Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

6-[C12-18-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid (penta-PSCA)

EC Number: -
CAS Number: -

CLH-O-0000006923-68-01/F

Adopted

10 December 2020

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 6-[C12-18-ALKYL-(BRANCHED, UNSATURATED)-2,5-DIOXOPYRROLIDIN-1-YL]HEXANOIC ACID

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: 6-[C12-18-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid
EC number: -
CAS number: -
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
09.04.2020	United Kingdom	IPI Global Ltd	Company-Manufacturer	1
Comment received				
page 3. It is very well recognized that closed loop system technology reduces the exposure of the operator below the threshold recommended by the EU as confirmed by our customers and the HSE study and that it is in agreement with the latest amended EU directives for CMD 2004[1] and in general with the (89/391/EEC) of 12 June 1989[2] and the 89/24/EC of 7 April 1998[3].				
Dossier Submitter's Response				
Thank you for the information on the possibility of safe handling of 6-[(C10-C13)-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid in closed loop systems. This information is not relevant for the classification process and the intrinsic properties of the substance.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.04.2020	Germany		MemberState	2
Comment received				
The substance is an UVCB substance. Thus, the purity is per definition 100 %, this could be stated in table 1 of the report instead of claiming the purity to be not relevant. The EC number (701-162-1) is missing in the dossier. Next to this, the source substance penta-PSCA Na TEA used for OECD 422 study as well				

as the dose range finding study is composed of 55.0 % Pentapropylenesuccinimido-capronate. penta-PSCA however is not a salt and has a purity of 100 %. The composition of the other tested source substance tetra-PSCA is unknown. Furthermore, no information on the manufacturing process of either the target or the source substances is given. It is therefore questionable for the German CA, if read across can be justified based on substance identity.
Dossier Submitter's Response
Thank you for your comment on purity. No amendments in the original document are done at this stage of the process. The substance ID was agreed with ECHA and used accordingly. The substance has the list number 701-162-1 but this must not be included in the CLH dossier as, the "700" numbers have no legal significance (https://echa.europa.eu/information-on-chemicals/registered-substances/information). The manufacturing process is confidential but the information is given in a confidential annex to this document. Constituents (including concentration ranges) of tetra-PSCA are given in the confidential annex to the substance-specific CLH dossier. The issue that the dissolved penta-PSCA Na TEA comprises about only 55% penta-PSCA (Pentapropylenesuccinimido-capronate) was considered in the discussion of SCL for tetra- and penta-PSCA.
RAC's response
Noted.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
23.04.2020	France		MemberState	3
Comment received				
The read-across between penta-PSCA Na-TEA and penta-PSCA is considered acceptable. We agree with the DS's proposal for classification of penta-PSCA Repr 1B, H360FD and the proposed SLC for high potency group. Maybe, the ED_{10} could be calculated taking into account molecular ratio correction between penta-PSCA and penta-PSCA Na-TEA. This would further support the proposed SCL.				
Dossier Submitter's Response				
Thank you for your support. Molecular ratio correction: For these UVCBs only ranges are available, therefore the medium molecular levels have to be taken into account: penta-PSCA NaTEA: ~531; penta-PSCA: ~421, tetra-PSCA: ~365 (the exact compositions for the UVCBs are given in the confidential annexes to the CLH dossier). The ED_{10}-value of 7.8 mg/kg bw (penta-PSCA NaTEA) would then result in an ED_{10} (penta-PSCA) of 6.2 mg/kg bw and an ED_{10} (tetra-PSCA) of 5.4 mg/kg bw. However, it still has to be considered that according to a certificate of analysis for the OECD 422 study penta-PSCA NaTEA comprises about only 55% penta-PSCA (which is not in line with the registrants information on UVCB composition).				
RAC's response				
Noted, and taken into account for the setting of SCL/GCL in the opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
16.04.2020	Germany		MemberState	4

Comment received

For penta-PSCA the classification Repr. 1B, H360FD is proposed. The proposal is based on effects seen in rats after administration of the read-across substance penta-PSCA Na-TEA by gavage.

