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, sodium and tris(2-hydroxyethyl)ammonium salts (Penta-PSCA Na-TEA)

EC Number: -
CAS Number: -

CLH-O-0000006925-64-01/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, SODIUM AND TRIS(2-HYDROXYETHYL)AMMONIUM SALTS

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, sodium and tris(2-hydroxyethyl)ammonium salts
EC number: -
CAS number: -
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
16.04.2020	Germany		MemberState	1
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 confidential information. No EC/list or CAS number was used for identifying the substance even though a CAS (according to SciFinder) and a list number is available. Next to this, the information provided in the report Annex II confidential information is not in accordance with the information provided by the registrant Clariant Ibérica Producción S.A. on 14/12/2016. No information is available, on which registration/dossier/information the substance identity is based. Annex I of the report also provides information on the composition of the substance which is neither consistent with the information provided in the registration dossier (mentioned above) nor with the information provided in Annex II of the report. 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 701-271-4 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 CAS number (CAS 1424148-97-9) was deleted during substance ID check. The information given in *Annex I – 3. Purity and Impurities* is based on an analysis certificate of the substance batch (liquid) used for the OECD 422 study as well as the dose range finding study with the Penta-PSCA Na TEA. The information given in *Annex II* on the composition of the substance is based on information from ECHA dissemination site, registration dossier and CSR. ε-caprolactam is given at ECHA dissemination site but not in the registration. The manufacturing process is confidential but the information is given in a confidential annex to this document.
RAC's response
Noted.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
22.04.2020	Netherlands		MemberState	2
Comment received				
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. Effects on/via lactation There were no data available on effects on or via lactation; therefore a conclusion cannot be drawn. Concentration limits The NL-CA agrees with the conclusion that application of the GCL is justified. Although it is a borderline case between medium and high potency, no additional modifying factor				

applies; the approach is in line with the CLP guidance.

Minor comment:
p43: "Based on read-across the substance 6-(C10-13-alkenyl-(even and odd, 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. " should be deleted or modified to reflect the substance Penta-PSCA Na-TEA.

Dossier Submitter's Response

Thank you for your support on Classification and GCL.

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

RAC's response

Noted. RAC agreed on a classification as Repr. 1B; H360FD. 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
23.04.2020	France		MemberState	3

Comment received

Based on the clear effects observed with Penta-PSCA Na-TEA in the OECD 422 study (dose range-finding and main studies), classification as Repro. 1B, H360FD is warranted. The findings could not be explained by the general toxicity observed in parental animals. The clear findings observed at ≥ 8mg/kg in OECD 414 rat study also support the classification for developmental toxicity of the substance.

It would be helpful to have ED10 calculated for all relevant developmental and fertility effects observed in the OECD 414 and 422 studies. Anyway, an SCL for high potency is warranted based on the most sensitive effect (ED10 for small spleen at 8 mg/kg). In the OECD 414 study, no NOAEL was observed and thus, small spleen occurrence below the threshold of 4 mg/kg for high potency group cannot be excluded.
In addition, this is also supported by the fact that strong effects were already observed in screening studies (OECD 422). In these studies (preliminary and main study) low number of animals were used (decreasing the sensibility of the study) and male reproductive function was not fully investigated (e.g. only 4 week pre-treatment in males instead of 10 weeks that would be needed). Therefore, the occurrence of reproductive effects below 40 mg/kg is plausible.

Dossier Submitter's Response

Thank you for your support.
The most sensitive endpoint (small spleen seen in OECD 414) was used for derivation of SCL. However, also the most sensitive endpoint for the OECD 422 study (post-implantation loss) was discussed. In addition, a 10% decrease of fertility was seen at 40 mg/kg bw (LOAEL, similar to ED10). Other endpoints have been preliminary investigated during dossier preparation leading to higher values or limited reliable of resulting values (limitations in available data or dose-response).
For Penta-PSCA Na-TEA not a SCL but a GCL is proposed in the CLH dossier but maybe modifying factors like low number of animals and the lack of a NOAEL can be considered.

