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 29.05.2019

Substance name: pyridalyl (ISO); 2,6-dichloro-4-(3,3-dichloroallyloxy)phenyl 3-[5-(trifluoromethyl)-2-pyridyloxy]propyl ether
CAS number: 179101-81-6
EC number: -
Dossier submitter: The Netherlands

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France	sumitomo chemical agro europe	Company-Manufacturer	1

Comment received

Classification of pyridalyl for reproductive toxicity (effects on development) as Repr. 2 (H361d: May damage the unborn child) was recently proposed in the CLH report based on delayed vaginal opening in the two-generation toxicity study in the rats.

Although the age at vaginal opening appeared slightly delayed at 200 and 1000 ppm in F1 females and 1000 ppm in F2 females achieving statistical significance, the differences were small and there was no effect on other sex-hormone-related parameters, such as mating indices, fertility indices, gestation indices, implantation sites, oestrus cycle, and uterine weight. There was no effect on ano-genital distance, measured in F2 offspring but omitted from the CLH report. The age and weight of control animals at vaginal opening in the F1 and F2 generations was at the lower end or below the range of historical controls; age and weight of putatively affected offspring remained within the HCD range. In addition, in a specifically-designed and acceptable 4-week toxicity study in rats, serum oestradiol concentration did not change even at 2000 ppm. In the in vitro sex hormone biosynthesis assay also graded as acceptable, pyridalyl did not affect oestradiol synthesis in ovarian cells.

Furthermore, QSAR analysis showed that, based on the structure of pyridalyl, no developmental toxicity alert was triggered, being consistent with the considerations described above.

Considering weight of evidence: the observed difference was minor, occurred in the absence of any other developmental effect, with no detectable MoA, appears fully reversible and without long term consequences, and is feasibly attributable to atypical control group values. Classification of pyridalyl for developmental toxicity (Reproductive toxicant, H361d) is not warranted.

More detailed justification is provided in the attached position paper, which includes summary tables of the relevant data.
The report of the QSAR analysis is also provided.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Sumitomo comments on CLH.docx
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment pyridalyl Derek Nexus DART report.pdf

Date	Country	Organisation	Type of Organisation	Comment number
24.05.2019	Sweden		MemberState	2
Comment received				
The SE CA agrees with the proposed classification of pyridalyl in Repr. 2 H361d based on the observed delay in vaginal opening in both F1 and F2 generations in the 500 and 1000 mg/kg bw/day dose groups with 2 days and 1.7 days, respectively. In contrast to the DS, we do not consider that there was any maternal toxicity evident during gestation and lactation (no statistical significant changes in body weight or body weight gain), thus the delayed sexual maturation in female offspring is clearly not a secondary effect of maternal toxicity. At the time of vaginal opening there were no significant decreases in female offspring body weight in F1 or F2. However, at time points (PND 21) preceding vaginal opening there were statistical significant decreases in offspring body weight in F1 and F2 generations, both in males and females, ranging from 7-10% compared to control indicating a general delay in development of the offspring. It is noted that there appears to be no functional consequences of the delayed development/maturation in the F1 generation in terms of oestrus cycling, mating performance or fertility.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
24.05.2019	Sweden		MemberState	3
Comment received				
The SE CA agrees with the proposed classification of pyridalyl in Skin sens. 1, H317. Although the criteria for classification in subcategory 1B are fulfilled, the classification for subcategory 1A cannot be excluded since the study did not evaluate intradermal induction dose at or below 1%. Therefore the substance should be classified in category 1. We note, however, that the dose selection of intradermal injection based on the dose-range finding study (using 0.1, 0.2, 0.5, 1, 2, and 5%) appears to be appropriate since intradermal injection with 2% induced slight erythema and no or slight oedema.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	United Kingdom		MemberState	4
Comment received				
Acute Aquatic classification: Given the exposure solution preparation method using DMF solvent and HCO-40, it is likely analytical measurement of treatments represented dissolved and undissolved test item. Therefore effects seen at concentrations above the quoted water solubility of 0.00015 mg/l may not have resulted from dissolved test item and could represent physical effects from the emulsion. For example the sudden high immobilisation in treatments above the quoted water solubility in the Gries, 2006b acute Daphnia magna study indicate this to be possible. For				

