Committee for Risk Assessment

RAC

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: 701-271-4
CAS Number: -

CLH-O-0000006925-64-01/F

Adopted

10 December 2020

10 December 2020

CLH-O-0000006925-64-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **6-[C12-18-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid, sodium and tris(2-hydroxyethyl)ammonium salts**

EC Number: **701-271-4**

CAS Number: **-**

The proposal was submitted by **Austria** and received by RAC on **9 January 2020.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Austria has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **24 February 2020**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **24 April 2020**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Christine Bjørge**

Co-Rapporteur, appointed by RAC: **Stine Husa**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **10 December 2020** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	6-[C12-18-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid, sodium and tris(2-hydroxyethyl)ammonium salts	701-271-4	-	Repr. 1B Eye Irrit. 2	H360FD H319	GHS08 GHS07 Dgr	H360FD H319			
RAC opinion	TBD	6-[C12-18-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid, sodium and tris(2-hydroxyethyl)ammonium salts	701-271-4	-	Repr. 1B Eye Irrit. 2	H360FD H319	GHS08 GHS07 Dgr	H360FD H319			
Resulting Annex VI entry if agreed by COM	TBD	6-[C12-18-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid, sodium and tris(2-hydroxyethyl)ammonium salts	701-271-4	-	Repr. 1B Eye Irrit. 2	H360FD H319	GHS08 GHS07 Dgr	H360FD H319			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

6-[C12-18-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid, sodium and tris(2-hydroxyethyl)ammonium salts (**hereafter penta-PSCA Na-TEA**) are salts of the weak acid, 6-[C12-18-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid (hereafter **penta-PSCA**) which is also structurally similar to 6-[(C10-C13)-alkyl-(branched, unsaturated)-2,5-dioxopyrrolidin-1-yl]hexanoic acid (hereafter **tetra-PSCA**). When penta-PSCA Na-TEA is dissolved in biological fluid an immediate dissociation to the sodium and triethanolammonium ions and penta-PSCA can be assumed.

Read across assessment

An analogue read-across approach between penta-(polypropenylsuccinimido)-caproic acid (penta-PSCA) (source), tetra-PSCA (source) and penta-PSCA sodium-triethanolamine (Na-TEA) (target, Figure) has been proposed by the DS based on similarities in structure, ions release in biological media and expected similar toxicity. All substances (source and target substances) belong to the group of 2,5 dioxo-pyrrolidin hexanoates. They differ only in the number of C-atoms of the alkyl side chain (branched, unsaturated) at position 3 of the ring structure. The three PSCA are UVCB substances.

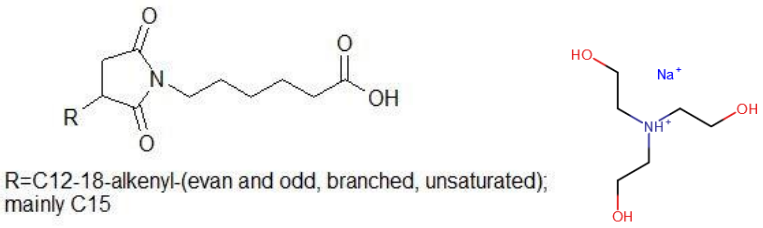

Figure: chemical structure of the salt penta-PSCA with sodium (Na^+) and triethanolammonium (TEA) ions

Three Member States Competent Authorities (MSCA) agreed with the read-across approach during the general consultation whereas two additional MSCA requested additional justifications. One commenting MSCA did not support the proposed read across for local toxicity due to uncertainties in the composition of the test substance. The DS argued that read across could be applied and clarified that additional information is available in a confidential annex to the CLH report. One MSCA noted that tetra-PSCA and penta-PSCA belong to a homologous series of (Polypropenylsuccinimido)-caproic acid and can thus be considered to belong to a "chain length category". The substances have a high structural similarity.

RAC agrees with the grouping approach and read across proposed by the DS for STOT RE. The assessment of the classification for reproductive toxicity is based on studies performed with the substance itself, penta-PSCA Na-TEA. For the assessment of the STOT RE a 28-day study in rats with exposure to tetra-PSCA was included for in addition to the OECD TG 422 performed with penta-PSCA Na-TEA. For local effects RAC considers that the classification should be based on data on penta-PSCA Na-TEA supported by data on penta-PSCA and triethanolamine (TEA; 2,2',2''-nitrilotriethanol, CAS no. 102-71-6, EC no. 203-049-8).

Purity of penta-PSCA Na-TEA

Based on the structure and the molecular weight of penta-PSCA Na-TEA (ranging from 465 to 549) the DS stated that the theoretic fraction of TEA will be 13-16%.

However, in the OECD TG 422 study as well as the associated dose range finding study with penta-PSCA Na-TEA a certificate of analysis for this batch gave the following result on the composition of the UVCB:

- Pentapropylenesuccinimido-caproate: 55.0%
- Sodium: 2.9%
- TEA: 31.2%
- Water: 9.2%
- Olefins: 1.7%

For the OECD TG 414 study with penta-PSCA Na-TEA no information on detailed composition was available. However, as the study was conducted at the same laboratory in the same time period as the OECD TG 422 study and associated dose-range finding study, sponsored by the same industry, the same composition was assumed.