RAC's response
Noted. RAC agreed on a classification as Repr. 1B; H360FD. 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
16.04.2020	Germany		MemberState	4
Comment received				
Fertility The proposed classification of Penta-PSCA Na-TEA as Repr. 1B, H360F is based on results from one dose range-finding study for an OECD TG 422 (3 animals/sex/dose) and the main study according to OECD TG 422. In a dose range-finding toxicity study, significant effects on fertility parameters were detected 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 statistically significant decrease 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. The 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 Na-TEA. Developmental toxicity The proposed classification of Penta-PSCA Na-TEA as Repr. 1B, H360D is based on results from one study according to OECD TG 422 and a prenatal developmental toxicity study ac-cording to OECD TG 414 with a reduced number of animals (5 per sex and dose). 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 Na-TEA as Repr. 1B, H360D is supported.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted.

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 Na-TEA for adverse effects on sexual function and fertility and for adverse effects on the development of the offspring as Repr. 1B, H360FD. 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.				
Dossier Submitter's Response				
Thank you for your support on classification and GCL for this substance.				
RAC's response				
Noted. RAC agreed on a classification as Repr. 1B; H360FD. 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
23.04.2020	France		MemberState	6
Comment received				
The proposed read-across is based on the expected rapid dissociation of the test material in the biological fluids to Penta-PSCA acid form, Na ion and TEA ion. Based on the available data, read-across for systemic toxicity could be supported on this basis but not for local toxicity. Therefore, the available study performed on Penta-PSCA Na-TEA only should be taken into account for this endpoint. Nevertheless, as a mixture was used, the influence of other components is unknown. Therefore, no classification based on lack of data may also be considered by the DS.				
Dossier Submitter's Response				
Thank you for your comment. It is correct that only limited data is available. However, as the substance is used as a liquid and dissolved Penta-PSCA will be available (at pH > 4,74), a read-across was applied also for this local effect resulting in no classification.				
RAC's response				
Noted.				

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 a test material containing 40 % Penta-PSCA resulted in a mean erythema score of 2 for 2 of 3 animals and an oedema score of 0.33 for 2 of 3 animals. These effects were fully reversible within 14 days. Thus, the criteria for classification of the substance as skin irritant category 2 are not met. In addition, further tests with dissociation products (Penta-PSCA, triethanolamine (TEA)) showed only mild irritation potential, if at all, or only at high doses and longer test durations. Therefore, the DE CA agrees that classification as skin irritant is not warranted.				
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
23.04.2020	France		MemberState	8
Comment received				
As for skin irritation the read-across for local toxicity is not supported. Therefore, no classification based on lack of data may also be considered by the DS.				
Dossier Submitter's Response				
Thank you for your comment. A study with the substance in a mixture is available with positive results, however, the influence of other components is unknown. As the salt dissolves in biological fluids (at pH > 4,74) the concept of generic concentration limits of ingredients of a mixture for their effects on eyes has be applied. Based on this, a classification as Eye Irrit. 2, H319 for Penta-PSCA Na-TEA is proposed.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.04.2020	Germany		MemberState	9
Comment received				
An acute eye irritation test according to OECD TG 405 with a test material containing 40 % Penta-PSCA resulted in a mean conjunctivae score ≥ 2 in 2 out of 3 animals. Thus, the criteria for classification as Eye irritant category 2 are met. Penta-PSCA Na-TEA only represents 40 % of the mixture and properties of the remaining constituents are not known. Additional tests with dissociation products show that Penta-PSCA is not irritating. Triethanolamine on the other hand is self-classified as Eye Irrit 2 and 2 studies in the dossier gave clear positive results meeting the criteria of an Eye Irrit 2 classification. Since TEA comprises 13- 16 % of the mixture (based on structure and molecular weight), a classification of the mixture is possible. According to the CLP regulation (Annex I, part 3, table 3.3.3) the generic concentration limit of ingredients classified as Eye Irrit 2 that				

trigger classification of the mixture is ≥ 10 %. Therefore, the DE CA supports the proposed classification as Eye Irrit 2, H319.
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
23.04.2020	France		MemberState	10
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 comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.04.2020	Germany		MemberState	11
Comment received				
The DE CA agrees that a classification as STOT RE is not indicated. In a 28-day study with the read-across substance Tetra-PSCA only slight adverse toxicological effects were found at concentrations within the guidance values (GVs) for STOT RE 2 (i.e. salivation, increased relative kidney weight in females, moderate to low incidence of eosinophilic 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).				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				