dimethomorph did not insert an estrogenic effect in the E-screen Assay in MCF-7 human breast cancer cells (Bitsch, 2002) but did result in anti-androgenic effects in MDA-kB2 reporter gene assays and the YAS assay (Orton, 2011; Orton, 2014; Archer, 2015). In a public literature study reporting on the Phase I of the ToxCast program dimethomorph was indicated to have no effects on estrogen or thyroid pathways but was reported to have a potential effect on the androgen pathway. A summary of the in vitro studies is included in Table 13: Summary of the in vitro on endocrine disruption.

Table 13: Summary of the in vitro on endocrine disruption

Test system	Result	Reference
Yeast androgen screening (YAS-assay) with hAR yeast strain	Anti-androgenic: positive Androgenic: negative	Woitkowiak, 2011d
Yeast estrogen screening (YES-assay) with hERα yeast strain	Anti-estrogenic: negative Estrogenic: negative	Woitkowiak, 2011e
E-Screen assay with MCF-7 breast cancer cells	Estrogenic: negative	Bitsch, 2002
YAS assay and MDA-kb2 cell line	Anti-androgenic: positive Androgenic: negative	Orton, 2011
Battery of 467 *in vitro* high-throughput	No effect on estrogen pathway	Reif, 2010

screening assays (Phase I of ToxCast)	or thyroid identified. Potential effect on androgen pathway	
MDA-kb2 cells	Potential anti-androgen	Orton, 2014
YAS assay	Weak anti-androgen	Archer, 2015

10.8.6 Comparison with the CLP criteria

Since no human studies are available for effects on development on the offspring, classification in Repr. 1A is not appropriate.

The classification of a substance in this Category 1B is largely based on data from animal studies. Such data shall provide 'clear evidence of an adverse effect on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate'.

According to the CLP criteria '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'. It should be noted that the adverse effects must be induced during pregnancy, or as a result of parental exposure.

In the extended one-generation a delay in preputial separation was observed at the high dose level of 1600 ppm (5.9 days). In addition, decreased anogenital length was observed in males (F1) at the 800 ppm and 1600 ppm (-6.3% and -9.5%; pup-based data). Both effects were outside of the historical control range.

A delay in preputial separation in days secondary to reduced maternal body weight is normally observed as a reduction in body weight for reaching preputial separation (Carney et al, 2004, Toxicological sciences 82: 237-249 table 3). However, with dimethomorph there is also an increase in body weight for reaching preputial separation. The same applies to anogenital distance.

A decrease in absolute and relative seminal vesicle and prostate weight was observed in the adult F1 at 800 and 1600 ppm without histopathological changes.

The reduced anogenital distance and delayed sexual maturation appear to reflect the anti-androgenic effects of dimethomorph. Dimethomorph was anti-androgenic in the Yeast Androgen Screening (YAS) assay using the hAR yeast strain and in the MDA-kB2 reporter gene assay. In the extended-one generation a reduction in absolute and relative seminal vesicle weight was observed which also gives an indication of the anti-androgenic properties of dimethomorph. However, some other typical effects of anti-androgenic substances such as nipple retention were not observed. However, as there was 95% nipple retention on day 12 and 0% on day 20, this may have been difficult to detect.

In the same study, at 1600 ppm, mean pup body weight was 13% below control at PND 1 and stil 9% below controls at PND 21.

In the 2-generation study, AGD and the time until puberty were not determined.

Where a causal relationship between maternal and developmental toxicity has been established, the level of concerns for the developmental effects is reduced. Therefore, the observed effects should be considered in relation to possible maternal toxicity. At the high dose level (1600 ppm) maternal toxicity consisted of slightly reduced maternal body weight (-5.7%), reduced body weight gain (-10.7%). Food consumption was also reduced in females (max -7.6%) but only during the lactation period. Increased liver weight (+14%) was observed in males and females. In females minimal or slight centrilobular hepatocellular hypertrophy was noted as well as apoptotic hepatocytes and an increase in the severity of lymphoid infiltration. In short, while some maternal toxicity was observed the effects are not considered to be severe. Based on the individual pup data it does not appear that the observed effect on preputial

separation and anogenital distance only occurs in litters with higher maternal toxicity. Moreover, based on the in vitro information a non-maternally mediated mode of action through the anti-androgenic properties of dimethomorph seems likely. The observed effects are therefore considered to be related to the anti-androgenic effect of dimethomorph and not secondary to maternal toxicity. This mode of action is considered to be relevant to humans and therefore classification for developmental toxicity is considered necessary.

The severity of the observed effects can be questioned as they could be considered a delay in normal development. However, the type of effects and the *in vitro* results indicate that the observed effects are due to an anti-androgenic mechanism although not all effects typically observed with anti-androgens were observed in this study. It is considered likely that the anti-androgenic mechanism will also induce other adverse effects not observed in standard studies. This includes effects on the brain by in utero exposure to anti-androgens such as phthalates (Miodovnik, 2014).

Based on reduced anogenital distance, delayed puberty, reduced pup weight and reduced seminal vesicle and prostate weight not secondary to maternal toxicity, we conclude that there is clear evidence for an adverse effect on development, which is relevant for humans. Therefore, dimethomorph should be classified as **Repr 1B for effects on development**.

10.8.7 Adverse effects on or via lactation

There are no effects meeting the CLP criteria for effects on or via lactation

10.8.8 Short summary and overall relevance of the provided information on effects on or via lactation

There are no effects meeting the CLP criteria for effects on or via lactation

10.8.9 Comparison with the CLP criteria

There are no effects meeting the CLP criteria for effects on or via lactation

10.8.10 Conclusion on classification and labelling for reproductive toxicity

Based on the reduced gestation length, delayed puberty and reduced pup weight observed in rat studies, we conclude that dimethomorph should be classified as **Repr. 1B; H360FD**

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 MSCA, 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 in the context of Regulations (EC) No 1107/2009 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 EOGRTS study with a second-generation cohort was proposed with the aim to clarify some uncertainties related to possible anti-androgenic effects (i.e. changes in anogenital distance/index of males, delayed sexual maturation, and decreased seminal vesicle weight) observed in males at the high dose in the present EORTGS.

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, anogenital 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 as indicated by statistically significant delays in preputial separation and vaginal opening at 800 ppm (males) and 1600 ppm (both sexes) was observed in the study.

The age at vaginal opening was delayed by two days and this delay was statistically significant at 1600 ppm ($p<0.01$), exceeding also the range of the submitted historical control data (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.

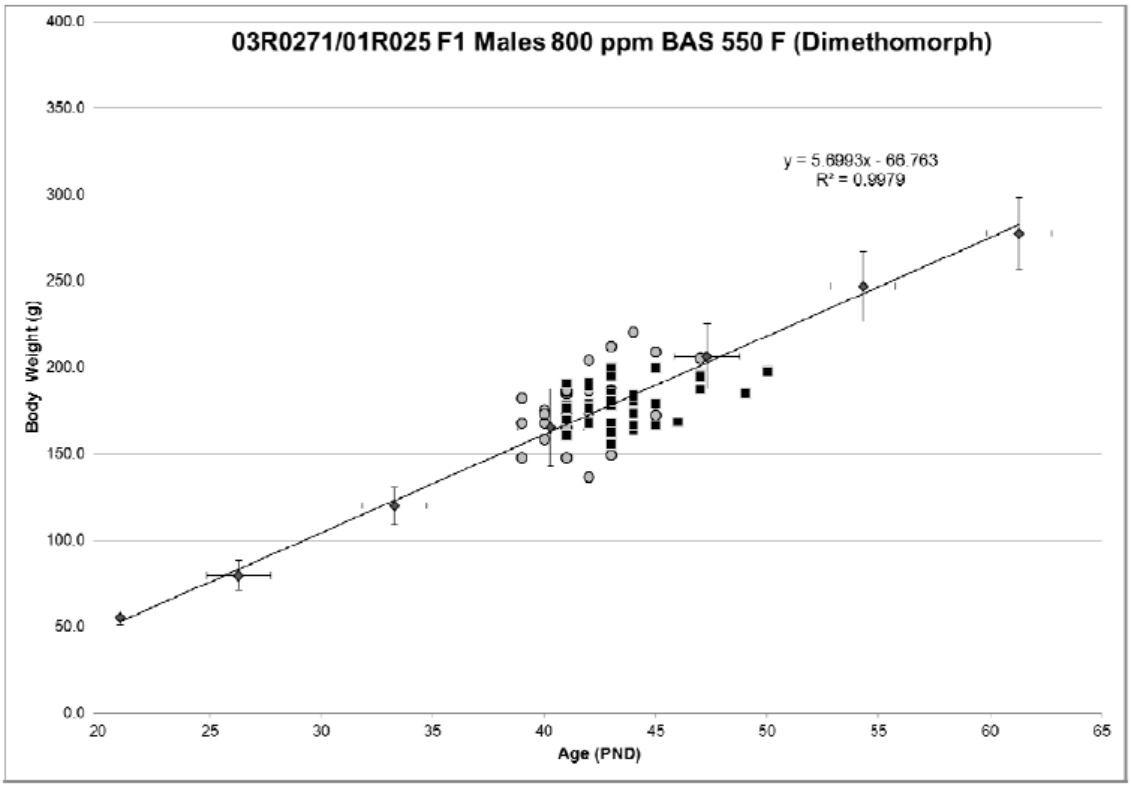
***Table**: Sexual maturation of F1 pups: age at vaginal opening in females*

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.