Fertility
The proposed classification of penta-PSCA as Repr. 1B, H360F is based on results from one dose range-finding study for an OECD TG 422 (3 animals/sex/dose) and a study according to OECD TG 422 with the source substance penta-PSCA Na-TEA.
In a dose range finding, toxicity study significant effects on fertility parameters were detect-ed using dose levels of 0, 100, 300 and 1000 mg/kg bw/day. Two of three females at the dose level of 1000 mg/kg bw/day were not pregnant. Consequently, fertility indexes (number of females achieving pregnancy as a percentage of females paired) and conception rates (number of females achieving pregnancy as a percentage of females mated) were 100 %, 100 %, 100 % and 33.3 % at the dose levels of 0, 100, 300 and 1000 mg/kg bw/day, respectively.
Also in the main study according to OECD TG 422 using dose levels of 0, 40, 200 and 1000 mg/kg bw/day effects on fertility parameters were detected.
Male and female body weights were significantly reduced at 1000 mg/kg bw/day as well as male absolute testes and epididymis weights. Also at 200 mg/kg bw/day, reduced body weight (males) is documented.
A dose dependent decrease, statistically significant in birth index (100 % at 1000 mg/kg bw/day), viability index (100 % at 1000 mg/kg bw/day) and fertility index (72 % at 1000 mg/kg bw/day) was observed. Post-implantation loss, reduced litter size and postnatal loss are already increased at 40 mg/kg bw/day. Complete litter loss occurred at 1000 mg/kg bw/day. LOAEL (Fertility) was 40 mg/kg bw/day.
The substance specific adverse effects on fertility already occur below the paternal LOAEL of 200 mg/kg bw/day. The DE CA agrees that a classification as Repr. 1B, H360F is warranted for penta-PSCA.

Developmental toxicity
The proposed classification of penta-PSCA as Repr. 1B, H360D is based on results from one study according to OECD TG 422 and a prenatal developmental toxicity study according to OECD TG 414 with a reduced number of animals (5 per sex and dose) with the source substance penta-PSCA Na-TEA.
In the screening study, developmental toxicity was seen from a dose level of 40 mg/kg bw/day with paternal LOAEL of 200 mg/kg bw/day. Developmental toxicity comprises significant increase in post-implantation losses in a dose dependent manner in all dose groups (40, 200, 1000 mg/kg bw/day), a dose dependent reduction of litter size and reduction in birth index (significant, dose dependent, complete litter loss at 1000 mg/kg bw/day). Postnatal mortality was significantly increased in the low and mid dose groups.
The modified prenatal developmental toxicity study was conducted with lower doses (0, 8, 40, 200 mg/kg bw/day. Mild maternal toxicity occurred only at 200 mg/kg/bw/day (reduced food consumption and body weight gain). Developmental effects on foetuses occurred from 8 mg/kg bw/day in a dose dependent manner (small spleen). From 40 mg/kg bw/day sub-numerary (rudimentary) ribs were found and skeletal malformations occurred at 200 mg/kg bw/day.
Since maternal toxicity is minimal, the classification of penta-PSCA as Repr. 1B, H360D is supported.

Specific concentration limit
For the substance investigated a specific concentration limit of 0.03% is proposed.
The concentration limit was based on the lowest ED_{10} value, which was 7.8 mg/ kg bw for one of the leading effects for reproductive toxicity (small spleen). According to the CLP Guidance a medium potency is therefore assumed for the substance as the boundaries for the medium potency group are 4 mg/kg bw/day< ED_{10} < 400 mg/kg bw/day. However, the ED_{10} value is very close to the boundary of the high potency group and modifying factors can be applied to consider a shift to the higher potency group. The available data on penta-PSCA Na-TEA only allowed the derivation of LOAELs and the lowest ED_{10} value is similar to the LOAEL of 8 mg/kg bw/day. Moreover, the studies were conducted with penta-PSCA Na-TEA, comprising only 55 % of penta-PSCA, which is likely causing the reproductive toxicity. Even lower effect levels can be considered for the acid.
The shift to the high potency group and the resulting SCL of 0.03 % is therefore supported.