Triethanolamine (TEA; 2,2',2''-nitrilotriethanol, CAS no. 102-71-6, EC no. 203-049-8), a dissolving product of penta-PSCA Na-TEA, is not considered to influence the anticipated (sub)chronic toxicity as shown by data (as presented by the DS) on repeated dose toxicity and reproductive toxicity on TEA. The corrected NOAELs/LOAELs for maternal toxicity were a factor of 10-80 higher following exposure to TEA than the derived values for penta-PSCA Na-TEA and tetra-PSCA. For reproductive toxicity a factor of 20-120 applies indicating that the observed effects were due to the dissolving product penta-PSCA and not due to TEA.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

For the evaluation of skin corrosion/irritation the DS included one study according to OECD TG 404 and GLP where 3 female New Zealand White rabbits were exposed to penta-PSCA Na-TEA (40% in teak oil, oleyl alcohol, polypropylene and water) under semi-occlusive conditions for 4 hours (Anonymous, 1993a). Signs of erythema and oedema were recorded 1, 24, 48 and 72 hours after patch removal. The recorded mean score for erythema per animal was 2, 3 and 3 (mean of 24, 48, 72h gradings), fully reversible within 14 days. The mean score for oedema per animal was 0.33, 0.33 and 0 (mean of 24, 48, 72h gradings) and was fully reversible within 2 days.

The DS included one study with penta-PSCA and several studies with TEA. In a study according to OECD TG 404 and GLP, 3 female New Zealand White rabbits were exposed to 0.5 mL penta-PSCA under semi-occlusive conditions for 4 hours (Anonymous, 1993b). Signs of erythema and oedema were recorded 1, 24, 48 and 72 hours after patch removal. The recorded mean score for erythema for three rabbits was 1.1 (mean of 24, 48, 72h for all three rabbits) while the mean score for oedema was 0. The effect was fully reversible within 7 days.

The skin irritation potential of TEA was investigated in five OECD TG 404 studies, two OECD TG 411 studies and two OECD TG 451 studies.

The OECD TG 404 study by Anonymous (1993b) with three Vienna White rabbits exposed to 0.5 mL 85% TEA and 15% diethanolamine for 4 hours (occlusive) showed a mean score of 0 (all three rabbits) for erythema as well as oedema.

In the OECD TG 404 study by Anonymous (1971a) two Vienna White rabbits were exposed to 85% TEA and 15% diethanolamine for 1, 5 and 15 min (occlusive) and two Vienna White rabbits were exposed to 85% TEA and 15% diethanolamine for 20 hours (occlusive). Mean erythema score at 24 hours were 0 for 1, 5 and 15 min and 2 for 20 hours application time.

In the OECD TG 404 study by Anonymous (1966a) two Vienna White rabbits were exposed to 0.5 mL lutrol 1, 5 and 15 min (occlusive) and two Vienna White rabbits were exposed to 0.5 mL lutrol for 20 hours (occlusive). Mean erythema score at 24, 48 and 72 hours were 0 for all animals exposed for 1, 5 and 15 min and 1 (for all animals) after 20 hours application time. Mean oedema score were 0 for all animals.

In the OECD TG 404 study by Anonymous (1956a) were rabbits (unknown number) were exposed to TEA unchanged or as 20% solution for 1, 5 and 15 minutes under occlusive conditions no skin irritation were observed.

In an OECD TG 404 study by Anonymous (1967a) two Vienna White rabbits were exposed to 0.5 mL TEA 1, 5 and 15 min (occlusive) and two Vienna white rabbits were exposed to 0.5 mL TEA for 20 hours (occlusive). Mean erythema score (24, 48 and 72 hours) were 0.5, 0.5, 0.75 and 2 for 1, 5 and 15 min and 20 hours application time respectively. Mean oedema score were 0 at all time points.

Overall, the five OECD TG 404 studies (all rather old, non GLP studies) with rabbits exposed to TEA, all showed no to mild irritation of the skin.

In a dermal 90-days study (OECD TG 411) with Fisher rats dermally exposed to TEA in acetone, inflammation of the skin and acanthosis were observed from 250 mg/kg bw/d (Anonymous, 1987). In a dermal 90-days study (OECD TG 411) with mice dermally exposed to TEA in acetone, dermal scaliness and erosion were observed at the highest dose of 4000 mg/kg bw/d (Anonymous, 1987).

In a 2-year carcinogenicity study (OECD TG 451) in rats, local effects like acanthosis, inflammation, ulceration and epidermal erosion were seen at 125 mg/kg bw/d and above. (Anonymous, 1999). In a similar study in B6C3F1 mice (OECD TG 451) exposed to TEA for 2 years, skin irritation with visible crust, epidermal hyperplasia, suppurative inflammation, ulceration and dermal chronic inflammation were observed from 100 mg/kg bw/d (the lowest dose tested) (Anonymous, 2004).

Based on these studies the DS did not propose any classification for skin corrosion/irritation.

Comments received during consultation

One commenting MSCA did not support the proposed read across for local toxicity and would only take the one study on the substance itself into account. Due to uncertainties in the composition of the test substance, the commenting MSCA was of the opinion that no classification due to lack of data should be considered. The DS argued that read across to penta-PSCA could be applied since the substance is used as a liquid, and dissociation to penta-PSCA could be expected.

Another/A second MSCA supported the proposed no classification for skin corrosion/irritation.