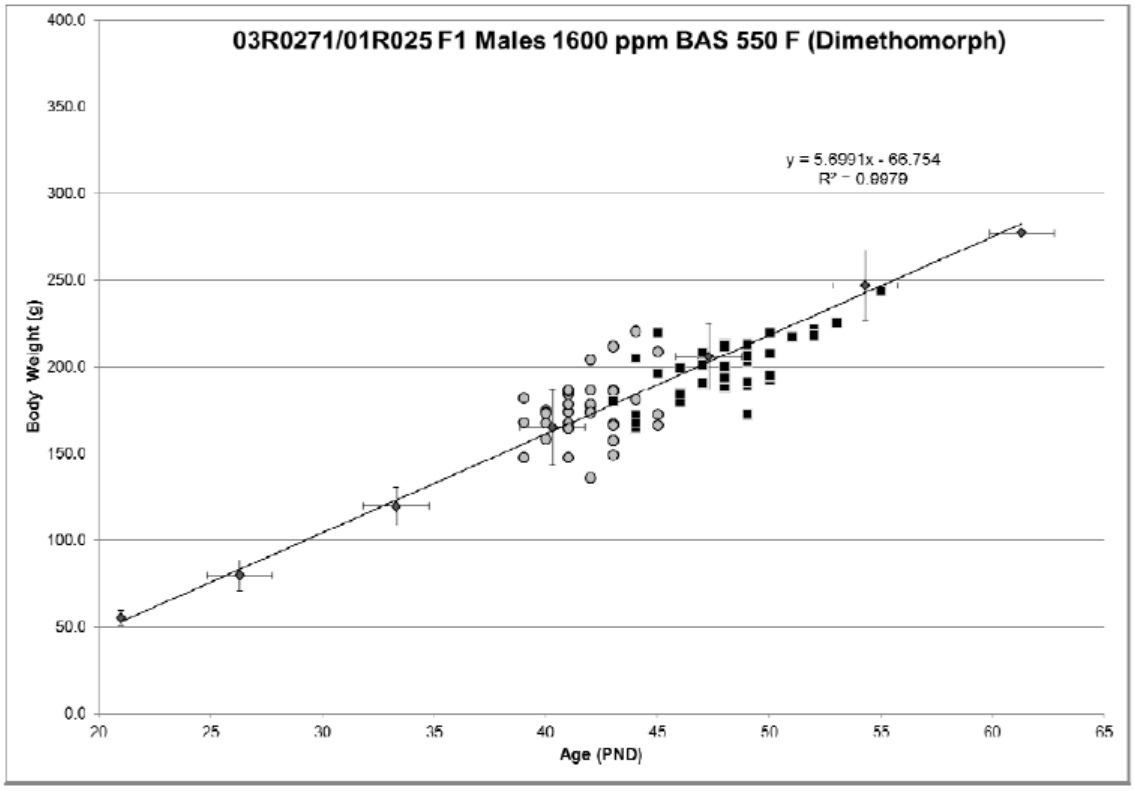


Figure: Age at sexual maturation of males exposed to dimethomorph at 800 ppm (upper panel) and 1600 ppm (lower panel) compared to body weight development. Round points: controls; square points: treated animals.

***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.

10.9 Specific target organ toxicity-single exposure

Not evaluated in this dossier

10.10 Specific target organ toxicity-repeated exposure

The information in this chapter is provided to support the assessment for reproductive toxicity and is not compared to the STOT RE criteria.

Table 14: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference

Oral 28 day study Method not specified in the report; however, the conduct of this study corresponds to EU Testing Method B7 and OECD 407. Deviations from current OECD 407: - reticulocytes and a measure of blood clotting time/potential not included. - epididymides, prostate and thymus were not weighed. - no histopathology was carried out Sprague-Dawley rats, 5/sex/group	Dimethomorph (ZTH 236 Z50); Batch No. L 5000; purity 99 % Diet: 0, 200, 1000 and 5000 ppm (males: 15.8, 80.9 and 305.9 mg/kg bw; females: 17.5, 81.1 and 283.3 mg/kg bw/day) 28 days	5000 ppm: soft feces, swollen abdomen, hunched posture, piloerection, emaciation, lethargy and unsteady gait, reduced body weight, reduced food consumption, increases in platelet and neutrophil counts, increased blood urea nitrogen. Moribund animals were sacrified. 5000 ppm, females only: decreased plasma albumin, increased plasma globulin, increased urine volume, increased relative liver weight ≥1000 ppm: increased blood urea nitrogen (females), not considered adverse NOAEL: 81 mg/kg bw	B.6.3.1.1 Reliability 3

Oral 28 day study Method not specified in the report; however, the conduct of this study corresponds to EU Testing Method B7 and OECD 407. Deviations from current OECD 407 guideline: - No haematological or clinical chemistry evaluation. - Adrenals, testes, epididymides, prostate, thymus were not weighed. - Histopapthology was only carried out on the liver. Sprague-Dawley rats, 10/sex/group	Dimethomorph (CME 151); Batch No. DW 11/86; purity 96.6 ± 0.8 % Diet: 0, 2000, 3000 and 4000 ppm (males: 175, 300 and 400 mg/kg bw; females: 200, 300 and 400 mg/kg bw/day) 28 days	4000 ppm: piloerection, swollen abdomen and emaciation, reduced body weight and body weight gain ≥3000 ppm: increased relative liver weight, hepatocellular hypertrophy ≥2000 ppm, females only: reduced body weight and body weight gain, increased relative liver weight, hepatocellular hypertrophy NOAEL: <200 mg/kg bw	B.6.3.1.2 Reliability 3

Oral 28 day study Method not specified in the report; however, the conduct of this study corresponds to EU Testing Method B7 and OECD 407. Deviations from current OECD 407: - A measure of blood clotting time/potential was not included in the haematological evaluation. - Epididymides, prostate and thymus were not weighed - Histopathology was only carried out on gross macroscopic lesions, adrenals, heart, intestines, kidneys, liver, pituitary, spleen and stomach. Fisher 344 rats, 7/sex/dose	Dimethomorph (SAG 151 - E isomer); Batch No. L4785; purity: E isomer 99.5 - 99.7 %, Z-isomer 0.3 - < 0.5 % Gavage: 0, 10, 100 or 750 mg/kg bw/day. 28 days	750 mg/kg bw: increased food intake (males), decreases in total blood haemoglobin, increased platelet counts, increased mean platelet volume (males), increases in protein, bilirubin, gamma glutamyl transpeptidase, cholesterol, calcium and triglyceride, increases in serum urea and creatinine, decreased splenic weight (males), increased relative liver weight, slight to moderate hepatic enlargement, dark discoloration of the liver, slight to moderate caecal enlargement and fluid caecal contents, patchy mid zonal hepatocellular cytoplasmic lipid vacuolation ≥100 mg/kg bw, males only: increased relative liver weight, increased absolute and relative adrenal weight, slight to moderate hepatic enlargement, dark discoloration of the liver NOAEL: 10 mg/kg bw	B.6.3.1.3 Reliability 2

Oral 28 day study Method not specified in the report; however, the conduct of this study corresponds to EU Testing Method B7 and OECD 407. Deviations from current OECD 407 guideline: - A measure of blood clotting time/potential was not included in the haematological evaluation. - Epididymides, prostate and thymus were not weighed - Histopathology was only carried out on gross macroscopic lesions, adrenals, heart, brain, intestines, kidneys, liver, pituitary, testes, spleen and stomach. Fischer 344 rats, 7/sex/dose	SAG 151 Z isomer; Batch No. Th H296, ST90/106; purity 95.6 % Diet: 0, 10, 100 and 750 mg/kg bw/day. 28 days	750 mg/kg bw/day: increases in serum bilirubin and protein, decreased albumin to globulin ration, slight caecal enlargement, fluid caecal contents (males) ≥100 mg/kg bw: increased relative liver weight, patchy midzonal cytoplasmic lipid vacuolation NOAEL: 10 mg/kg bw	B.6.3.1.4 Reliability 2
Oral, 28 day, immunotoxicity study. EPA Guideline 870.7800/ GLP Wistar rats, 8 male/dose	Dimetomorph, batch no AC9978-131, purity 97.5% 0, 300, 800 and 2400 ppm in diet (23, 61 and 184 mg/kg bw/d) 28 days	2400 ppm: reduced bw gain No immunotoxic effects observed. NOAEL (immunotoxicity): 2400 ppm (184 mg/kg bw/d) NOAEL (general toxicity): 800 ppm (61 mg/kg bw/day)	B.6.8.2.15

Oral 6 week study No guideline specified Only limited number of endpoints evaluated CD-1 mice, 10/sex/group	Dimethomorph (CME 151); Batch No. DW 11/86; purity not specified Diet: males: 0, 300/10000, 800 and 2000/5000 ppm; females: 0, 300/8000, 800 and 2000/4000 ppm 6 weeks	All dose groups (females) and 300/10000 and 2000/5000 males showed significant increases in absolute and relative liver weight	B.6.3.1.5 Reliability 3
Oral 14 day study No guideline specified Beagle dogs, 1/sex/dose	Dimethomorph CME 151; Batch No. DW 11/86, purity not specified Part A: Diet: 1000, 750, 900 and 1200 ppm for 7 days Part B: Diet: 1200 ppm for 14 days	≥900 ppm: body weight loss (males) 1000 ppm: reduced food intake	B.6.3.1.6 Reliability 3
Oral 90 day study plus 4 weeks recovery (US EPA Guideline 82-1 and OECD Guideline 408 claimed by the author); EU Testing Method B 26 Deviations from current OECD guideline 408: - Epididymides and thymus were not weighed Sprague-Dawley rats, 20/sex/dose	Dimethomorph (CME 151); Batch No. T2/85; purity 98.7 ± 1.5 % Diet: 0, 40, 200 and 1000 ppm (males: 2.9, 14.2 and 73 mg/kg bw/day; females: 3.2, 15.8 and 82 mg/kg bw/day) for 13 weeks	1000 ppm males: decreased PCV, RBC, MCHC, total white blood cell count and lymphocyte counts, decreased urinary pH 1000 ppm females: decreased heart weight, increased liver weight, decreased urinary pH ≥200 ppm males only: decreased relative liver weight ≥40 ppm females only: decreased kidney weight (not dose related NOAEL: 200 ppm (16 mg/kg bw)	B.6.3.2.1 Reliability 2

Oral 90 day neurotoxicity study (US EPA Guideline 870.6200 and OECD Guideline 424; GLP) Wistar rats, 10/sex/dose	Dimetomorph (Batch No: AC9978-131; purity 98.3%) Diet: 0, 300, 800 and 2400 ppm (males: 0, 21.7, 58.7, and 177.9 mg/kg bw/day, females: 0, 25.7, 69.6, and 204.0 mg/kg bw/day) 90 days	2400 ppm: reduced food consumption, impaired body weight gain and food efficiency. No neurotoxic effect observed. NOAEL (general toxicity): 800 ppm NOAEL (neurotoxicity): 2400 ppm	B.6.7.1.2 Reliability 1
Oral 90 day study EU Testing Method B 27 (OECD Guideline 409 and US EPA Guideline 82-1 claimed by the author) Beagle dogs, 4/sex/group	Dimethomorph (CME 151); Batch No. DW 11/86; purity 96.6 ± 0.8 % Diet: 0, 150, 450 and 1350 ppm (males: 5, 15 and 43 mg/kg bw/day; females: 6, 15 and 44 mg/kg bw/day) for 13 weeks	1350 ppm: lip-licking, occasional subdued behaviour, body tremors, increased serum alkaline phosphatase activity (males), increased absolute and relative thymus weight (males), increased relative liver weight (females), decreased absolute prostate weight (males), prostate fibrosis increased (males) NOAEL: 450 ppm (15 mg/kg bw)	B.6.3.2.2 Reliability 1
Oral 52 week study Directive 96/54/EC B 30 (OECD Guideline 409 and US EPA Guideline 83-1 claimed by the author) Beagle dogs, 4/sex/dose	Dimethomorph (SAG 151; CME 151); Batch No. DW 11/86; purity 96.6 % Diet: 0, 150, 450 and 1350 ppm (males: 4.9, 14.7 and 44.6 mg/kg bw/day; females: 5.0, 15.7 and 47 mg/kg bw/day) for about 12 months	1350 ppm: increased serum alkaline phosphatase, increased absolute (males only) and relative liver weight, decreased absolute prostate weight together with interstitial fibrosis, ≥450 ppm males: increased relative testes weight ≥450 ppm females and ≥150 ppm males: reduced body weight (150 ppm females: increased body weight) ≥450 ppm females: increased hepatic lipid (in males only at 1350 ppm) NOAEL: 150 ppm (4.9 mg/kg bw/day)	B.6.3.2.3 Reliability 1
Dermal 28 day study OECD 410, EPA 870.3200 Crl:WI(Han) rats, 10/sex/dose	AS 550 F (Dimethomorph). Lot/Batch #: COD-001244. Purity: 99.8% Dermal: 0, 100, 300, and 1000 mg/kg bw/day for 28 days	No treatment-related findings observed NOAEL: 1000 mg/kg bw	B.6.3.3.1 Reliability 1