Dossier Submitter's Response

Thank you for your support.

RAC's response

Noted. RAC agrees on a classificaiton as Repr. 1B; H360FD. Further, RAC notes that according to the CLP Guidance (paragraph 3.7.2.6.6.1) separate SCL should be set for effects on sexual function and fertility and developmental toxicity. Therefore, RAC has assessed separately the SCL for effects on sexual function and fertility and developmental toxicity. RAC concludes that the GCL should be applied for adverse effects on sexual function and fertility as well as development.

Date	Country	Organisation	Type of Organisation	Comment number
24.04.2020	Sweden		MemberState	5

Comment received

The Swedish CA agrees with the proposed classification of penta-PSCA for adverse effects on sexual function and fertility and for adverse effects on the development of the offspring as Repr. 1B, H360FD.

Since the CLH-proposal for reproductive toxicity is entirely based on read-across from the sodium and triethanolamonium salt of penta-PSCA, we think it is crucial that the read-across justification (based on non-confidential information) is included in the CLH-report to allow a transparent and independent assessment.

Specific concentration limits
The Swedish CA agrees that the generic concentration limits apply for both adverse effects on fertility and for developmental toxicity. We are of the opinion that potency should only be determined if the available data allow and it is maybe not appropriate for UVCBs since they comprise of variable components. Moreover, since the current CLH-proposal for reproductive toxicity of penta-PSCA is based on read-across of data from reproductive toxicity studies conducted with its sodium and triethanolamonium salt, this further adds to the uncertainty of the data for potency determination.

Dossier Submitter's Response

Thank you for your support.

No amendments in the original CLH document are done at this stage of the process. As the CLH template gives no guidance on the reporting of read-across, it was included in a non-confidential Annex I for better to readability.

Specific concentration limits
SCLs have been derived as severe effects were seen at low doses, based on the CLP guidance. Constituents are described in the relevant confidential annexes of the CLH report. The main components of the UVCBs are similar molecules where the number of C-atoms of the alkyl side chain (branched, unsaturated) at position 3 of the ring structure is varying. The read across from the salt (which is dissolved in a biological fluid) to the toxic relevant acid is described in detail in Annex I to the report.

RAC's response

Noted. RAC agreed on a classificaiton as Repr. 1B; H360FD. Further, RAC notes that according to the CLP Guidance (paragraph 3.7.2.6.6.1) separate SCL should be set for effects on sexual function and fertility and developmental toxicity. Therefore, RAC has assessed separately the SCL for effects on sexual function and fertility and developmental toxicity. RAC concludes that the GCL should be applied for adverse effects on sexual function and fertility as well as development.

Date	Country	Organisation	Type of Organisation	Comment number
22.04.2020	Netherlands		MemberState	6

Comment received

Read-across approach
No data are available on this substance with respect to reproduction toxicity. The structurally similar chemical penta-PSCA Na-TEA is used as a source substance for read-across. Upon dissolving in a biological fluid, it is assumed that penta-PSCA Na-TEA will immediately dissociate in sodium ion, triethanolammonium ion and penta-PSCA. It is agreed that, based on the available data, the reproductive toxicity of penta-PSCA Na-TEA as noticed in the OECD 422 and 414 studies does not seem to be related to TEA (NOAELs/LOAELs – corrected for TEA content – are a factor 10-80 higher for maternal toxicity, and a factor 20-120 higher for developmental toxicity than penta-PSCA Na-TEA). Overall, the NL-CA agrees with the proposed read-across approach.