example no significant immobilisation was observed for treatments up to an including 0.0207 mg/l and 95% immobilisation was observed at the next treatment 0.0455 mg/l. It would be useful to include further details of measured concentrations including if samples were filtered before analysis to aid interpretation.
In the acute toxicity to mysid study (Lima, 2002) with a quoted EC50 of 0.001 mg/l, we note that there was no observed effects up to the quoted water solubility (NOEC 0.0004 mg/l) and effects were only observed in emulsion treatments above the water solubility at 0.0019 mg/l and above. However we do note that solutions were observed to be clear and colourless. Measured concentrations are considered to be 88 to 100% of nominal – are there further details of the sample procedure such as filtration to help assess if treatments represented dissolved fractions?
Overall, at present it is not clear if L(E)C50 values represent dissolved test item or if quoted L(E)50 reflect physical effects due the emulsion treatment / concentrations above the quoted water solubility. Their application for acute hazard classification is therefore unclear.

Chronic Aquatic classification:
Chronic studies also employed emulsion exposure solutions.
Chronic NOECs for fish (0.0014 mg/l) and Daphnia magna (0.024 mg/l) are significantly above the quoted water solubility.
The 28-day chronic toxicity to mysid study (Lima, 2002) identified significant differences in reproduction compared to the solvent control for all treatments including concentrations below the quoted water solubility i.e. 0.000066 and 0.00012 mg/l treatments based on mean measured concentrations. However, it is noted that for these and further additional treatments above the water solubility, the effect was a positive increase in offspring. It is unclear if this is due to a poor performing solvent control as significant differences were noted between the solvent and procedural controls and it is also unclear if this apparent effect is relevant for hazard classification.
A decrease in reproduction was only observed at the highest treatment of 0.0009 mg/l and the quoted NOEC of 0.00045 mg/l is based on a 12% reduction in reproduction at 0.0009 mg/l. This indicates that while an EC10 endpoint would exceed the quoted experimental water solubility of 0.00015 mg/l it is within the same classification range and applicable for hazard classification.
We note that solutions were observed to be clear and colourless and measured concentrations are quoted as 84-120% of nominal. Are there further details of the sample procedure such as filtration to help assess if treatments represented dissolved fractions?

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	France		MemberState	5
Comment received				
FR agrees with the classification for environmental hazards and the M factor values (acute and chronic) proposed in the CLH report.				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2019	Belgium		MemberState	6
Comment received				
Although exposure concentrations of the dissolved fractions of pyridalyl in the aquatic toxicity studies are unknown and no information is available neither about micelles formation nor about the potential physical effects of the non-dissolved pyridalyl which makes interpretation of the result difficult, we agree with the dossier submitter that				

toxicity was seen in excess of the water solubility in fish and invertebrates. In such case L(E)C50/NOEC may be considered to be equal or below the measured WS.
We support the setting of the L(E)C50 and NOEC below or equal to the water solubility (15µg/L) and classification of the substance with Aquatic Acute 1, H400 and Aquatic Chronic 1, H4100.
BE CA also support the proposed M-factors : Macute = 1000 ((0.0001mg/l <L(E)C50 ≤0.001 mg/l) and Mchronic=100 (NRD, (0.0001mg/l <NOEC ≤0.001 mg/l).

PUBLIC ATTACHMENTS
1. Sumitomo comments on CLH.docx [Please refer to comment No. 1]

CONFIDENTIAL ATTACHMENTS
1. pyridalyl Derek Nexus DART report.pdf [Please refer to comment No. 1]