Assessment and comparison with the classification criteria

Individual animal scores were not available for all studies in the background document. Therefore, for these studies only a qualitative comparison with the CLP criteria could be achieved. According to the CLP criteria a classification as Skin Irrit. 2 is warranted if the mean value of $\geqslant$ 2,3 - $\leqslant$ 4,0

for erythema/ eschar or for oedema is observed in at least 2 of 3 tested animals, from gradings at 24, 48 and 72 hours after patch removal.

One acute dermal irritation study (anonymous, 1993a) with penta-PSCA Na-TEA (40%) show a mean score for erythema of 2 (animal # 1 and # 3) or 3 (animal #2), and mean oedema scores of 0.33 (animal # 1 and 2) or 0 (animal #3). Effects were fully reversible within 14 days. It is noted that in this study an influence of other components of the mixture cannot be excluded.

A study (anonymous, 1993b) with the acid form of the substance (penta-PSCA) resulted in a mean erythema score (24, 48, 72h) of 1.1 with a maximum score of 2. Mean oedema score (24, 48, 72h) was 0. The effect was fully reversible within 7 days.

Several studies on TEA were also included in the assessment by the DS. These were all negative for skin irritation, however, repeated dose toxicity studies show an irritating potential (inflammation, acanthosis, epidermal erosion) at higher doses and longer exposure durations after dermal application.

Overall, RAC concurs with the opinion of the DS that **no classification for skin corrosion/irritation is warranted for penta-PSCA Na-TEA**.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

For the evaluation of serious eye damage/eye irritation the DS included one study according to OECD TG 405 and GLP where three New Zealand White rabbits were exposed to 0.1 mL penta-PSCA Na-TEA (40%) in the conjunctival sac on one eye of each test animal (Anonymous, 1993c). Other components of the test material included teak oil, oleyl alcohol, polypropylene and water. The treated eyes were washed out with physiological saline 24 hours after application. The scores are presented in the table below.

Table: *Scoring from OECD TG 405*

	Mean score (24, 48, 72 h)	**Max score**	**Reversibility (days)**
Corneal opacity	0.4	1	3
Iris score	0.4	1	3
Conjunctivae score	2	3	7
Chemosis score	0.9	3	3

In this study the mean conjunctivae score of 2 with a maximum score of 3 and individual animals scores of 1.0, 2.7, and 2.3 were reported. Based on this study a classification as Eye Irrit. 2 is indicated. It is noted that the tested mixture is not defined in detail.

Further, the DS included one study with penta-PSCA and several studies with TEA. These studies are described in the table below.

Table: *Studies with penta-PSCA and TEA*

<table>
<tr><th>Methods, guideline, test substance</th><th>Species, strain, sex, no/group, dose levels, duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr><td>OECD TG 405, GLP
penta-PSCA (purity unknown)</td><td>Rabbit,
New Zealand White
3
Single application
Observation 7 days</td><td>Cornea opacity mean score (24, 48, 72h) = 0.3 (max. 1)
Iris mean score (24, 48, 72h) = 0.4 (max. 1)
Conjunctivae mean score (24, 48, 72h) = 1.3 (max. 3)
Chemosis mean score (24, 48, 72h) = 0.6 (max. 3)
All effects were fully reversible within 7 days.</td><td>Anonymous, 1993d</td></tr>
<tr><td>Similar to OECD TG 405
GLP unknown
TEA 98%
No vehicle</td><td>Rabbit,
New Zealand White
n=6/dose
0.01, 0.03 and 0.1 mL
21 days observation</td><td>Draize scores (mean±SE)<table><tr><th>Dose Volume</th><th colspan="5">Days</th></tr><tr><td></td><td>1</td><td>3</td><td>7</td><td>14</td><td>21</td></tr><tr><td>0.01</td><td>0±0</td><td>0±0</td><td>0±0</td><td>0±0</td><td>0±0</td></tr><tr><td>0.03</td><td>1±1</td><td>0±0</td><td>0±0</td><td>0±0</td><td>0±0</td></tr><tr><td>0.1</td><td>4±1</td><td>2±2</td><td>2±2</td><td>0±0</td><td>0±0</td></tr></table></td><td>Griffith, 1980</td></tr>
<tr><td>Similar to OECD TG 405
TEA 98%
No vehicle</td><td>Rabbit
n=2 (m/f)
0.5 mL (single dose)
Readings at 10 min, 1 and 24h, 3 and 8 days
8 days observation</td><td>Not irritating
Cornea opacity = 0
Mean conjunctive score (1h, 24h) = 1
Mean chemosis score (1h) = 1
Mean chemosis score (1d, 8d) = 0</td><td>Anonymous, 1971b</td></tr>
<tr><td>Similar to OECD TG 405
TEA</td><td>Rabbit
0.5 mL</td><td>Treatment of rabbits with the diluted test compound at pH 10 and pH 8 (neutralised with HCl) did not result in any signs of eye irritation.</td><td>Anonymous, 1956b</td></tr>
<tr><td>Similar to OECD TG 405
TEA</td><td>Rabbit, albino
0.05 mL</td><td>Irritating
Cornea opacity, mean score (24, 48, 72h) = 1, not fully reversible within 8 days
Conjunctivae, mean score (24, 48, 72h) = 2, fully reversible within 8 days
Chemosis, mean score (24, 48, 72h) = 1.75, fully reversible within 8 days</td><td>Anonymous, 1967b</td></tr>
<tr><td>Similar to OECD TG 405
TEA</td><td>Rabbit, Vienna white
N=2 (m/f)
0.05 mL
8 days observation</td><td>Irritating
Cornea opacity, mean score (24, 48, 72h) = 1, not fully reversible within 8 days
Conjunctivae, mean score = 1.08, fully reversible within 8 days
Chemosis, mean score = 1.08, fully reversible within 8 days</td><td>Anonymous, 1966b</td></tr>
</table>