Long term toxicity and carcinogenicity study EU Testing Method B 30 (US EPA Guideline 83-5; Guidelines of OECD and Japanese MAFF, claimed by the author) Deviations from current OECD guideline: - Cholesterol not measured. - Thyroid and uterus were not weighed Sprague-Dawley rats, 20/sex/dose	Dimethomorph (SAG 151; CME 151); Batch No. DW 11/86; purity 96.6 % Diet: 0, 200, 750, and 2000 ppm (males: 9.4, 36.2 and 99.9 mg/kg bw/day; females: 11.9, 57.7 and 157.8 mg/kg bw/day) for 104 weeks.	2000 ppm: reduced body weight and body weight gain, decreased red blood cell count, decreased hemoglobin (females), decreased hematocrit (females), increased bone marrow cellularity (females), increased incidence of hepatocellular hypertrophy and/or increased amount of pigment in hepatocytes (females), increased incidences of dilated mesenteric blood vessels, arteritis and testicular interstitial cell proliferation (males) ≥750 ppm: increased incidence of ”ground-glass” foci of cellular alteration in the liver (males only at 2000 ppm) NOAEL: 200 ppm (9 mg/kg bw)	B.6.5.1.1 – study 1 Reliability 2
Long term toxicity and carcinogenicity study EU Testing Method B 32 (US EPA Guideline 83-5; Guidelines of OECD and Japanese MAFF claimed by the author) Sprague-Dawley rats, 50/sex/dose	Dimethomorph (SAG 151; CME 151); Batch No. DW 11/86; purity 96.6 % Diet: 0, 200, 750, and 2000 ppm (males: 8.8, 33.9 and 94.6 mg/kg bw/day; females: 11.3, 46.3 and 132.5 mg/kg bw/day) for 104 weeks	2000 ppm: decreased food intake (females), increased incidence of dilated mesenteric blood vessels and arteritis in the abdominal vessels, predominantly in the pancreas (males), increase in “ground-glass” foci of cellular alteration in the liver, increased incidence in hepatocellular pigmentation and hypertrophy and increased severity of bone marrow cellularity (females) ≥750 ppm: reduced body weight gain (males only at 2000 ppm) NOAEL: 200 ppm (9 mg/kg bw/day)	B.6.5.1.1 – study 2 Reliability 1

Long term toxicity and carcinogenicity study EU Testing Method B.32 (US EPA Guideline 83-2; Guidelines of OECD and Japanese MAFF, claimed by the author) Charles River CD-1 mice, 50/sex/dose	Dimethomorph (SAG 151; CME 151); Batch No. DW 11/86; purity 96.6 % Diet nominal dose: 0, 10, 100, and 1000 mg/kg bw/day for 104 weeks	1000 mg/kg bw/day: reduced body weight (males) and body weight gain (females also at 100 mg/kg bw/day), increased alkaline phosphatase activity (males), increased aspartate aminotransferase activity (females), increased absolute and relative (females) liver weight NOAEL: 100 mg/kg bw/day	B.6.5.2 Reliability 1

10.10.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

The short-term toxicity of dimethomorph technical (E/Z racemat) was investigated in 2 dietary 28-day studies in Sprague-Dawley rats. In addition 2 dietary 28-day studies in Fisher 344 rats with E isomer and with Z isomer respectively were performed. Furthermore, dimethomorph technical (E/Z racemat) was investigated in a dietary 90-day study in Sprague-Dawley rats and Beagle dogs each, a 6 week dietary dose range finding study in CD-1 mice and a one-year dietary study in Beagle dogs.

Short-term (28-day) exposure of Sprague-Dawley rats to dimethomorph at dietary concentrations of 200, 1000, and 5000 ppm resulted in a NOAEL of 1000 ppm (equal to 80 mg/kg bw/day based on food consumption data). The highest dietary concentration tested (5000 ppm, equal to 280-300 mg/kg bw) induced increased morbidity and clinical signs of toxicity, reductions in body weight gains and in food consumption, increased liver to body weight ratios and increased blood urea nitrogen for both sexes. No microscopic examinations were performed.

In a second short-term (28-day) toxicity study in Sprague-Dawley rats, using dietary concentrations of 0, 2000, 3000, and 4000 ppm, the NOAEL was less than 2000 ppm based on decreased body weight gains for both sexes at all dietary concentrations, and dose-related increases in liver-to-body weight ratios and hepatocellular hypertrophy for both sexes at 3000 and 4000 ppm and for females at 2000 ppm. Based on food consumption data, the 2000 ppm concentration is equal to 150 mg/kg bw/day.

A 28-day exposure of Fisher 344 rats to E isomer dimethomorph at dietary concentrations of 10, 100 or 750 mg/kg bw/day resulted in a NOAEL of 10 mg/kg bw/day, based on a dark discoloration and enlargement of the liver, an increase in adjusted liver weight in the males and a mid-zonal hepatocellular cytoplasmic lipid vacuolation in male and female rats at 100 mg/kg bw/day.

A 28-day exposure of Fisher 344 rats to Z isomer dimethomorph at dietary concentrations of 0, 10, 100 and 750 mg/kg bw/day resulted in a NOAEL of 10 mg/kg bw/day, based on a slight mid-zonal lipid vacuolation at 100 or 750 mg/kg bw/day in both sexes.

In a 28-day oral immunotoxicity study in Wistar rats, no immunotoxic effects were noticed.

In the subchronic (90-day) feeding study in Sprague-Dawley rats with dimethomorph, the NOAEL of 200 ppm was based on increased liver weights for females at 1000 ppm. Based on food consumption data, the NOAEL of 200 ppm is equal to approximately 16 mg/kg bw/day.

In a 6 week dietary dose range finding study in mice a liver weight increase in males (5000 ppm and above) and females (4000 ppm and above) was observed.

In the subchronic (90-day) feeding study in Beagle dogs with dimethomorph, increases in alkaline phosphatase activity (both sexes), increases in relative liver weight in females, reductions in absolute and relative prostate weights, and an increased incidence of prostatic interstitial fibrosis in males were observed at 1350 ppm (highest concentration tested). The NOAEL for this study is 450 ppm, equal to approximately 15 mg/kg bw/day as based on food consumption data.

In a 90-day oral neurotoxicity study in Wistar rats, no neurotoxic effects were noticed.

In the 1-year feeding study in beagle dogs with dimethomorph technical, increased relative liver weights in females and increased relative testes weights in males occurred at 450 ppm. The NOAEL for this study is 150 ppm, equal to an approximate daily intake of 5 mg/kg bw/day as based on food consumption data.

A 28-dermal study was performed in Wistar rats, no systemic or local treatment-related effects were observed.

Long-term dietary toxicity studies were conducted in rats and mice. In both species liver effects were observed at high doses.

In the 2-year dietary toxicity study in Sprague-Dawley rats with dimethomorph, effects on the liver occured in females at 750 ppm. The NOAEL for chronic toxicity in this study was 200 ppm, equal to approximately 9 mg/kg bw/day, based on food consumption data.

Similarly, for the 2-year carcinogenicity study in Sprague-Dawley rats, the NOAEL for chronic toxicity was 200 ppm (equal to approximately 9 mg/kg bw/day), as based on a decrease in overall body weight gain for females at 750 ppm. In both 104 week dietary toxicity studies in rats, there was an increased incidence of testicular tumors. However, the differences are not considered to be an oncogenic effect of dimethomorph (see Annex I for explanation).

In the 104-week carcinogenicity study with dimethomorph in CD-1 mice, the data support a systemic toxicity NOAEL of about 97 mg/kg bw/day, based on reduced body weight in males and reduced body weight gains in males and females at about 1000 mg/kg bw/day.

10.10.2 Comparison with the CLP criteria

Not discussed in this dossier

10.10.3 Conclusion on classification and labelling for STOT RE

Not applicable.

10.11 Aspiration hazard

Not evaluated in this dossier

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Table 15: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference

Method	Results	Remarks	Reference
OECD Guideline 301B and D Ready biodegradability	No degradation observed in both studies	Not readily biodegradable (Ri 2)*	Turner (1988)
OECD Guideline 111 Hydrolysis	stable at environmentally relevant conditions	(Ri 2)*	Ochsenbein (1989)
Photochemical degradation in water (US-EPA, OECD and BBA guidelines)	Half-life: 25 to 107 days	Degradation product detected at <10% of the applied dose (Ri 2)*	Knoch and Holman (1998), Panek et al. (2001), Van Dijk (1990)
OECD 302C Inherent biodegradability	maximum biodegradation of 27 % ThOD	Some evidance of inherent, primary biodegradability (Ri 2)*	Battersby (1993)
OECD Guideline 309 Surface water simulation	Half-life: 621 days	Result from one trial, other trials showed no significant degradation (Ri 2)*	Yeomans (2015)
Aquatic-sediment simulation study	Dissipation half-lives for the whole system: 2.6-58.4 days	Bound residues were observed in the range of 47 to 75% of the applied radiation (Ri 2)*	Ebert (2002), Knoch (1993), Knoch (1994b), Knoch (1994a), Maleri (2015)

* Reliability according to Klimisch et al. (1997), since assessment is based on summaries in the DAR, Ri=1 is not given.

11.1.1 Ready biodegradability

The following study was available in the original registration dossier, the description below is based on the summary in the RAR.

