COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

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Last data extracted on 12.03.2019

Substance name: dimethomorph (ISO); (E,Z)-4-(3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl)morpholine
CAS number: 110488-70-5
EC number: 404-200-2
Dossier submitter:

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
07.03.2019	Denmark		MemberState	3
Comment received				
We propose to make it clear that the CLH proposal was only open for reproductive toxicity on human health. Hence, other endpoint such as STOT RE has not been taken into consideration. This is important as often the harmonized classification after renewals of pesticides are considered to cover all toxicological endpoints.				

Date	Country	Organisation	Type of Organisation	Comment number
07.03.2019	Germany		MemberState	4
Comment received				
We agree that the endpoints reproduction and development are of most concern for this substance and should be considered in detail. However, the prostate findings as observed in short-term studies in dogs (see below) might also trigger classification for STOT-RE 2 if not used to support the prosed classification for reproductive toxicity. This approach has been also discussed in the re-evaluation of dimethomorph under Regulation (EC) 1107/2009. In fact, STOT-RE 2 has been proposed by the RMS (i.e., the Netherlands) and was supported by the Co-RMS (Germany) and, very recently, by MS experts. Therefore, we would like to suggest to the RAC that also this endpoint is taken into consideration even though it was not specifically assessed by the DS. The used CAS and EC numbers are for the E/Z isomer. There is also a list number available for the single Z-isomer. In case this "pure" isomer should also be covered by the CLH proposal this needs to be clearly stated in chapter 1 of the report and also on the front page of the report. Otherwise the classification will apply only to the isomeric mixture. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment by the DE-CA on the CLH proposal for dimethomorph as Repr. 1B.pdf				

Date	Country	Organisation	Type of Organisation	Comment number

05.03.2019	France		MemberState	5
Comment received				
FR: - p.1: Identity of the substance, Table 1: Unit (g/mol) of the molecular weight should be added. - p.4: Table 7: For the following hazard classes – explosives, flammable solids, oxidizing solids – it should be better to indicate in the column reason for no classification, "data conclusive but not sufficient for classification" rather than "hazard class not assessed in this dossier" as data are available in RAR of the substance - p.5-6: Physicochemical properties, Table 8: purity of the test substance could be added for each property. - p.6: For flash point and viscosity, it should be better to add "non relevant as the substance is solid". - p.6: For the following properties – self-ignition temperature, granulometry and stability in organic solvents – it should be better to add "no data". - p.6-7: Evaluation of physical hazards: for explosives, flammable solids and oxidising solids points: data are available in the RAR of the substance (the used method, the results and the reference of the studies), this should be added in the CLH report.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
28.02.2019	Denmark	DTU Food	Academic institution	6
Comment received				
Reproductive toxicity and Endocrine disruption. The report (see references below) concludes: Deltamethrin does not meet the WHO definition of an endocrine disruptor, but fulfil the WHO definition of a potential endocrine disruptor. Also deltamethrin fulfil the proposed Danish criteria for being a suspected ED. Hass, U., Christiansen, S., Andersen MD, Rosenberg SA, Egebjerg KM, Brandt S, Nikolov NG, Holbech H, Morthorst JE (2018) List of Endocrine Disrupting Chemicals. Report from Danish Centre on Endocrine Disrupters for Danish EPA link to report: http://cend.dk/files/DK_ED-list-final_2018.pdf, link to appendix http://cend.dk/files/DK_ED-list-final_appendix1_2018.pdf I have uploaded deltamethrin information and litterature only (page 1-20) ECHA note – An attachment was submitted with the comment above. Refer to public attachment DK_ED list final_appendix Deltamethrin_2018.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
08.03.2019	Spain		MemberState	7
Comment received				
Fertility In the dog 90-day and 1-year study increased prostate weight combined with prostatic interstitial				

fibrosis was observed. These effects were observed in presence of other general toxicity. Besides, no such effects were observed in the repeated dose studies with rats and mice. These effects doesn´t seem as sufficiently convincing to warrant classification for fertility.

In the reproductive toxicity studies no effect on the mating index, fertility index, gestation index, live birth index and sperm parameters was observed.