Two studies with TEA gave clear positive results with mean scores (24, 48, 72h) of 2, 1, 1.75 (Anonymous, 1967) and 1.08, 1, 1.08 (Anonymous, 1966) for conjunctiva redness, corneal opacity and chemosis respectively. It is further noted that Triethanolamine as well as triethanolammonium compounds are (self-)classified as Eye Irrit. 2. Penta-PSCA Na-TEA dissolves in biological fluids. The DS is of the opinion that the concept of generic concentrations limits of ingredients of a mixture for their effects on eyes can be applied (CLP regulation, Annex I, part 3, Table 3.3.3) for the classification of penta-PSCA Na-TEA. Based on the structure and the molecular weight of penta-PSCA Na-TEA (ranging from 465 to 549) the fraction of TEA will be 13-16% and a classification of the mixture is indicated.

On this basis the DS proposed a classification of penta-PSCA Na-TEA as Eye Irrit. 2, H319.

Comments received during consultation

One commenting MSCA did not support the proposed read across for local toxicity and would take into account only the one study on the substance itself. The MSCA was of the opinion that no classification due to lack of data should be considered. Since the substance dissolves in biological fluids, the DS argued the concept of generic concentration limits for ingredients in a mixture should be considered and that a classification as Eye Irrit. 2 could be justified on this basis.

A second MSCA supported the proposed classification for serious eye damage/irritation as Eye. Irrit. 2, H319.

Assessment and comparison with the classification criteria

Individual animal scores were not available for all studies in the background document. Therefore, for these studies only a qualitative comparison with the CLP criteria could be achieved. According to the CLP criteria, a classification for eye irritation (Eye Irrit. 2) is warranted if in at least 2 of 3 tested animals a positive response of corneal opacity $\geqslant$ 1 and/or iritis $\geqslant$ 1, and/or conjunctival redness $\geqslant$ 2 and or conjunctival oedema (chemosis) $\geqslant$ 2 calculated as the mean scores following grading at 24 48 and 72 hours after installation of the test material is reported and which is fully reversible within 21 days.

In a study on serious eye damage/eye irritation according to OECD TG 405 and GLP, three New Zealand White rabbits were exposed to 0,1 mL 40% penta-PSCA Na-TEA (other components in the tested mixture included teak oil, oleyl alcohol, polypropylene and water) in the conjunctival sac on one eye of each test animal (Anonymous, 1993c). The observed mean scores (24, 48, 72h) were 0.4, 0.4, 2 and 0.9 for cornea opacity, iris, conjunctivae redness and chemosis respectively. Individual animal data for conjunctivae score are 1.0, 2.7 and 2.3. The conjunctiva score observed in this study fulfils the criteria for a classification as Eye Irrit. 2. It is however noted that there are uncertainties related to the composition of the mixture tested, and how the other substances in the tested mixture would contribute to the eye irritation observed in this study.

A study with penta-PSCA showed mean scores (24, 48, 72h) of 0.3, 0.4, 1.3 and 0.6 for corneal opacity, iris, conjunctival redness and chemosis respectively (Anonymous, 1993d), and hence penta-PSCA does not fulfil the criteria for classification for serious eye damage/irritation.

The DS also included several studies with TEA. Two studies gave clear positive results with mean scores (24, 48, 72h) of 2, 1, 1.75 (Anonymous, 1967) and 1.08, 1, 1.08 (Anonymous, 1966) for conjunctiva redness, corneal opacity and chemosis respectively. It is also noted that TEA (triethanolamine) as well as triethanolammonium compounds are (self-)classified as Eye Irrit. 2.

It is noted that penta-PSCA Na-TEA dissociate in biological fluids or water to sodium ion, triethanolammonium ion and penta-PSCA. Therefore, the concept of generic concentrations limits of ingredients of a mixture for their effects on eyes can be applied (CLP regulation, Annex I, part 3, Table 3.3.3). Based on the structure and the molecular weight of penta-PSCA Na-TEA, the fraction of TEA will be 13-16% and a classification of penta-PSCA Na-TEA is indicated.

Overall, taking into account one study with penta-PSCA Na-TEA (40%) and two studies with TEA which fulfils the criteria for a classification as Eye Irrit. 2 H319, RAC is of the opinion that **classification as Eye Irrit. 2, H319 for penta-PSCA Na-TEA is warranted**.

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

For the assessment of STOT RE, the DS included a combined repeated dose toxicity study with the reproduction/developmental toxicity screening study (OECD TG 422) (Anonymous, 2012c) and an associated dose range finding (DRF) study to the OECD TG 422 (Anonymous, 2013a). Both studies were performed in Han Wistar rats with exposure to penta-PSCA Na-TEA. The DS also included a 28-day study (OECD TG 407) in CD(SD) rats with exposure to tetra-PSCA in a read across assessment (Anonymous, 1995).