Ready biodegradability of dimethomorph (94% purity, E/Z isomer ratio 45/55) has been assessed by Turner (1988) in a GLP study following the OECD 301B and 301D guidelines. Three tests were performed: a Closed Bottle Test; a Modified Sturm Test; and a Microbial Inhibition Test. For the Closed Bottle Test and Modified Sturm Test dimethomorph was emulsified with a non-biodegradable detergent (Dobane PT sulphonate) and this solution was added to the inoculum. For the closed bottle test a nominal concentration of dimethomorph of 3 mg/L was applied and for the Modified Sturm Test the concentration of dimethomorph in the inoculum was 20 mg/L. A reference control system used sodium benzoate to monitor the viability of the microbial population. A test system containing both the test and reference substances as the sole sources of carbon was used to evaluate the toxicity of the test compound. The amount of oxygen consumed was measured over time. In the Microbial Inhibition Test, the inhibition of the growth of a pure culture of *Pseudomonas fluorescens* by dimethomorph was studied. An acetone solution of dimethomorph was added to a mixture of *P. fluorescens* in a growth medium at a concentration of 50 mg a.s./L. A known microbial growth inhibitor, sodium pentachlorophenate, was also evaluated. The growth of the organism was measured over time. In the Closed Bottle Test, no oxygen was consumed in 28 days. Therefore it was concluded that dimethomorph was not degraded. There was no inhibition of microbial activity under the test conditions. In the Modified Sturm Test, there was no evolution of carbon dioxide from dimethomorph over 28 days. Therefore it was concluded that dimethomorph was not degraded. There was no inhibition of microbial activity under the test conditions. It was concluded that Dimethomorph is not “readily biodegradable” and does not inhibit the growth or activity of microorganisms. The results are considered reliable (Ri 2) and can be used for classification purposes.

11.1.2 BOD_5/COD

Not evaluated in this dossier

11.1.3 Hydrolysis

In the original registration dossier one study on hydrolytic degradation of dimethomorph was available. No additional studies were added to the dossier for the renewal. The description below is based on the summary in the RAR.

Hydrolysis of radiolabelled and unlabelled dimethomorph (E/Z ratio 49.5/50.5) was tested in a GLP study by Ochsenbein (1989) in three buffer solutions of pH 4, 7 and 9 and at temperatures of 70 and 90 °C. The incubation was performed under a constant stream of nitrogen. The incubation flasks were connected to two traps to collect $^{14}CO_2$ and organic volatiles. Samples were taken at start and after 2, 3, 4, 6, 8 and 10 weeks. At pH 4, 7 and 9 the substance was stable at both test temperatures. On the basis of this, it can be concluded that the substance is stable at pH 4 to 9 which are environmental relevant pHs. The results are considered reliable (Ri 2) and can be used for classification purposes.

11.1.4 Other convincing scientific evidence

Not evaluated in this dossier

11.1.4.1 Field investigations and monitoring data (if relevant for C&L)

In the RAR some information from public literature on field investigations and monitoring data is reported. This included environmental monitoring of various pesticides in surface water, groundwater and/or sediment outside EU (e.g. China, South Africa). Most studies lacked standard methods or quantitative information. Frequency of detections were rare and concentrations not indicated or very low. It was reported that DT50 values of 10.3 to 31.5, 9.5 to 9.7 days or 14.6 days in soil were stated in several studies. It is unclear if these half-lives are for degradation or dissipation.

11.1.4.2 Inherent and enhanced ready biodegradability tests

Inherent biodegradability has been assessed by Battersby (1993) in a GLP study following the OECD 302c guideline. The inherent biodegradability of dimethomorph was assessed by the modified MITI (II) test using fresh activated sludge as the inoculum, and 97.5 % pure dimethomorph (E/Z isomer 46/54). The MITI (II) inherent biodegradability test is similar to the modified MITI (I) ready biodegradability test except that the ratio of biomass to test substance is greater, therefore providing greater potential for biodegradation. A buffered salts medium was inoculated with activated sludge to get a mixed liquor suspended solids (MLSS) concentration of 100 mg/L. Duplicate respirometer flasks were set up containing 500 mL of inoculated medium amended with the test substance at 30 mg/L. Dimethomorph was added as an emulsion. A biodegradable reference with sodium benzoate was also performed. The flasks were equilibrated to the test temperature (20 °C) for one hour. Logging of oxygen uptake was then started and monitored every two hours over 28 days. At the end of this period, logging was stopped and each flask analysed for pH and N_{ox}- (NO_2^-, NO_3^-) concentrations. The following parameters were calculated: net oxygen uptake, biochemical oxygen demand (BOD), nitrogenous oxygen demand (NOD) and percent biodegradation. Biodegradation was expressed as a percentage of the theoretical maximum (ThOD). In one of the two replicate flasks the amount of oxygen uptake was 27 % ThOD. In the other replicate there was slight inhibition of oxygen uptake. Over 60 % of the biodegradable reference substance was degraded after 7 days of incubation, and the test was therefore considered valid. It was concluded that **t**he maximum biodegradation of dimethomorph of 27 % ThOD in one of the replicate flasks was some evidence of "inherent, primary biodegradability". The results are considered reliable (Ri 2) and can be used for classification purposes.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

In the dossier for the original registration two water/sediment simulation studies were available, these studies were reassessed for the RAR. In the renewal dossier, a new study on the aerobic mineralisation in surface water is also available, the descriptions below are based on the summaries in the RAR.

Knoch (1993, 1994b, 1994a) examined the degradation of radiolabelled dimethomorph (E/Z isomer ratio: 48.9/51.1) in two water-sediment systems. The labelling was performed on the chlorophenyl-moiety of the molecule, isomers were not determined separately. Two systems with water/sediment from different locations were used in the test. Dimethomorph was added directly to the surface of the water layer to give an initial concentration of 0.128 mg a.s./L. The samples were incubated at 20°C with a steady stream of CO_2-free air passing over the water/sediment system and through traps to collect $^{14}CO_2$ and organic volatiles. Total recovery was in the range of 93-106% for both systems. In both systems the dimethomorph moved quickly to the sediment and was fixed as bound residues. After 105 days of exposure, the complete mineralisation was 14- 22% of the applied radiation. No metabolites >10% were detected. 57 to 69% of the applied radiation was reported as non-extractable radiation in the sediment after 105 days. In a re-evaluation of the data by Maleri (2015), half-lives for the total systems determined according to the FOCUS degradation kinetics were 3.6 and 2.6 days, in this the fraction non-extractable from sediment was considered as degradated. These half-lives should be considered as dissipation half-lives since it is unclear if the fraction non-extractable from sediment has actually been degraded or is still the parent compound. The results are considered reliable (Ri 2) and can be used for classification purposes.

Ebert (2002) examined the degradation of two forms of radiolabelled dimethomorph (E/Z ratio: 42/58) in two water-sediment systems. The labelling was performed on the chlorophenyl- or the morpholine-moiety of the molecule. Two systems with water/sediment from different locations were used in the test. Dimethomorph was added directly to the surface of the water layer at a rate of 70 µg per test vessel and 210 µg per test vessel for isolation and determination of potential degradation products. The samples were incubated for 100 days (or 139 days for the degradation products) at 20°C. Total recovery was in the range of 93-106% for both systems. In both systems the dimethomorph moved quickly to the sediment and was fixed as bound residues in levels of 46 to 75% of the applied radiation. After 100 days of exposure, the complete mineralisation was 3.2-8.6% of the applied radiation. No metabolites >10% were detected. In a re-evaluation of the data by Maleri (2015), dissipation half-lives for the total systems were determined to be 15.4 and 58.4 days, in this the fraction non-extractable from sediment was considered as dissipated. The results are considered reliable (Ri 2) and can be used for classification purposes.

Yeomans (2015) examined the mineralization and degradation rates of dimethomorph (BAS 550F) in an aquatic system under dark conditions. The study was performed according to OECD guideline 309. The test was performed at two concentrations (10 and 100 µg a.s./L) using two differently ^{14}C labelled test items (morpholine and chlorophenyl labels), respectively. Sterile samples were tested for each label at the higher concentration. The test vessels were attached to a flow-through system for continuous aeration and incubated at a temperature of 20 ± 2°C in the dark. Samples for the experiment were taken at days 0, 3, 7, 14, 22, 36 and 59. The amount and nature of radioactivity in the water samples was determined by liquid scintillation counting (LSC) and radio-HPLC. Volatiles were trapped in 2 M sodium hydroxide and also analyzed by LSC. Parent substance identification was done by co chromatography with the corresponding reference items of the E and Z isomer on HPLC. From the obtained results it was concluded that dimethomorph was not significantly degraded in the test system. After 59 days, at least 86.2 and 91.6% of the total applied radioactivity 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% applied radiation, In one single sample a component with 7.6% of the applied radiation was detected. During the test, no systematic change to the isomer ratio was observed for either the morpholine or chlorophenyl label. At the end of the study, the radioactivity in the water accounted for 92.4 to 96.5% of the applied radiation for the viable test vessels and for 95.3 to 96.0% of the applied radiation for the sterilized vessels. Radioactivity in the volatile traps did not exceed 2.1 or 0.7% of the applied radiation 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. Degradation kinetics were not reported as no significant degradation was observed. In the RAR, the RMS has confirmed that for 5 out of 6 of the experiments with

dimethomorph, no degradation can be demonstrated because the rate of degradation does not significantly differ from 0 and/or the t-test is > 0.05. The results are considered reliable (Ri 2) and can be used for classification purposes.

11.1.4.4 Photochemical degradation

Three GLP studies on direct photochemical degradation in water were present in the original registration dossier, no additional studies were added to the dossier for the renewal. The descriptions below are based on the summary in the RAR.

Van Dijk (1990) examined photodegradation of radiolabelled dimethomorph in water in a GLP study according to a US-EPA guideline (US EPA Pesticide Assessment Guidelines, Subdivision N, Chemistry: Environmental Fate, Section 161-2: Photodegradation Studies in Water). Dimethomorph was dissolved in a buffer at pH 5 at a concentration of 6 µg/L. The solutions were continuously exposed at 25°C for 15 days. The light intensity was 90-92 KLux. Samples were taken at start and days 1, 2, 4, 7 and 15. A steady stream of air passed through the system, and passed over traps to collect $^{14}CO_2$ and organic volatiles. A recovery of the radiolabels was achieved of 95 to 99.6% and the recovery in the control (dark) samples was 99.7 to 102.9%. After 15 days, only 0.5% of the applied radioactivity was retrieved the volatile traps and 70% of the parent compound was still present in the test solutions. Individual metabolites did not exceed 10%. The half-live of the parent was calculated to be 25-28 days. The results are considered reliable (Ri 2) and can be used for classification purposes.