Sexual function and fertility
The NL-CA agrees with the proposed Repr. 1B (H360F) classification for adverse effect on sexual function and fertility. The data of the OECD 422 study with penta-PSCA Na-TEA provide clear evidence of an adverse effect on sexual function and fertility. These adverse effects included reduced fertility index, reduced gestation index and increased pre-implantation loss. Though also general toxicity was observed (including reduced growth and food consumption, liver hypertrophy), the adverse effects on reproduction are considered not to be a secondary non-specific consequence of other toxic effects.

Developmental toxicity
The NL-CA agrees with the proposed Repr. 1B (H360D) classification for adverse effects on development. The data of the OECD 422 and OECD 414 studies with penta-PSCA Na-TEA provide clear evidence of an adverse effect on development. These adverse effects included reduced birth index, reduced litter size, increased post-implantation loss and increased postnatal loss observed in the OECD 422 study. In addition, in the OECD 414 study, external (cleft palate), visceral (small spleen) and several skeletal abnormalities

were found. Though also maternal toxicity was observed (including reduced growth and food consumption), the adverse effects on development are considered not to be a secondary non-specific consequence of other toxic effects.

The chemical moiety responsible for the reprotoxic effects (fertility and developmental toxicity) of penta-PSCA Na-TEA is assumed to be 2,5 dioxopyrrolidin hexanoate (TEA showed no reproductive toxicity in an OECD 421 study).

Effects on/via lactation
There were no data available on effects on or via lactation; therefore a conclusion cannot be drawn.

Concentration limit
The NL-CA agrees with the conclusion that application of an SCL of 0.03% for developmental toxicity is justified for penta-PSCA. The read-across substance penta-PSCA Na-TEA is a borderline case between medium and high potency. Given that penta-PSCA Na-TEA contains only 55% penta-PSCA and considering that for penta-PSCA lower effective dose levels would be expected, a shift to a high potency can be considered. However, the guidance on the application of CLP criteria (paragraph 3.7.2.6.6.1) describes that "concentration limits have to be determined separately for the two main types of reproductive toxic effects. In case the potency and resulting specific concentration limits are different for sexual function/fertility and development for a substance, the substance needs to be assigned one SCL for developmental toxicity and another SCL for effects on sexual function and fertility." The dossier submitter is asked to reflect on the need for assigning two separate SCLs for developmental toxicity and sexual function & fertility.

Minor comment:
p.36 (6th paragraph): In the sentence beginning "Based on read-across…" the name of the substance in incorrect; "6-(C10-13-alkenyl-(even and odd, branched, unsaturated)-2,5-dioxopyrrolidin-1-yl)hexanoic acid" should be "6-[C12-18-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid".

Dossier Submitter's Response

Thank you for your support.

Assignement of SCLs:
For the derivation in the CLH dossier the adverse effect "small spleen" in pups reported in an OECD 414 study (dosing with 0, 8, 40, 200 mg/kg bw, GD 6-20) has been used which resulted in an ED_{10} of 7.8 mg/kg bw.

The main study for evaluation of effects on fertility is the OECD 422 study with a higher dosing (0, 40, 200, 1000 mg/kg bw) already starting in premating phase. The following parameters relevant for classification have been identified:

	0 mg/kg/day	40 mg/kg/day	200 mg/kg/day	1000 mg/kg/day
Fertility index (%)	100.0	90.0	90.9	72.7
Gestation index (%)	100.0	100.0	90.0	0.0##
Implantation (mean incidence)	12.2	12.7	12.1	8.5
Post-implatation loss (mean incidence)	0.4	2.0##	3.8#	8.5##

Steel test, significant at 5% (#), 1% (##); Fischer´s Exact test, signif. at 5% (*), 1% (**)

(for details on data see CLH dossier)