In the OECD TG 422 study, rats (11/sex/group) were exposed to 0, 40, 200 and 1000 mg/kg bw/d and in the associated DRF study (3/sex/group) to 0, 100, 300 and 1000 mg/kg bw/d penta-PSCA Na-TEA (28 days (m) and 42 days (f)). The effects reported in rats were not considered sufficiently severe (loss of appetite, reduction in body weight, and at higher levels moderate toxicity such as reduced body temperature, reduced locomotor activity) to warrant a classification for STOT RE 2.

In the 28-day study, rats were exposed to 0, 8, 40, 200 and 1000 mg/kg bw/d tetra-PSCA. The main target organ following exposure to tetra-PSCA were the liver in both sexes and the kidney and forestomach in male rats. The effects observed at 200 mg/kg bw/d were not considered by the DS sufficiently severe (moderate and low incidence eosinophilic bodies in the kidneys of males, increased relative liver weight in females (+10%), no significant changes in haematology and clinical chemistry) to warrant a classification for STOT RE 2.

Relevant studies with TEA

The DS clarified that the toxicity of penta-PSCA Na-TEA was not related to exposure to TEA by assessing three repeated dose toxicity studies with TEA:

In a 90-day oral repeated dose toxicity study, Cox CD rats (20/sex/group) were exposed to 0, 250, 500 and 1000 mg/kg bw/d TEA in feed (Anonymous, 1989). No dose-response-related systemic effects of TEA were reported up to the highest dose tested, 1000 mg/kg bw/d.

A 28-day inhalation study, in rats (Gamer, 2008) with exposure to 0, 0.02, 0.1 and 0.5 mg TEA/L (aerosol) showed only local irritating effects in the submucosa of the larynx region of the rats. No systemic effects were reported.

In a dermal 90-day study, Fisher rats (Anonymous, 1987) were exposed to 0, 125, 250, 500, 1000 or 2000 mg TEA/kg bw/d (vehicle acetone),for the main exposure related effects reported were inflammation of the skin and acanthosis from 250 mg/kg bw/d in male rats and from 500 mg/kg bw/d in female rats. No exposure related microscopic lesions were seen in examined organs. Haematological changes reported in the high dose groups of both sexes could be related to the inflammatory response resulting from dermal irritation. At 2000 mg/kg bw/d the final body weight was statistically significantly reduced in male and female rats accompanied by a depression in body weight gain.

Overall, the DS was of the opinion that the oral repeated dose toxicity studies with penta-PSCA Na-TEA, tetra-PSCA and TEA (ion) indicate that there is no need for a classification for STOT RE for any of these substances.

Comments received during consultation

Comments were received from two MSCAs. Both MSCAs supported no classification for STOT RE since the observed effects below the Guidance Value for classification were insufficient for a classification. One MSCA noted that the data available for a classification for STOT RE was limited.

Assessment and comparison with the classification criteria

In the DRF toxicity study (Anonymous, 2013a) Han Wistar rats were exposed to 0, 100, 300 and 1000 mg/kg bw/d penta-PSCA Na-TEA (90% purity, 3/sex/dose). Male rats were dosed 14 days during pre-mating and 14 days during mating (total 28 days). Females were dosed during pre-mating, mating and 14 days during gestation (total 42 days). During the treatment bedding in mouth was noted in all dose groups (m, f) in a dose-dependent manner. Further, salivation was noted in the high dose group, and these findings were considered to be treatment related.

Differences in mean food consumption of males at 100, 300 and 1000 mg/kg bw/d compared to the control animals were, respectively: -8%, -8% and -29% during the pre-mating period and ±0%, -9% and -17% after the mating period. Differences in mean food consumption of females at the dose levels of 100, 300 and 1000 mg/kg bw/d compared to the control animals were, respectively: -6%, -12% and -29% during the pre-mating period and -5%, -5% and -19% during the gestation period. Differences in mean body weight gain of males at the dose levels of 0, 100, 300 and 1000 mg/kg bw/d were, respectively: +14%, +14%, +13% and +4% during the pre-mating period, +4%, +4%, +2% and +2% during the paring period and +8%, +9%, +7% and +8% after the mating period. Differences in mean body weight gain of females at the dose levels of 0, 100, 300 and 1000 mg/kg bw/d were, respectively: +9%, +9%, +9% and +4% during the pre-mating period and +25%, +25%, +29% and +20% during the gestation period.

No macroscopic findings were noted in males and females. Clinical chemistry investigations showed statistically significant lower relative haematocrit value (0.4 compared to 0.44 in control) and lower albumin concentration (45.72 g/L compared to 53.99 g/L in control) in females in the high dose group. No further test item-related changes in haematology or clinical biochemistry parameters were noted in males or females at any dose level. No organ parameters were examined. A effective dose of 1000 mg/kg bw/d was derived based on statistically significant reduction in food consumption, reduction of body weight and body weight gain at 1000 mg/kg bw/d in males and females as well as significant changes in clinical biochemistry in females.

In the OECD TG 422 study Wistar rats (11/sex/dose) were exposed to 0, 40, 200 and 1000 mg/kg bw/d penta-PSCA Na-TEA (> 90% purity) by oral gavage (Anonymous, 2012c). The male rats were exposed for 28 days in total and the female rats for 14 days prior to mating, through the mating and gestation periods until the F1 generation reached day 4 post-partum (in total for approx. 42 days).