In the extended one generation study, there were significant variations of the relative weight of
some reproductive organs in both F1 cohorts, as decrease of the seminal vesicle and reduction in
the prostrate relative weight. However, they were not accompanied by effects in gross necropsy
or histopathology. Due to lack of correlates between weight changes and morphology, findings
observed are not specific hallmarks for adverse effects on reproductive functions.

There is evidence for a statistically significantly reduced gestation length in the extended one generation study. The reduced gestation length was observed in the presence of maternal toxicity. We consider this marginal reduction in gestation length of low concern in absence of alteration in mating/ sexual behavior.

Effects observed are due to in utero exposure and are supportive of developmental toxicity and that no classification is required for dimethomorp for effects on sexual function and fertility.

On overall, the Spanish CA concludes that there is no clear evidence for an adverse effect on sexual function or fertility. No classification for effects on fertility is warranted.

Development

In the extended one-generation a decreased anogenital length and a delay in preputial separation was observed in males (F1) at the 800 ppm and 1600 ppm (both effects were outside of the historical control range). 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. Besides, at 1600 ppm, mean pup body weight was 13% below control at PND 1 and still 9% below controls at PND 21. Parental toxicity was evident from the dose of 800 ppm (decreased body weight gain in males F0, liver toxicity).

The statistical significance decrease of anogenital distance (AG) in F1 pups at 800 ppm was
unclear as the AG index at 800 ppm was within the range of historical controls. Only the statistical significance decrease of AG in F1 males at the high dose of 1600 ppm is considered
treatment related. However, this was a very weak effect, as the anogenital index of 1.57 at
1600 ppm in F1 males was only slightly below historical controls (1.58-1.67). Besides, the statistical significance of these reductions in the anogenital distance at 800 and 1600 ppm can
be influenced by the high value of the anogenital distance in controls (3.15) since it represents
the highest value in the provided historical control range (2.99-3.15). In addition, this effect was
not associated with changes in sex ratio/ or sexual development.

The delay in preputial separation (PPS) at the mid dose of 800 ppm was shown to be caused by the decreased body weight of the offspring. For the high dose group a specific effect on PPS could not be excluded. The delay in preputial separation at 1600 ppm is considered to be only a developmental effect as there was no impairment of the sexual function in the two reproduction toxicity studies.

The Spanish CA is of the opinion that findings observed in the extended one-generation study (reduced anogenital distance, delay in preputial separation, reduced pup weight and reduced seminal vesicle and prostate weight) are indicative of effects on development. 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. However, the whole available data indicate that severity of the effects is not sufficiently convincing to classified dimethomorph as Repr 1B for effects on development as proposed by the dossier submitter. The Spanish CA considers that the overall available evidence is deemed to best match the criteria for classification as category 2 for developmental effects.

Date	Country	Organisation	Type of Organisation	Comment number
07.03.2019	Denmark		MemberState	8

Comment received

Repro 1B:
DK agrees with the proposed classification Repr 1B (H360FD) for the following reasons:

Development
Based on decreased anogenital distance, delayed sexual maturation observed as delayed preputial separation in males and delayed vaginal opening in females, decrease seminal vesicle, decrease prostate weight, and decreased pup weight observed in the extended one-generation classification on development is warranted. Maternal toxicity was not so severe and cannot explain the developmental findings. The effects are relevant for humans. Hence, classification as Repr. 1B; H360D is warranted.

Sexual function and fertility
Based on reduced gestation length observed in the extended one generation toxicity study a classification on sexual function and fertility is warranted. This effect was also indicated in the older 2-generation study.
The effects on prostate (90-day and 1-yr dog studies and extended one generation study) and testes (hyperplasia in 2-yr rat and increased weight 1-yr dog) also indicate potential damage of the male fertility and could be taken into consideration for classification.
Effects on parturition (reduced gestation length) relevant for humans was observed in addition to alterations of the male reproductive system. Hence, classification as Repr. 1B; H360F is warranted.