Panek et al. (2001) examined photodegradation of radiolabelled dimethomorph (E/Z ratio: 42/58) in water in a GLP study according to a US-EPA guideline (US EPA Pesticide Assessment Guidelines, Subdivision N, Chemistry: Environmental Fate, Section 161-2: Photodegradation Studies in Water). Two different labels of dimethomorph were tested separately ([^{14}C(U)-chlorophenyl]-dimethomorph, > 98 % and 2,3,5,6-^{14}C-morpholine]-dimethomorph, > 99 %). The substances were dissolved in a buffer at pH 5 at a concentration of 5.3 µg/L. The solutions were continuously exposed at 25°C for 21 days. The light intensity was 489-490 W/m2 and wavelengths <290 nm were filtered out. Samples were taken at start and days 4, 8, 15 and 21. A steady stream of air passed through the system, and passed over traps to collect $^{14}CO_2$ and organic volatiles. A recovery of the radiolabels was achieved of 100-103% and the recovery in the control (dark) samples was 99.5-106.2%. After 21 days, at most 2.2% of the applied radioactivity was retrieved from the volatile traps and at least 97.9% of the radioactivity was still present in the test solutions. 80.9-87.2% of the applied radioactivity was present as the parent. Individual metabolites did not exceed 10%. The half-live of the parent was calculated to be 107 and 86 days for the chlorophenyl and morpholine label, respectively. The results are considered reliable (Ri 2) and can be used for classification purposes.

Knoch and Holman (1998) examined photodegradation of unlabelled dimethomorph (E/Z isomer ratio: 44/56) in water in a GLP study according to a BBA and draft OECD guideline (Richtlinien für die Prüfung von Pflanzenschutzmitteln im Zulassungsverfahren Teil IV, 6-1; Biologische Bundesanstalt für Land- und Forstwirtschaft (BBA), D-38104 Braunschweig", July 1990; Organisation for Economic Co-operation and Development (OECD), OECD Draft Test Guideline: "Phototransformation of Chemicals in Water", December 1992). Dimethomorph with a purity of 97.6% was dissolved in a buffer at pH 7 at a concentration of 3.9 µg/L. The solutions were continuously exposed at 25°C for 72 hours. Wavelengths <290 nm were filtered out and the relative intensity of the light was 2.3 sun hours per intrument hour. Degradation was observed and the half live under test conditions was determined to be 303 hours. Normalised to normal sunlight the half live is estimated to be 29.2 hours. Metabolites were not reported. The results are considered reliable (Ri 2) and can be used for classification purposes.

11.2 Environmental transformation of metals or inorganic metals compounds

Not relevant

11.3 Environmental fate and other relevant information

In the RAR data on photochemical oxidation in the atmosphere is presented, considering the low vapour pressure (9.7×10^{-7} and 1.0×10^{-6} Pa at 50°C) and low Henrys law constant of (5.4×10^{-6} and 2.5×10^{-5} Pa m^3/mol), this data is considered not relevant for classification purposes.

11.4 Bioaccumulation

Table 16: Summary of relevant information on bioaccumulation

Method	Results	Remarks	Reference
log Pow	E-isomer: 2.63 Z-isomer: 2.73	Measured (HPLC-method)	RAR
OECD 305 *Lepomis macrochirus*	1.4 and 2.0	based on the parent concentration and normalised to 5% fat (Ri=2)	B.9.2.3.1 (1999)

11.4.1 Estimated bioaccumulation

-None

11.4.2 Measured partition coefficient and bioaccumulation test data

Reference B.9.2.3.1 (1999) examined the bioconcentration of dimethomorph (BAS 550F) in *Lepomis macrochirus*. The fish were exposed for 28 days to radiolabelled dimethomorph at nominal concentrations of 0.020 mg/L and 0.200 mg/L (corresponding to mean measured concentrations of 0.021 mg/L and 0.210 mg/l). Steady state was achieved by day 14 of the uptake period. The exposure was followed by a 14 day depuration period. In each treatment 120 fish were exposed and fish were sampled for analysis at days 7, 14, 21 and 28 of the uptake period and days 1 and 3 of the depuration period. The lipid content of the fishwas 8.41 % and 8.07% for whole fish in the low and high treatment groups respectively. The kinetic BCFs calculated from total radioactive residues are 16 and 22 for the low and high exposure respectively. Normalised to 5% fat, the BCF valus are 10 and 13 respectively. Kinetic BCFs based on the concentration of dimethomorph are 2.4 and 3.2 for the low and high exposure respectively. Normalised to 5% fat, the BCF valus are 1.4 and 2.0 respectively. The endpoints are considered reliable (Ri2) and can be used for classification purposes.

The highest BCF reported for dimethomorph is 2.0 (normalised to 5% fat) and the measured $LogK_{ow}$ values range from 2.63-2.73. Therefore it is considered to have a low potential for bioaccumulation.

11.5 Acute aquatic hazard

Table 17: Summary of relevant information on acute aquatic toxicity

The dimethomorph used in the aquatic toxicity studies was of technical grade, the E/Z ratio was not specified in the RAR.

Method	Species	Test material	Results	Remarks	Reference
Fish					
Static toxicity study according to OECD guideline 203	*Oncorhychus mykiss*	Dimethomorph Purity: 94.8%	LC50 = 6.1 mg a.s. /L (mortality; mean measured)	Study is considered reliable (Ri=2)*	B.9.2.1.1 (1986), B.9.2.1.4 (2010)

Flow through toxicity study according to OECD guideline 203	*Oncorhychus mykiss*	Dimethomorph Purity: 98%	LC50 = 6.8 mg a.s./L (mortality; mean measured)	Study is considered reliable (Ri=2)*	B.9.2.1.7 (2001)
Flow through toxicity study	*Cyprinodon variegatus*	Dimethomorph Purity: 98.0%	LC50 = 11.3 mg a.s./L (mortality; mean measured)	Study is considered reliable (Ri=2)*	B.9.2.1.8 (1997)
Static GLP toxicity study according to OECD guideline 203	*Cyprinus carpio*	Dimethomorph Purity: 94.8%	LC50 = 16.6 mg a.s./L (mortality; mean measured)	Study is considered reliable (Ri=2)*	B.9.2.1.3 (1986), B.9.2.1.2 (2010)
Static GLP toxicity study according to OECD guideline 203	*Lepomis macrochirus*	Dimethomorph Purity: 96.6%	LC50 >13.7 mg a.s./L (mortality; mean measured)	Study is considered reliable (Ri=2)*	B.9.2.1.5 (1988), B.9.2.1.6 (2010)
Flow through toxicity study according to OECD guideline 203	*Lepomis macrochirus*	Dimethomorph Purity: 98%	LC50 >9.5 mg a.s./L (mortality; mean measured)	Study is considered reliable (Ri=2)*	B.9.2.1.9 (2001)
Flow through toxicity study	*Pimephales promelas*	Dimethomorph Purity: 99.7%	LC50 >8.4 mg a.s./L (mortality; mean measured)	Study is considered reliable (Ri=2)*	B.9.2.1.10 (2014)
Invertebrates					
Static GLP study according to OECD guideline 202	*Daphnia magna*	Dimethomorph Purity: 94.8%	EC50 = 20.1 a.s. mg/L (mobility; mean measured)	Study is considered reliable (Ri=2)*	Ellgehausen (1986a), Habekost (2010)
Static GLP study according to OECD guideline 202	*Daphnia magna*	Dimethomorph Purity: 98.3%	EC50 >10.6 a.s. mg/L (mobility; mean measured)	Study is considered reliable (Ri=2)*	Mitchell (2001)
Flow through toxicity study according to EPA guideline 72-3	*Americamysis bahia*	Dimethomorph Purity: 98.0%	EC50 = 7.92 mg a.s./L (mobility; mean measured)	Study is considered reliable (Ri=2)*	Mitchell (1997a)
Flow through toxicity study according to EPA guideline 72-3	*Crassostrea virginica*	Dimethomorph Purity: 98.0%	EC50 = 4.42 mg a.s./L (shell growth; mean measured)	Endpoint for shell growth. Study is considered reliable (Ri=2)*	Mitchell (1997b)
Algae/Aquatic Plants					
Static GLP study according to OECD guideline 201	*Scenedesmus subspicatus*	Dimethomorph Purity: 94.8%	E_bC50 = 29.2 mg a.s./L (biomass; nominal) E_rC50 = not available (growth rate)	Study is considered unreliable for classification purposes (Ri=3)*	Ellgehausen (1986b)

Static GLP study according to OECD guideline 201	*Pseudokirchneriella subcapitata*	Dimethomorph Purity: 99.57%	EC50 = 82.2 mg a.s./L (growth rate; nominal) EC50 = 41.1 mg a.s./L (biomass; nominal)	Study is considered unreliable for classification purposes (Ri=3)*	Jatzek (2001)
Static study	*Lenma minor*	Dimethomorph	EC50 = not reported	Study is considered unreliable (Ri=3)*	Megateli and al. (2009), Megateli and al. (2013)

* Reliability according to Klimisch et al. (1997), since assessment is based on summaries in the DAR, Ri=1 is not given.

11.5.1 Acute (short-term) toxicity to fish

One additional study on acute toxicity to fish was included in the renewal dossier for dimethomorph since the previous evaluation. Some studies from the previous evaluation were reevaluated for the renewal. The descriptions below are based on the summaries in the RAR.

Reference B.9.2.1.1 (1986) has tested *Oncorhynchus mykiss* at five exposure concentrations for 96 hours in a batch exposure according to OECD guideline 203. The dimethomorph was technical grade with a purity of 94.87% and the five nominal test concentrations were 1, 2, 5, 7 and 10 mg/L. Mortality was observed in concentrations of 2 mg/L and higher. In the control ans solvent control no mortalities were observed. Test concentrations were verified by analysis and were 2.4, 4.0, 8.0, 10.3 and 14.1 mg/L. Sub-lethal effects were observed at the lowest exposure concentration and higher. In a reassessment (B.9.2.1.4, 2010), the LC50 based on mean measured concentrations was determined to be 6.1 mg/L. The endpoint is considered reliable and can be used for classification purposes.

Reference B.9.2.1.3 (1986) has tested *Cyprinus carpio* at four exposure concentrations for 96 hours in a batch exposure according to OECD guideline 203 at 21-23°C. The dimethomorph was technical grade with a purity of 94.87% and the four nominal test concentrations were 12, 14, 16 and 20 mg/L. Mortality was observed in concentrations of 14 mg/L and higher. In the control ans solvent control no mortalities were observed. Test concentrations were verified by analysis and were 115.6 – 129.2% of nominal. Sub-lethal effects were observed at the lowest exposure concentrations and higher. In a reassessment (B.9.2.1.2, 2010), the LC50 based on mean measured concentrations was determined to be 18.1 mg a.s./L but in the RAR, the RMS has recalculated the LC50 to 16.6 mg/L. The latter endpoint is considered reliable and can be used for classification purposes.