The NOAEL for parental toxicity was 40 mg/kg bw/d based on reduced body weight gain and reduced food consumption (see table below). Further from 200 mg/kg bw/d reduced locomotor activity (m, f) and increased salivation (m, f) were reported. At 1000 mg/kg bw/d significantly reduced body temperature (m, f), significantly increased liver weight (m) and liver hypertrophy (m, f), reduced testis and epididymis weights (without histopathological findings) (m), hyaline droplets in kidneys (m), squamous hyperplasia in the forestomach (m, f), follicular cell hypertrophy in the thyroid gland (m, f) were reported. A higher kidney weight to body weight ratio in males in the high dose group as well as a higher brain weight to body weight ratio in high dosed females were considered to be due to the lower body weights.

Table: *Parental toxicity from OECD TG 422.*

	Dose (mg/kg bw/d)	**Males**		**Females**		
Period		Pre-mating	Mating**	Pre-mating	gestation	lactation
Food consumption (g/animal/day)	0	26.1		19.5	26.1	30.3
	40	25.4 (-2.7%)		18.8 (-3.6%)	23.7 (-9.2%)*	27.6 (-8.9%)
	200	23.4 (-10.3%)*		17.2 (-11.8%)*	22.4 (-14.2%)*	20.0 (-34.0%)*
	1000	17.9 (-31.4%)*		13.5 (-30.8%)*	19.0 (-27.2%)*	15.9 (-47.5%)*
Body weight gain (%)	0	+11%	+6%	+9%	+57%	+5%
	40	+8%	+8%	+6%	+55%	+6%
	200	+7%*	+7%	+6%	+49%	+4%
	1000	-1%*	+9%*	+2%*	+33%*	±0%*

* Fisher's Exact Test: statistically significant different from controls; ** food consumption not reported.

In the 28-day study (OECD TG 407) study Wistar rats (6/sex/dose) were exposed to 0, 8, 40, 200 and 1000 mg/kg bw/d of tetra-PSCA by oral gavage (Anonymous, 1995). The study included a recovery period of 14 days for animals exposed to 200 and 1000 mg/kg bw/d tetra-PSCA.

No deaths were reported. Further, no effects were reported on body weight, food consumption and urine-analysis. Clinical signs reported included salivation in males and females from 200 mg/kg bw/d, decreased spontaneous movement and decreased respiratory rate in males at 200 mg/kg bw/d. At 1000 mg/kg bw/d in males and females a decrease in spontaneous movement, decrease in respiratory rate, soiling around the nose and mouth, hunchback posture, soiling around the anus and depilation in the lower neck region were reported. No clinical effects were seen at the end of the recovery period. Relative kidney weight (percentage not reported) was increased in females from 200 mg/kg bw/d and males at 1000 mg/kg bw/d. Male and female liver weight was increased in the 1000 mg/kg bw/d group (24% and 35%, respectively). After recovery, liver weight in the high dosed group was still increased with 9% in males and 11% in females. Histopathological examinations showed swelling of hepatocytes in males and females at 1000 mg/kg bw/d as well as granulation tissue accompanied by calcification. In addition, effects on forestomach (mucosa degeneration) and kidney (eosinophilic bodies) in males as well as haematological and clinical alteration were observed in males and females. Most of the effects were reversible within the recovery period.

In summary RAC supports the assessment of the repeated dose toxicity studies performed by the DS. In the OECD TG 422, the relevant effects induced following exposure to penta-PSCA Na-TEA were observed from a dose of 200 mg/kg bw/d (within the GV of 30 < C $\leqslant$ 300 mg/kg bw/d (males, 28d) and just at the GV of 20 < C $\leqslant$ 200 mg/kg bw/d (females, 42d) for a classification as STOT RE 2. The effects reported in the rats were not considered sufficiently severe (loss of appetite, reduction in body weight, and at higher levels moderate toxicity such as reduced body temperature, reduced locomotor activity). RAC therefore supports the DS and concludes that no classification for STOT RE is justified based on the CLP criteria.

In the 28-day study in rats with tetra-PSCA, effects were reported from 200 mg/kg bw/d (within the GV of 30 < C $\leqslant$ 300 mg/kg bw/d for STOT RE 2). However, the effects observed at 200 mg/kg bw/d were not considered sufficiently severe (moderate and low incidence of eosinophilic bodies in the kidneys of males, increased relative liver weight in females, no significant changes in haematology and clinical chemistry). RAC therefore supports the DS and concludes that no classification for STOT RE is justified based on the CLP criteria.

In conclusion: Based on the data available for penta-PSCA Na-TEA and the read across to tetra-PSCA, RAC is of the opinion that **no classification for STOT RE is warranted for penta-PSCA Na-TEA** according to the CLP criteria.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Effects on sexual function and fertility

For the assessment of effects on sexual function and fertility the DS included an OECD TG 422 study (Anonymous, 2012c) and an associated DRF study (Anonymous, 2013a) in Han Wistar rats and in compliance with GLP.

In the OECD TG 422 study, penta-PSCA Na-TEA induced adverse effects on fertility in the absence of marked parental toxicity. The fertility parameters that were affected included the birth index and the pup viability index. These parameters were already significantly altered at the low dose of 40 mg/kg bw/d. In addition, increased pre-implantation loss and reduced litter size and reduced fertility index were reported in a dose dependant manner. Further, in the high dose group (1000 mg/kg bw/d) a high incidence of post-implantation loss was reported, and all pregnant females lost their litter before the first litter check (day not available). These effects were not considered as secondary non-specific consequences of parental toxicity.