STOT RE 2:
Classification as STOT-RE 2 should be considered based on the prostate findings such as histopathology (interstitial fibrosis) and decrease prostate weight in both the 90 day and 1 year dog studies. The effects were observed at 43 and 47 mg/kg bw/d and were reproducible within the species and with different dossing pattern (90 day vs 1 year). In

addition, reduced prostate weight was observed in the extended one generation study in rats.
The prostate is a target organ of dimethomorph. However, the effects on prostate could perhaps also be considered for the classification on fertility.

Date	Country	Organisation	Type of Organisation	Comment number
07.03.2019	France	BASF	Company-Manufacturer	9
Comment received				
1/ BASF strongly disagrees with the dossier submitters proposal for Repr. 1B H360FD. The classification for fertility and development is clearly disproportionate in relation with the observed effects. See details in the attached documents "Commenting table" and Doc 2017/1033551. 2/ STOT RE2 is not proposed in the CLH report and BASF fully agree with that. (CLH report 10.10.1 p 28). See details in the document "Commenting table" 3/ Following the new EFSA/ECHA Guidance document for identification of ED, a full Assessment is provided to EFSA, which should be added for completeness. (Annex I 3.10.3). See details in the attached documents "Commenting table and Doc 2018/1202679. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Documents to ECHA.zipx				

Date	Country	Organisation	Type of Organisation	Comment number
07.03.2019	Germany		MemberState	10
Comment received				
see attached comment ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment by the DE-CA on the CLH proposal for dimethomorph as Repr. 1B.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
05.03.2019	France		MemberState	11
Comment received				
FR: - 10.8.3 Comparison with the CLP criteria (fertility) The proposal for classification repr. cat1B H360F is supported based on effects observed in the EOGRT in line with anti-androgenic properties of Dimethomorph: * Decreased gestation length (also observed in the two generation reproductive study) * Decreased anogenital distance * Delay in preputial separation Furthermore, prostate effects (decreased weight and fibrosis) observed in dogs also support potential impact on male fertility. - 10.8.3 Comparison with the CLP criteria (development) 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. However, since those effects are induced during pregnancy, and/or result from parental exposure, classification repr.cat1B H360D seems also warranted.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
08.03.2019	United Kingdom		MemberState	12
Comment received				
Dimethomorph EC: 404-200-2; CAS: 110488-70-5) We agree the data support chronic classification endpoints in the range 0.1 to 1 mg/l resulting in Aquatic Chronic 2. We are unclear if the P. Promelas 34-d NOEC of 0.107 mg/l (mm) based on embryo hatching is a true NOEC as a clear dose-response effect was not observed due to effects only at one treatment and none at the treatment above which was highest treatment. For example has the data been tested for an outlier? It might be useful to consider if similar mortality was observed in across the replicates for the 0.33 mg a.s./l (nominal) treatment. We note that test concentrations have been measured in the chronic toxicity study with A. bahia - while the NOEC has been based on mean measured concentrations, the EC10 reproduction is based on nominal concentrations. As measured concentrations are not within 20% of the nominal, for completeness it would be useful to present the EC10 based mean measured concentrations.				

Date	Country	Organisation	Type of Organisation	Comment number
07.03.2019	France	BASF	Company-Manufacturer	13
Comment received				
The CLH report states that the algal study by Jatzek is not reliable because actual mean measured concentrations were not presented in the RAR and a NOEC cannot be determined. This study is considerable acceptable by the RMS in the revised RAR, so please consider the additional information. (CLH report 11.6.3 p42) See additional information in the attached document "Commenting table" ECHA note – An attachment was submitted with the comment above. Refer to public attachment Documents to ECHA.zipx				

Date	Country	Organisation	Type of Organisation	Comment number
07.03.2019	Germany		MemberState	14
Comment received				
We support the proposal for classification as Aquatic chronic 2 (H411). ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment by the DE-CA on the CLH proposal for dimethomorph as Repr. 1B.pdf				

Date	Country	Organisation	Type of Organisation	Comment number

05.03.2019	France		MemberState	15
Comment received				
FR: We agree with the proposal of classification for environmental hazards.				

PUBLIC ATTACHMENTS
1. Documents to ECHA.zipx [Please refer to comment No. 9, 13]
2. Comment by the DE-CA on the CLH proposal for dimethomorph as Repr. 1B.pdf [Please refer to comment No. 4, 10, 14]