Reference B.9.2.1.5 (1988) has tested *Lepomis macrochirus* at five exposure concentrations for 96 hours in a batch exposure according to OECD guideline 203 at 20-21°C. The dimethomorph was technical grade with a purity of 96.67% and the five nominal test concentrations were 2.5, 4.5, 8.0, 14 and 25 mg/L. Mortality was observed in concentrations of 8.0 mg/L and higher, the mortality in the highest test concentration was 50%. In the control ans solvent control no mortalities were observed. Test concentrations were verified by analysis and were 1.9, 3.3, 5.3, 8.1 and 13.7 mg/L. Sub-lethal effects were observed at the 4.5 mg/L nominal exposure concentration and higher. In a reassessment (B.9.2.1.6, 2010), the LC50 based on mean measured concentrations was determined to be >13.7 mg/L. The endpoint is considered reliable and can be used for classification purposes.

Reference B.9.2.1.7 (2001) has tested *Oncorhynchus mykiss* at five exposure concentrations for 96 hours in a flow-through exposure according to OECD guideline 203. The dimethomorph was technical grade with a purity of 98% and the five nominal test concentrations were 2.6, 4.4, 7.2, 12 and 20 mg/L. Mortality was observed in concentrations of 4.4 mg/L and higher. In the control ans solvent control no mortalities were observed. Test concentrations were verified by analysis and were 1.75, 3.13, 4.71, 7.84 and 12.0 mg/L. Sub-lethal effects were observed at the nominal exposure concentration of 4.4 mg/L and higher. The LC50 was determined to be 6.79 mg/L. The endpoint is considered reliable and can be used for classification purposes.

Reference B.9.2.1.8 (1997) has tested *Cyprinodon variegatus* at five exposure concentrations for 96 hours in a flow-through exposure according to OECD guideline 203. The dimethomorph was technical grade with a purity of 98.0% and the five nominal test concentrations were 2.6, 4.4, 7.2, 12 and 20 mg/L. Mortality was observed in concentrations of 4.4 mg/L and higher. In the control ans solvent control no mortalities were observed. Test concentrations were verified by analysis and were 2.00, 3.29, 5.27, 8.82 and 14.6 mg/L. Sub-lethal effects were observed at the nominal exposure concentration of 4.4 mg/L and higher. The LC50 was determined to be 11.3 mg/L. The endpoint is considered reliable and can be used for classification purposes.

Reference B.9.2.1.9 (2001) has tested *Lepomis macrochirus* at five exposure concentrations for 96 hours in a flow-through exposure according to OECD guideline 203. The dimethomorph was technical grade with a purity of 98% and the five nominal test concentrations were 2.6, 4.4, 7.2, 12 and 20 mg/L. Mortality was observed in the highest test concentration (5%). In the control and solvent control no mortalities were observed. Test concentrations were verified by analysis and were 1.62, 2.78, 4.19, 6.75 and 9.53 mg/L. Sub-lethal effects were not observed. The LC50 was determined to be >9.53 mg/L. The endpoint is considered reliable and can be used for classification purposes.

Reference B.9.2.1.10 (2014) has tested *Pimephales promelas* at five exposure concentrations for 96 hours in a flow-through exposure according to OECD guideline 203. The dimethomorph had a purity of 99.7% and the five nominal test concentrations were 0.63, 1.3, 2.5, 5.0 and 10 mg/L. Mortalities were not observed in any test concentration, control or solvent control. Test concentrations were verified by analysis and were 0.60, 1.3, 2.5, 4.9 and 8.4 mg/L. Sub-lethal effects were not observed. The LC50 was determined to be >8.4 mg/L. The endpoint is considered reliable and can be used for classification purposes.

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

No additional studies on acute toxicity to aquatic invertebrates were included in the renewal dossier for dimethomorph since the previous evaluation. Some studies from the previous evaluation were reevaluated for the renewal. The descriptions below are based on the summaries in the RAR.

Acute toxicity of dimethomorph to *Daphnia magna* was tested in a static test by Ellgehausen (1986a) according to OECD guideline 202. The test compound was technical grade with a purity of 94.8% and eight concentrations were test of 7.81, 15.6, 31.3, 62.5, 125, 250, 500, and 1000 mg/L. Test concentrations were verified by analysis and were 3.6, 11.8, 19.0, 27.3, 35.9, 42.7, 49.9 and 58.0 mg/L. After 48 hours immobilisation was observed in the solutions with nominal concentration of 15.6 mg a.s.and higher. In a reassessment (Habekost, 2010), the EC50 based on mean measured concentrations was determined to be 20.1 mg/L. The endpoint is considered reliable and can be used for classification purposes.

Acute toxicity of dimethomorph to *Daphnia magna* was tested in a static test by Mitchell et al. (2001) according to OECD guideline 202. The test compound of technical grade had a purity of 98.3% and five concentrations were test of 1.3, 2.5, 5.0, 10 and 20 mg/L. Test concentrations were verified by analysis and ranged from 53 to 97% of nominal. were 1.26, 2.38, 4.66, 6.98 and 10.6 mg/L. After 48 hours immobilisation (5%) was only observed in the highest testconcentration. The EC50 based on mean measured concentrations was >10.6 mg/L. The endpoint is considered reliable and can be used for classification purposes.

Acute toxicity of dimethomorph to *Americamysis bahia* was tested in a flow-through test by Mitchell et al. (1997a) according to EPA guideline 72-3. The test compoundof technical grade had a purity of 98.0% and five concentrations were test of 1.3, 2.2, 3.5, 6.0 and 10 mg/L. Test concentrations were verified by analysis and were 1.21, 2.16, 3.45, 5.89 and 9.75 mg/L. After 48 hours immobilisation was observed in the nominal test concentration of 2.2 mg a.s./L and higher. The EC50 based on mean measured concentrations was 7.92 a.s. mg/L. The endpoint is considered reliable and can be used for classification purposes.

Acute toxicity of dimethomorph to *Crassostrea virginica* was tested in a flow-through test by Mitchell et al. (1997b) according to EPA guideline 72-3(b). The test compound of technical grade had a purity of 98.0% and five concentrations were test of 1.3, 2.2, 3.5, 6.0 and 10 mg/L. Test concentrations were verified by analysis and were 1.33, 2.24, 3.63, 6.15 and 10.1 mg/L. After 96 hours mortality of one oyster was observed in the highest test concentration. Shell growth was statistically significantly inhibited at the three highest test

item concentrations compared to the control. The EC50 based on mean measured concentrations for shell growth inhibition was 4.42 a.s. mg/L. The endpoint is considered reliable and can be used for classification purposes.

11.5.3 Acute (short-term) toxicity to algae and other aquatic plants

No additional studies on acute toxicity to algae and other aquatic plants were included in the renewal dossier for dimethomorph since the previous evaluation. Some studies from the previous evaluation were re-evaluated for the renewal. From a literature search four publications were included in the RAR and assessed on their reliability. The descriptions below are based on the summaries in the RAR.

Aquatic toxicity to algae was tested by Ellgehausen (1986b) on *Scenedesmus subspicatus* in a 72 hours exposure according to OECD test guideline 201. The dimethomorph of technical grade with a purity of 94.8% was test in nominal concentrations of 10, 20, 40, 80 and 160 mg/L in three replicates. Test concentrations were verified by analysis and were within 80 to 123% of nominal for the concentrationof 20 mg/L but 23.5 to 45.1% for the higher test concentrations. The latter two solutions were turbid because the concentrations exceed the water solubility and only clear solutions were analysed. The actual mean measured concentrations are not available. Over the exposure period inhibition of growth was observed from the lowest test concentration and the EC50 based on nominal concentrations was determined to be 29.2 mg/L. In the RAR for the assessment of the renewal dossier it was requested that the endpoint had to be based on mean measured concentration. In the absence of the raw data, this was not possible. The test is considered unreliable and will not be used for classification purposes.

Aquatic toxicity to algae was tested by Jatzek (2001) on *Pseudokichneriella subcapitata* in a 72 hours exposure according to OECD test guideline 201. The dimethomorph of technical grade with a purity of 98.3% was tested in nominal concentrations of 6.25, 12.5, 25, 50 and 100 mg/L in three replicates. Test concentrations were verified by analysis and the concentrations ranged from 75.8 to 82.5% of the nominal concentrations at 0 hours, to 77.6 to 94.0% of the nominal concentrations at 72 hours. It is also reported that the two highest test concentrations which are at or above the water solubility, were turbid. It is unclear if analysis of the two higher test solution is performed on clear solutions or that undissolved substance is included in the analysis. The actual mean measured concentrations are not presented in the RAR. Over the exposure period inhibition of growth was observed from the lowest test concentration and the EC50 based on nominal concentrations was determined to be 41.1 mg/L for biomass and 82.2 for growth rate. In the RAR comments of the RMS are not provided on this study. However for the study of Ellgehausen (1986b) on *Scenedesmus subspicatus* it was requested that the endpoint had to be based on mean measured concentrations. It is presumed that this also applies to the endpoints of the study of Jatzek (2001), especially since reported measured endpoints are lower than 80% and turbidity is observed in the two higher test solutions. In the absence of an endpoint based on measured data, the test is considered unreliable and will not be used for classification purposes.

Megateli et al. (2009, 2013) studied the effect of dimethomorph, as single substance or in combination with copper sulfat, on the growth of the aquatic plant *Lemna gibba* in a 168 h static toxicity test. The dimethomorph of technical grade with a purity of 97% was tested in nominal concentrations of 0.040, 0.200, 0.400, 0.800 and 1.000 mg/L in three replicates. The tests with copper sulfate are not relevant for classification and therefore not further discussed in this report. Test concentrations were verified by analysis and concentrations lower than 80% of the nominal concentrations were reported (10-40% of nominal). Raw data are not available and endpoint are based on nomnal concentrations. EC50 values are not reported in the RAR and it was stated that the study could not be used for be used for the renewal application especially since endpoints are based on nominal concentrations while measured concentrations are well below the nominal concentrations. For the same reasons the study is considered unreliable and will not be used for classification purposes.

11.6 Long-term aquatic hazard

Table 18: Summary of relevant information on chronic aquatic toxicity

The dimethomorph used in the aquatic toxicity studies was of technical grade, the E/Z ratio was not specified in the RAR.