Based on the adverse effects reported on sexual function and fertility the DS proposal was to classify penta-PSCA Na-TEA as Repr. 1B; H360F.

Developmental toxicity

For the assessment of developmental toxicity following exposure to penta-PSCA Na-TEA the DS included an OECD TG 422 study (combined repeated dose toxicity study with the screening test) in Han Wistar rats (11/sex/group) with exposure to 0, 40, 200 and 1000 mg/kg bw/d (Anonymous, 2012c) and a developmental toxicity study (OECD TG 414) in Wistar rats (5/females/group) with exposure to 0, 8, 40 and 200 mg/kg bw/d penta-PSCA Na-TEA from gestation day 6-20 (Anonymous, 2013b). The prenatal developmental toxicity (PNDT) study was performed according OECD TG 414 but with a reduced number of animals. This reduction was chosen as the study was designed to clarify whether the effects found in the OECD TG 422 originated from fertility impairment or was related to foetotoxicity. Both studies were with exposure to penta-PSCA Na-TEA by oral gavage.

In the OECD TG 422 screening study penta-PSCA Na-TEA induced adverse effects on development including a statistically significant increase in post-implantation loss at all dose levels as well as a decrease in the viability index at 40 and 200 mg/kg bw/d. Further, in the high dose group (1000 mg/kg bw/d), all pregnant females had a total litter loss. These effects were not considered to be a secondary non-specific consequence of parental toxicity. In the developmental toxicity study foetotoxic effects such as cleft palate formation, visceral abnormalities (small spleen) and skeletal abnormalities were observed from the lowest dose tested (8 mg/kg bw/d). The effects were seen at doses that were not associated with a maternal toxicity.

No developmental toxicity study in rats or rabbits (i.e. OECD TG 414) was presented by the DS on TEA.

Based on the adverse developmental effects reported the DS proposal was to classify penta-PSCA Na-TEA as Repr. 1B; H360D.

Adverse effects on or via lactation

No data were presented by the DS in the CLH report.

Setting of specific concentration limits (SCLs)

The DS considered that post-implantation loss reported in the OECD TG 422 screening study and small spleen reported in the developmental toxicity study were the leading effects for reproductive toxicity following exposure to penta-PSCA Na-TEA. The resulting ED_{10} values for penta-PSCA Na-TEA for these effects are summarised in the table below.

Table: *ED10 values from OECD TG 422*

	Statistically modelling	
Effect	**Linear response**	**Sigmoidal response**
Post-implantation loss	107.7 mg/kg bw/d	117.6 mg/kg bw/d
Small spleen	23.3 mg/kg bw/d	7.8 mg/kg bw/d

The lowest ED_{10} value from the two reproductive toxicity studies for effects warranting classification determined the overall ED10 of the substance. For a preliminary potency evaluation, the boundaries according CLP guidance are summarised in the table below.

Table: *Potency boundaries for SCL setting*

Potency group	**Boundaries**
High potency group	ED_{10} value ≤ 4 mg/kg bw/d
Medium potency group	4 mg/kg bw/d < ED_{10} value < 400 mg/kg bw/d
Low potency group	ED_{10} value ≥ 400 mg/kg bw/d

Based on the potency boundaries and the calculated ED_{10} values a medium potency was assumed for penta-PSCA Na-TEA by the DS. In addition, the CLP Guidance (ECHA, 2017, version 5 point 3.7.2.6.5), state that other factors, so called modifying factors, should be taken into account to establish whether the preliminary calculated potency needs to be modified. These factors, and the conclusion on each of them with regards to the potency of penta-PSCA Na-TEA, were assessed by the DS and are summarised below.

- *Type and severity of the effect:* The type of severe effects observed in the reproductive toxicity studies following exposure to penta-PSCA Na-TEA are post-implantation loss and small spleen. As the lowest ED_{10} for these effects is close to the boundary of a higher potency group, a change of the potency group was considered.
- *Data availability:* The data available for penta-PSCA Na-TEA (OECD TG 422 and OECD TG 414 study, full reports available) were considered adequate. The PNDT study was done according OECD TG 414 but with a reduced number of animals. This reduced design was chosen as the study aimed to clarify whether the effects found in the OECD TG 422 originated from fertility impairment or fetotoxicity.
- *Dose-response relationship:* The lowest ED_{10} (7.8 mg/kg bw/d, small spleen) of penta-PSCA Na-TEA was close to the effective dose of 8 mg/kg bw/d.
- *Mode or mechanism of action*: No information was available.
- *Toxicokinetic:* No information was available.
- *Bioaccumulation:* penta-PSCA Na-TEA was not considered to be bioaccumulating based on the REACH registration data.

Conclusion on modifying factors

Based on the available data, penta-PSCA Na-TEA is considered as a medium potency toxicant. As the ED_{10} is closed to the high potency group and the reported developmental toxicity effects are severe with a LOAEL at 8 mg/kg bw/d a shift into the high potency group can be considered. No additional modifying factor applies.

