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-[(C10-C13)-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid (tetra-PSCA)

EC Number: -

CAS Number: 2156592-54-8

CLH-O-0000006924-66-01/F

Adopted

10 December 2020

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 6-[(C10-C13)-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-[(C10-C13)-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid
EC number: -
CAS number: 2156592-54-8
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
09.04.2020	United Kingdom	<confidential>	Company-Manufacturer	1
Comment received				
It is very well recognized that closed loop system technology reduces the exposure of the operator below the threshold recommended by the EU. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 6-[(C10-C13)-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid .pdf				
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. No EC/list or CAS number was used for identifying the substance even though a CAS (accord-ing to SciFinder) and a list number is available. Moreover, the molecular weight				

should not be a confidential information. A range could be given instead.

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. Tet-ra-PSCA however is not a salt and has a purity of 100 %. Furthermore, no information on the manufacturing process of either the target or the source substances is given. It is therefore questionable, 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 CAS No 2156592-54-8 was used for the CLH dossier. The substance also has the list number 701-118-1 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 previous EC No 800-xxx-x was deleted in the course of an SID adaptation request.

The molecular formular ist C19H31NO4 - C23H39NO4. The corresponding MW is >= 337 - <= 393 g/mol. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/19944/11/?documentUUID=7ba87fd3-91ca-4f0d-bfba-110dacd0d1f9

The manufacturing process is confidential information. The relevant information is given in a confidential attachment to this document.

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 is considered acceptable. Nevertheless, there is no data on potential differences in potency related to the shorter size chains of Tetra-PSCA. 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.
It is correct that there is no data on potential differences related to the chain length.

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. 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 proposed to separate the SCL for effects on sexual function and fertility and developmental toxicity. RAC concluded 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	4

Comment received

The Swedish CA agrees with the proposed classification of Tetra-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 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. Since the current CLH-proposal for reproductive toxicity of Tetra-PSCA is based on read-across of data from reproductive toxicity studies conducted with the sodium and triethanolamonium salt of Penta-PSCA, 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 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 proposed to separate the SCL for effects on sexual function and fertility and developmental toxicity. RAC concluded 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	Belgium		MemberState	5

Comment received
Sexual function and fertility: BECA supports the proposal to classify Tetra-PSCA as Repro 1B for fertility due to concerning effects reported in the combined Screening Test (fertility index decrease, reduced conception rate or pre-implantation loss increase in parents animals). Development: BECA supports the proposal to classify Tetra-PSCA as Repro 1B for development due to the severe effect on development seen at doses as low than 8 mg/kg bw/d (statistically significant dose dependent increase of small spleen incidence, reaching 100% in fetuses of mother exposed to 200 mg/kg bw/d) or 40 mg/kg bw/d (more than 70% of fetuses with supernumerary ribs) observed during prenatal developmental toxicity study. Moreover, severe effects on development were also observed at 40 mg/kg bw/d during combined Screening test, for example viability index reduction, post implantation loss and increase of litter affected by dead pups at first check. Considering the severity of the effect, the low exposition of the groups affected and the fact that the tested product only contain 55% of Penta-PSCA in both studies, BECA supports the SCL of 0.03% General question: Post-implantation loss and small spleen have been chosen to calculate the ED_{10} for reproductive toxicity. But both of this data are more linked to development toxicity. Would it not be good to choose also a criteria affecting fertility specifically? (As fertility index for example?)
Dossier Submitter's Response
Thank you for your support of proposed classification and SCL. For your question on alternative ED_{10} values please refer to our response to comment No 7.
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 evaluated separately the data to set 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
16.04.2020	Germany		MemberState	6

Comment received

For Tetra-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 Tetra-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 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 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 Tetra-PSCA.

Developmental toxicity
The proposed classification of Tetra-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 Tetra-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 E D_{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 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 evaluated separately the data to set 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	7

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. Both substances belong to the group of 2,5 dioxopyrrolidin hexanoates. 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. Tetra-PSCA and Penta-PSCA can be considered to belong to a similar "chain length category". They have a high structural similarity and differ only in the number of C-atoms of the alkyl side chain. Sub-acute toxicity seems to be similar between target and source substance. Overall, the NL-CA agrees with the 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 Tetra-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, considering that for Penta-PSCA lower effective dose levels would be expected and taking into account the read-across approach for Tetra-PSCA, a shift to a high potency can be considered for Tetra-PSCA.
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.

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.

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 evaluated separately the data to set 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
23.04.2020	France		MemberState	8
Comment received				
We agree with the DS' proposal for no classification based on the available study on the substance.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.04.2020	Belgium		MemberState	9
Comment received				
BECA supports the proposal to do not classify Tetra-PSCA for skin corrosion/ irritation				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.04.2020	Germany		MemberState	10
Comment received				
In acute dermal irritation test according to OECD TG 404 with Tetra-PSCA no irritant or corrosive effects were observed. Both erythrema and oedema score were zero. Therefore, the DE CA agrees that classification of Tetra-PSCA 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	11
Comment received				
We agree with the DS' proposal for classification of the substance as Eye Irrit. 2, H319 based on the available eye irritation study on the substance.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.04.2020	Belgium		MemberState	12
Comment received				
BECA supports the proposal to classify Tetra-PSCA as Eye Irrit Cat. 2, H319				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.04.2020	Germany		MemberState	13
Comment received				
An acute eye irritation test according to OECD TG 405 with Tetra-PSCA resulted in mean scores of 1.8, 1, 2.33 and 2.5 for corneal opacity, iris, conjunctival redness and chemosis re-spectively. Effects were fully reversible within 18 days. Thus, the criteria for classification of the substance are met and the classification as eye irritant category 2 is supported.				
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	14
Comment received				
We agree with the DS' proposal for no classification. Nevertheless, it could be pointed out that the data on the repeated dose toxicity of the substance are very limited (28-day study).				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.04.2020	Belgium		MemberState	15
Comment received				
Regarding the effects observed at doses below 1000 mg/kg bw/day on parents during reproduction tests (combined Screening Test and prenatal developmental toxicity test) and rats during 28 D repeated dose study, the DS submitter propose not to classify Tetra-PSCA. Nevertheless, salivation and locomotion troubles are already visible in two studies at 200 mg/kg bw/day after 28D (49D for females of the prenatal toxicity test). In the 28D repeated dose study, necrosis of the mucosa of the glandular stomach in males is observed even after the recovery period in 200 mg/kg bw/day exposition group. Rats exposed to 1000 mg/kg bw/d of Tetra-PSCA presents an increase of both liver and kidney weight with histopathological findings (presence of moderate/severe eosinophilic bodies and granulation tissue accompanied by calcification in kidney and swelling hepatocytes in liver) and are in a poor clinical state (changes in fur, reddish tears, ptosis and soft feces).				
Dossier Submitter's Response				
Thank you for your comment. The (read-across) substance shows some effects after repeated dosing, however, as described in the dossier they are not considered severe enough by the dossier submitter to warrant classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.04.2020	Germany		MemberState	16
Comment received				
Specific target organ toxicity – repeated exposure was investigated based on a study with Tetra-PSCA and 2 studies with the read-across substance Penta-PSCA Na-TEA. In a 28-day study according to OECD TG 407 only slight adverse toxicological effects were found at concentrations within the guidance values 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 activi-ty). 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.

PUBLIC ATTACHMENTS
1. 6-[(C10-C13)-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid .pdf [Please refer to comment No. 1]