Method	Species	Test material	Results	Remarks	Reference
Fish					
GLP, flow through, Early Life Stages test according to OECD guideline 210	*Oncorhynchus mykiss*	Dimethomorph Purity: 97.6%	NOEC (96d) = 0.056 mg a.s./L (weight; mean measured) EC_{10} = 0.116 mg a.s./L (weight; mean measured) EC_{10} > 0.897 mg a.s./L (length; mean measure)	The study is considered reliable (Ri = 2)* Calculation of EC_{10} values	B.9.2.2.2 (2015), B.9.2.2.1 (1997) B.9.2.2.2 (2015)
GLP Static Early Life Stages test according to EPA guideline 850.1400	*Cyprinodon variegatus*	Dimethomorph Purity: 97.5%	NOEC (40 d) = 0.136 mg a.s./L (hatching, weight and length; mean measured) EC10 = 0.150 mg a.s./L (weight; mean measured) EC10 = 0.759 mg a.s./L (length; mean measured)	The study is considered reliable (Ri = 2)* Calculation of EC_{10} values	B.9.2.2.2 (2015), B.9.2.2.6 (2010) B.9.2.2.2 (2015)
GLP Static Early Life Stages test according to OECD guideline 210	*Pimephales promelas*	Dimethomorph Purity: 98.3%	NOEC (34 d) = 0.107 mg a.s./L (hatchingmean measured) EC10 > 0.92 mg a.s./L (weight; mean measured)	The NOEC for hatching is considered reliable (Ri = 2)* The EC10 for weight is considered unreliable (Ri=3)*	B.9.2.2.5 (2002) B.9.2.2.2 (2015)
GLP 21 day Short term reproduction assay flow-through study	*Pimephales promelas*	Dimethomorph Purity: 99.7%	NOEC (21-d) ≥ 0.488 mg a.s./L (survival, weight, length, behaviour; mean measured)	The study is considered reliable (Ri = 2)*	B.9.2.4.1 (2014)
Invertebrates					
GLP 22 day renewal study according to OECD guideline	*Daphnia magna*	Dimethomorph Purity: 95.6%	NOEC = 0.10 mg a.s./L (survial and reproduction; nominal) EC10 = 0.15 mg a.s./L (reproduction; nominal)	The study is considered reliable (Ri = 2)*	Anonymous (1993), Brausch (2015), Memmert and Knoch (1993)
GLP 21 day flow-through study according to OECD guideline	*Daphnia magna*	Dimethomorph Purity: 97.6%	NOEC = 0.22 mg a.s./L (length; mean measured) EC10 = 0.42 mg a.s./L (reproduction; mean measured) EC10 > 2.0 mg a.s./L (length; mean measured) EC10 = 1.343 mg a.s./L (weight; mean measured)	The study is considered reliable (Ri = 2)*	Brausch (2015), Murrell (1997)

GLP 28 day flow-through study according to OECD guideline	*Americamysis bahia*	Dimethomorph Purity: 97.5%	NOEC = 0.24 mg a.s./L (reproduction; mean measured) EC10 = 0.24 mg a.s./L (reproduction; nominal)	The study is considered reliable (Ri = 2)*	Hicks (2010)
24 day static study according to OECD guideline	*Chironomus riparius*	^{14}C-dimethomorph Purity: 99.3%	NOEC = 4.11 mg a.s./L (emergence and weight; mean measured, initial) EC10 = 3.02 mg a.s./L (weight; nominal) EC10 > 15.6 mg a.s./L (emergence; nominal)	Water spiked water-sediment system, the study is considered reliable (Ri = 2)*	Brausch (2015), England and al. (1997)
Algae/Aquatic Plants					
Static GLP study according to OECD guideline 201	*Scenedesmus subspicatus*	Dimethomorph Purity: 94.8%	NOEC/EC10 = not available	The study is considered unreliable (Ri = 3)*	Ellgehausen (1986b)
Static GLP study according to OECD guideline 201	*Pseudokirchneriella subcapitata*	Dimethomorph Purity: 98.3%	EC10 = 27.3 mg a.s./L (growth rate; nominal) EC10 = 9.23 mg a.s./L (biomass; nominal)	Study is considered unreliable for classification purposes (Ri=3)*	Jatzek (2001)
Static study	*Lenma minor*	Dimethomorph	NOEC/EC10 = not reported	Study is considered unreliable (Ri=3)*	Megateli and al. (2009), Megateli and al. (2013)

* Reliability according to Klimisch et al. (1997), since assessment is based on summaries in the DAR, Ri=1 is not given.

11.6.1 Chronic toxicity to fish

Three new studies on chronic toxicity to fish were included in the renewal dossier for dimethomorph since the previous evaluation. Some studies from the previous evaluation were re-evaluated for the renewal. The descriptions below are based on the summaries in the RAR.

Chronic toxicity in fish was determined in *Onchorhynchus mykiss* according to the OECD test guideline 210 by Reference B.9.2.2.1. (1997). The test compound of technical grade with a purity of 97.6% was tested in five nominal concentrations of 0.033, 0.065, 0.13, 0.25, 0.50, and 1.0 mg/L, and mean measured concentrations were 0.0341, 0.0562, 0.120, 0.240, 0.449 and 0.897 mg/L (89.7 to 103% of nominal). The experiment started with fertilised egg and exposure lasted for 96 days. At completion of hatching, 100% survival was observed for the control and 98-100% for the treatments. This was not significantly different. At test termination, survival was not significantly affected in any of the treatments. For growth, mean weight was significantly affected at mean measured concentration of 0.12 mg/L. Therefore, the NOEC (for weight), based on mean measured concentrations, was determined to be 0.056 mg a.s./L. In a reassessment (B.9.2.2.2, 2015), the LC10 for weight, based on mean measured concentrations, was determined to be 0.116 mg a.s./L. The study is considered reliable and the NOEC and EC10 can be used for classification purposes.

Chronic toxicity in fish was determined in *Pimephales promelas* according to the OECD test guideline 210 by Reference B.9.2.2.5 (2002). The test compound of technical grade with a purity of 98.3% was tested in five nominal concentrations of 0.01, 0.033, 0.1, 0.33 and 1 mg a.s./L, and mean measured concentrations were 0.0082, 0.0310, 0.107, 0.347 and 0.92 mg/L (82 to 107% of nominal). The experiment started with fertilised egg and exposure lasted for 34 days. At completion of hatching, 85% survival was observed for the control and 71-87% for the treatments. Only in the nominal concentration of 0.33 mg a.s./L, embryo survival was significantly lower (71%) than the control. Embryo survival in the highest test concentration of 1 mg/L (nominal) was also lower (75%) than the control but this effect was not significant. At test termination,

survival of the hatched larvae was not significantly affected in any of the treatments. Growth and mean weight was significantly increased at the nominal concentration of 0.33 mg a.s./L and not in the highest concentration of 1 mg/L (highest). This observation was considered an artifact because of the lower number of in the replicates of this group due to the increased mortality rate until hatch. And an effect of the test substance was considered not plausible since body weight and length in the highest test concentration group were comparable to the control. Because in the highest test concentration no significant effects were observed there was no clear dose-response relation. Alltogether only the reduction in embryo survival is considered an effect of the test item since this is confirmed by the (not-significant) reduction in the highest test concentration. This results in a NOEC for hatching based on mean measured concentrations of 0.107 mg a.s./L. An EC10 of >0.92 mg a.s./L is also calculated for weight and length but as the observation is probably due to an artifact and there is no dose-response relation this value is considered unrelliable. The NOEC for hatching is considered sufficiently reliable for classification purposes (Ri=2).

Chronic toxicity in fish was determined in *Cyprinodon variegatus* according to the EPA test guideline 850-1400 by Reference B.9.2.2.6 (2010). The test compound of technical grade with a purity of 97.5% was tested in five nominal concentrations of 0.065, 0.13, 0.25, 0.50, 1.0 and 2.0 mg a.s./L, and mean measured concentrations were 0.0630, 0.136, 0.266, 0.536, 1.02 and 2.01 mg/L (94 to 112% of nominal). The experiment started with fertilised egg and exposure lasted for 40 days. At completion of hatching, 84% survival was observed for the control and 84-91% for the treatments. The time to hatch was significantly longer for the nominal test concentration of 0.25 mg a.s./L and higher.At test termination, survival of the hatched larvae was not significantly affected in any of the treatments. Length and mean weight was significantly affected at the nominal concentration of 0.25 mg a.s./L and higher. The NOEC (for hatching, weight and length), based on mean measured concentrations, was determined to be 0.136 mg a.s./L. EC10 values were determined is a re-assessment (B.9.2.2.2, 2015). The EC10 for mean length is 0.759 mg a.s./L and the EC10 for mean weight is 0.150 mg a.s./L. The study is considered reliable and the NOEC and EC10 can be used for classification purposes.

Potential endocrine activity of dimethomorph to *Pimephales promelas* was determined by Reference B.9.2.4.1 (2014). The test compound of technical grade with a purity of 99.7% was tested in five nominal concentrations of 0.047, 0.15 and 0.48 mg a.s./L, and mean measured concentrations were 0.046, 0.143 and 0.488 mg/L (at test start 80.7 to 92.7% of nominal and at termination 110.7-115.2% of nominal). The fish were approx. 5 months old at test initiation. Exposure lasted for 21 days. The evaluated endpoints were survival, fecundity, fertilization success, nuptial tubercle score, fish weight and length, blood plasma vitellogenin (VTG) concentration, histological examination of gonadal tissues as well as behavior and appearance, including secondary sexual characteristics. The biological results are based on mean measured concentrations. Percent survival of males, females and the survival rates based on combined data sets in the control were 100%. No statistically significant effects on fish wet weight and total length compared to the control were observed at any test concentration. The vitellogenin concentration in the blood plasma of male fish in comparison to the control group was statistically significantly increased in the 0.15 mg a.s./L test group only by using the Wilcoxon test. However, the median vitellogenin values of the males were not dose-dependently altered. The percentage of fertilized eggs in the control and all test item concentrations was 99.8%. The mean number of eggs per female per day was not statistically significantly different in comparison to the control group. Tubercles were not observed in females; therefore, they were not scored. For males, no statistically significant differences in mean tubercle scores compared to the control were determined in any test concentration. Furthermore, no notable abnormalities were observed with regards to behavior, coloration/banding, changes in ovipositor appearance or size of dorsal nape pad. Dimethomorph did not demonstrate any (anti-)estrogenic or (anti-)androgenic potential when tested at the maximum tolerated dose (MTC) in fathead minnow. The overall NOEC (21 d) for dimethomorph was determined to be ≥ 0.488 mg a.s./L based on mean measured concentrations. The study is considered reliable and the NOEC can be used for classification purposes.

11.6.2 Chronic toxicity to aquatic invertebrates

In addition to the existing studies, one new study on chronic toxicity to invertebrates was included in the renewal dossier for dimethomorph since the previous evaluation. Some studies from the previous evaluation were re-evaluated for the renewal. The descriptions below are based on the summaries in the RAR.

A GLP 22 day static renewal test on *Daphnia magna* was performed by Memmert and Knoch (1993) with technical grade dimethomprph (95.6%). The test was performed according to OECD guideline 202. The nominal exposure concentrations were 0.10, 0.31, 0.96, 3.1 and 9.6 mg a.s./L. Ten animals were tested at each exposure concentration. The test concentrations were analytically determined (Anonymous, 1993) and the mean measured concentrations were 86.9 to 105.5% of the nominal concentrations. The results are based on the nominal concentrations. Survival of the first generation was 100% for the solvent control and the lowest test concentration. 10% mortality was observed in the control. Significant mortality of the parents was only observed in the highest test cocentration. The number of offspring per surviving adult was significantly affected at exposure concentration 0.31 mg a.s./L and higher. The NOEC for survival of the parents, based on nominal concentrations, was determined to be 0.1 mg/L. The NOEC for number of offspring is 0.1 mg a.s./L. In a reassessment (Brausch, 2015), the EC10 for reproduction, based on nominal concentrations, was determined to be 0.152 mg a.s./L. The endpoints are considered reliable and can be used for classification purposes.