The ED_{10} is defined as an effective dose with a 10% effect level above the background. A decrease of 10% in fertility can be seen at 40 mg/kg bw (LOAEL). For the effect post-implantation loss, which is an effect that can be assigned to fertility (ECHA guidance R.7a), an ED_{10} has been calculated as described in the Annex to the dossier resulting in a value of 107.1 mg/kg bw (and a LOEAL of 40 mg/kg bw).
For the discussion on SCL this would mean that a medium potency can be assigned for fertility. The ED_{10}/LOAEL values are more than a factor of 10 above the lower boundary. Modifying factors can be considered (severe effect, screening study and only LOAEL identified).
In addition it has to be considered here also that the study was conducted with the source substance penta-PSCA Na-TEA and the reprotoxic effects may be due to the dissolving product penta-PSCA. The dissolved UVCB comprises about only 55% penta-PSCA. Therefore for the pure substance even lower effect levels can be assumed.
All together potency for this endpoint is not as clear as for developmental toxicity, but medium to high potency is indicated.

Thank you for your minor comment. The sentence should be as following: Based on read-across the substance 6-[C12-18-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid has to be classified for its adverse effects on fertility and development as Repro 1B, H360FD.

RAC's response

Noted. RAC agreed on a classificaiton as Repr. 1B; H360FD. Further, RAC notes that according to the CLP Guidance (paragraph 3.7.2.6.6.1) separate SCL should be set for effects on sexual function and fertility and developmental toxicity. Therefore, RAC has assessed to separately the SCL for effects on sexual function and fertility and developmental toxicity. RAC concludes that the GCL should be applied for adverse effects on sexual function and fertility as well as development.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
16.04.2020	Germany		MemberState	7

Comment received

An acute dermal irritation test according to OECD TG 404 with penta-PSCA resulted in a mean erythrema score of 1.1 with a maximum of 2 and an oedema score of 0. Effects were fully reversible within7 days. Thus, the criteria for classification of the substance as skin irri-tant are not met.
Therefore, the DE CA agrees that classification of penta-PSCA as skin irritant is not warranted.

Dossier Submitter's Response

Thank you for your support.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
23.04.2020	France		MemberState	8
Comment received				
Based on the available study on the substance, we agree with no classification for skin irritation.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
16.04.2020	Germany		MemberState	9
Comment received				
An acute eye irritation test similar to OECD TG 405 (7 days observation) with penta-PSCA resulted in mean scores of 0.3, 0.4, 1.3 and 0.6 for corneal opacity, iris, conjunctival redness and chemosis respectively. Effects were fully reversible within7 days. Thus, the criteria for classification of the substance as eye irritant are not met. Therefore, the DE CA agrees that classification of penta-PSCA as eye irritant is not warranted.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
23.04.2020	France		MemberState	10
Comment received				
Based on the available eye irritation study on the substance, we agree with no classification for eye irritation.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
16.04.2020	Germany		MemberState	11
Comment received				
Specific target organ toxicity – repeated exposure was investigated based on a study with the read-across substance tetra-PSCA and 2 studies with the read-across substance				

penta-PSCA Na-TEA. In a 28-day study according to OECD TG 407 with tetra-PSCA only slight adverse toxicologi-cal effects were found at concentrations within the guidance values for STOT RE 2 (i.e. sali-vation, increased relative kidney weight in females, moderate to low incidence of eosino-philic bodies in male kidneys, increased relative liver weight in females). The other two Studies (OECD TG 422 and range finding study) with penta-PSCA Na-TEA also showed, if any, only effects with moderate adversity within the GVs (e.g. reduction of body weight (gain), reduced food consumption, reduced body temperature and locomotor activity). Based on the available data DE CA agrees, that a classification as STOT RE is not indicated.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
23.04.2020	France		MemberState	12
Comment received				
The observed effects below the guidance value for classification are insufficient for classification. Nevertheless, it could be pointed out that the data on the repeated dose toxicity of the substance are very limited (OECD 422 screening study, 28-day study on a structurally similar substance).				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				