A GLP 21 day flowh-through study on *Daphnia magna* was performed by Murrell et al. (1997) with technical grade dimethomprph (97.6%). The test was performed according to EPA guideline 72-4. The nominal exposure concentrations were 0.13, 0.25, 0.50, 1.0 and 2.0 mg a.s./L. Four replicatees were perforemd with ten adults each. The test concentrations were analytically determined and the mean measured concentrations were 85 to 95% of the nominal concentrations. The results are based on mean measured concentrations. Survival of the first generation was 95% in the control. In the exposures, no significant effects were observed on adult survival. The number of offspring per surviving adult was significantly affected at the two highest exposure concentrations. Mean length of surviving adults was significantly affected at concentrations 0.50 mg a.s./L and higher. The overall NOEC, based on mean length, was determined to be 0.22 mg a.s./L (mean measured). In a reassessment (Brausch, 2015), EC10s for off spring per adult, length and body weight were determined to be 0.421, >2.0 and 1.343 mg a.s./L respectively. The endpoints are considered reliable and the EC10 for number of offspring can be used for classification purposes.

A GLP 28 day flowh-through study on *Americamysis bahia* was performed by Hicks (2010) with technical grade dimethomprph (97.5%). The test was performed according to EPA guideline 72-4. The nominal exposure concentrations were 0.065, 0.13, 0.25, 0.50 and 1.0 mg a.s./L. Three replicates were performed with 15 adults each. The test concentrations were analytically determined and the measured concentrations ranged from 78 to 122% of the nominal concentrations. The results are based on mean measured concentrations. Survival of the first generation (F0) was 93% in the control. In the exposures, no significant effects were observed on F0 and F1 survival. The number of offspring per female was significantly affected at the two highest exposure concentrations. For mean length of F0, some significant effects were observed but these did not indicate a dose-effect relation. The overall NOEC, based on reproduction, was determined to be 0.24 mg a.s./L (mean measured) and the EC10 was 0.238 mg a.s./L. The endpoints are considered reliable and can be used for classification purposes.

A GLP 24 day water spiked water-sediment study on *Chironomus riparius* was performed by England et al. (1997) with radiolabelled dimethomprph (99.3%). The test was performed according to EPA guideline 72-4. The nominal exposure concentrations were 1.13, 2.25, 4.50, 9.00 and 18.0 mg a.s./L (corresponding to initially mean measured concentrations: 1.08, 2.15, 4.11, 7.97 and 15.6 mg a.s./L). 14 replicates were performed for each treatment of which eight with test organisms and six for anaytical sampling. The test concentrations were analytically determined and the initial measured concentrations ranged from 87 to 96% of the nominal concentrations. The concentrations in the water phase declined to one thirth of the initial concentration during the 24 days of expopsure. The concentrations in the sediment phase increased in this period. The results are based on initial mean measured concentrations. Emergence in the control was 94% at day 24. Survival and number emerged were not significantly affected. Time to emerge and weight was

significantly affected at the two highest concentration. The overall NOEC was determined to be 4.11 mg a.s./L (initial mean measured). In a reassessment (Brausch, 2015), EC10 for weight was determined to be 3.022 mg a.s./L. For emergence (time and number of males and females) the EC10 values was >15.6 mg a.s./L. The endpoints are considered reliable and can be used for classification purposes.

11.6.3 Chronic toxicity to algae and other aquatic plants

One additional studies on chronic toxicity to aquatic plants was included in the renewal dossier for dimethomorph since the previous evaluation. Some studies from the previous evaluation were re-evaluated for the renewal. From a literature search four publications were included in the RAR and assessed on their reliability. The descriptions below are based on the summaries in the RAR.

Aquatic toxicity to algae was tested by Ellgehausen (1986b) on *Scenedesmus subspicatus* in a 72 hours exposure according to OECD test guideline 201. The dimethomorph of technical grade with a purity of 94.8% was test in nominal concentrations of 10, 20, 40, 80 and 160 mg/L in three replicates. Test concentrations were verified by analysis and were within 80 to 123% of nominal for the concentrationof 20 mg/L but 23.5 to 45.1% for the higher test concentrations. The latter two solutions were turbid because the concentrations exceed the water solubility and only clear solutions were analysed. The actual mean measured concentrations are not available. Over the exposure period inhibition of growth was observed from the lowest test concentration but significany of the observed inhibition is not reported in the RAR. Thereforte a NOEC cannot be determined. Also an EC10 is not reported. In the RAR it was requested that the endpoint had to be based on mean measured concentration. In the absence of the raw data, this was not possible. Therfore it is also not expected that reliable chronic endpoints can be determined from this study. The test is considered unreliable and will not be used for classification purposes.

Aquatic toxicity to algae was tested by Jatzek (2001) on *Pseudokichneriella subcapitata* in a 72 hours exposure according to OECD test guideline 201. The dimethomorph of technical grade with a purity of 98.3% was tested in nominal concentrations of 6.25, 12.5, 25, 50 and 100 mg/L in three replicates. Test concentrations were verified by analysis and the concentrations ranged from 75.8 to 82.5% of the nominal concentrations at 0 hours, to 77.6 to 94.0% of the nominal concentrations at 72 hours. It is also reported that the two highest test concentrations which are at or above the water solubility, were turbid. It is unclear if analysis of the two higher test solutions is performed on clear solutions or that undissolved substance is included in the analysis. The actual mean measured concentrations are not presented in the RAR. Over the exposure period inhibition of growth was observed from the lowest test concentration but significany of the observed inhibition is not reported in the RAR. Thereforte a NOEC cannot be determined. EC10 values for this study are reported in the List of end points of the RAR and are 27.3 mg a.s./L for growth rate and 9.23 mg a.s./L for biomass, both based on nominal data. In the RAR comments of the RMS are not provided on this study. However for the study of Ellgehausen (1986b) on *Scenedesmus subspicatus* it was requested that the endpoint had to be based on mean measured concentrations. It is presumed that this also applies to the endpoints of the study of Jatzek (2001), especially since reported measured endpoints are lower than 80% and turbidity is observed in the two higher test solutions. Therfore it is also not expected that reliable chronic endpoints can be determined from this study. The test is considered unreliable and will not be used for classification purposes.

Megateli et al. (2009, 2013) studied the effect of dimethomorph, as single substance or in combination with copper sulfate, on the growth of the aquatic plant *Lemna gibba* in a 168 h static toxicity test. The dimethomorph of technical grade with a purity of 97% was tested in nominal concentrations of 0.040, 0.200, 0.400, 0.800 and 1.000 mg/L in three replicates. The tests with copper sulfate are not relevant for classification and therefore not further discussed in this report. Test concentrations were verified by analysis and concentrations lower than 80% of the nominal concentrations were reported (10-40% of nominal). Raw data are not available and endpoints are based on nominal concentrations. NOECs or EC10 values are not reported in the RAR and it was stated that the study could not be used for the renewal application especially since endpoints are based on nominal concentrations while measured concentrations are well below the nominal concentrations. For the same reasons the study is considered unreliable and will not be used for classification purposes.

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

For dimethomorph, there are reliable acute data for fish and invertebrates. The lowest endpoint for fish is the value of 6.1 mg a.s./L for *Oncorhynchus mykiss* and for invertebrates this is 4.42 mg/L *Crassostrea virginica*. The lowest value of 4.42 mg a.s./L is above 1 mg/L, classification of dimethomorph as Aquatic acute is not applicable.

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Dimethomorph is hydrolytically stable at pH 4 to 9 which are environmental relevant pHs. There are two ready biodegradability studies (OECD 301B and 301D) available for dimethomorph. In the 301D test, no oxygen was consumed in 28 days and in the 301B, there was no evolution of carbon dioxide over 28 days. It was concluded that dimethomorph is not readily biodegradable. Inherent biodegradability was also assessed in a GLP study following the OECD 302C test guideline. Some evidence of inherent-primary biodegradability was observed (27% maximum biodegradation over 28 days). Low half-lives for some water-sediment systems are reported but since these are based on irreversible sorption to sediment, these cannot be considered as actual biodegradation and cannot be used for conclusion on rapid degradability.

On this basis, dimethomorph is considered not rapidly degradable and the chronic classification will be based on the criteria for non-rapidly degradable substances.

The highest BCF reported for dimethomorph is 2.0 and the measured $LogK_{ow}$ values range from 2.63 - 2.73. Therefore it is considered to have a low potential for bioaccumulation.

Reliable experimental chronic toxicity endpoints are available for fish and invertebrates. Where more than one acceptable toxicity value (NOEC and EC_{10}) is available for a study, the EC_{10} value is considered for classification. Where EC_{10} values are available for a species, they are preferred over NOEC values for the same endpoint (ECHA, 2015, OECD, 2006).

The following toxicity values are available for fish: *O. mykiss* EC_{10}= 0.116 mg/L, *C. variegatus* EC_{10}=0.150 mg/L and *P. promelas* NOEC = 0.107 mg/L. The most sensitive chronic endpoint for fish is the NOEC of 0.107 mg/L for *Pimephales promelas* therefore it is selected as key study. For invertebrates the lowest values are EC_{10} = 0.15 mg/L for *Daphnia magna,* NOEC/EC_{10} of 0.24 mg/L for *A. Bahia* and EC_{10} = 3.02 mg/L for *C. riparius.* The most sensitive chronic endpoint for invertebrates is the EC_{10} of 0.15 mg/L.

There are no adequate acute and chronic data for algae and as a consequence the surrogate method cannot be applied for this substance.

The lowest value is of 0.107 mg/L and the substance is considered non-rapidly biodegradable. Based on the criteria set out in CLP, Annex I, section 4.1, Table 4.1.0(b) (i), dimethomorph fulfils the criteria for classification as Aquatic Chronic 2.

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

A classification for aquatic acute toxicity is not required.

The proposed classification for aquatic chronic toxicity is Aquatic chronic 2.

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).**

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

Not evaluated in this dossier

13 ADDITIONAL LABELLING

Not evaluated in this dossier

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15 ANNEXES

An Annex I dossier without confidential information is available.

An Annex II with a confidential reference list is provided

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON DIMETHOMORPH (ISO); (E,Z)-4-(3-(4-CHLOROPHENYL)-3-(3,4-DIMETHOXYPHENYL)ACRYLOYL)MORPHOLINE