Conclusion on concentration limit

The potency of penta-PSCA Na-TEA was a borderline case between medium and high potency. Small spleen was the most sensitive adverse effects seen down to the dose level of 8 mg/kg

bw/d with an ED_{10} of 7.8 mg/kg bw/d. All other adverse effects in the foetuses (increased number of supernumerary ribs, skeletal abnormalities) were found at exposure to 40 mg/kg bw/d penta-PSCA Na-TEA and/or higher, therefore the DS considered that the generic concentration limits should apply.

In absence of data, the DS did not propose a classification for effects on or during lactation.

Comments received during consultation

Comments were received from three MSCAs, with one MSCA submitting two comments. All comments supported a classification as Repr. 1B; H360FD, no classification for lactation and that the GCL should be applied. As regards the assessment of a concentration limit one MSCA noted that in addition to the ED_{10} values calculated by the DS for effects on development a 10% decrease in the fertility was reported in the OECD TG 422 from 40 mg/kg bw/d supporting a GCL for effects on fertility and sexual function.

Assessment and comparison with the classification criteria

Effects on sexual function and fertility

For the assessment of effects on sexual function and fertility the DS included an OECD TG 422 study (Anonymous, 2013a) with an associated OECD TG 422 DRF study (Anonymous, 2012c) in Han Wistar rats and in compliance with GLP. No historical control data for the effects on sexual function and fertility were included in the CLH dossier.

Based on the results from the OECD TG 422 dose-range finding study with exposure to 0, 100, 300 and 1000 mg/kg bw/d of penta-PSCA Na-TEA (90% purity) showing a decreased fertility index and conception rate in the high dose group in the presence of decreased body weight gain and reduced food consumption, the doses for the main OECD TG 422 study were 0, 40, 200 and 1000 mg/kg bw/d (> 90% purity).

In the OECD TG 422 study rats 11/sex/dose group were orally dosed by gavage. Males were exposed for 4 weeks and females for approximately 7 weeks.

The percentage of mating was 100%, assessed by the presence of copulation plug or sperm in all dose-groups. No effects were reported on the gestation length and corpora lutea as well as implantations. A reduction in the fertility index and gestation index was reported in the high dose group and a reduction in the birth index and viability index in all dose-groups, see table below.

Table: *Reproductive parameters*

Dose (mg/kg bw/d)	**0**	**40**	**200**	**1000**
Fertility index (%)	100.0	90.9	90.9	72.7
Gestation index (%)	100.0	100.0	90.0	0.0*
Birth index (%)	96.7	84.3*	68.8*	0.0*
Viability index (%)	99.2	91.6*	69.3*	na

*Fisher's Exact Test, significant at 1%; na, not applicable

Further, and increase in post-implantation losses at all dose levels (mean incidence per dam: 0.4, 2.0*, 3.8* and 8.5* at 0, 40, 200 and 1000 mg/kg bw/d), a reduction of litter size (mean number of living pups per dam 11.9, 10.7, 8.8 and 0* respectively), in viability index (days 0-4) in the low- and mid-dose groups (no live pups in the high dose group) were reported, see table below. It should be noted that in male rats a statistically significant decrease in the left and right testis and epididymis weight was reported, however, no histopathological changes were found.

Table: *Breeding parameters*

Dose (mg/kg bw/d)	0	40	200	1000
Number of litters	11	10	10	8
Post-implantation loss (total/mean)	4/0.4	20**/2.0##	34**/3.8#	68*/8.5##
Living pups at first check (total/mean)	131/11.9	107/10.7	88/8.8	0##/0
Dead pups at first litter check (total/litters affected)	0/0	5/4*	24/4*	7/2
Living pups on PND 4 (total/mean)	130/11.8	98/9.8	61/6.1#	0/0.0##
Pup mortality PND 0-4 (total/litters affected)	1/1	9**/1	27**/5	0/0

Steel test, significant at 5% (#), 1% (##); Fischer´s Exact test, statistically significant at 5% (*), 1% (**); PND, postnatal day

Parental toxicity: Salivation was noted in the high dose group in males and females. Reduced body weight gain and food consumption in the mid- and high-dose group was reported, see table below.

Table: *Food consumption and body weight gain in males and females*

	Dose (mg/kg bw/d)	Males		Females		
Period		Pre-mating	Mating**	Pre-mating	gestation	lactation
Food consumption (g/animal/d)	0	26.1		19.5	26.1	30.3
	40	25.4 (-2.7%)		18.8 (-3.6%)	23.7 (-9.2%)*	27.6 (-8.9%)
	200	23.4 (-10.3%)*		17.2 (-11.8%)*	22.4 (-14.2%)*	20.0 (-34.0%)*
	1000	17.9 (-31.4%)*		13.5 (-30.8%)*	19.0 (-27.2%)*	15.9 (-47.5%)*
Body weight gain (%)	0	+11%	+6%	+9%	+57%	+5%
	40	+8%	+8%	+6%	+55%	+6%
	200	+7%*	+7%	+6%	+49%	+4%
	1000	-1%*	+9%*	+2%*	+33%*	±0%*

* Fisher's Exact Test: statistically significant different from controls; ** food consumption not reported.

Summary

In the OECD TG 422 study penta-PSCA Na-TEA induced adverse effects on fertility. The fertility parameters affected included a decrease in the birth index and the viability index. These parameters were already statistically significantly altered at 40 mg/kg bw/d. In addition, a reduced litter size and reduced fertility index were reported in a dose dependent manner. Further, in the high dose group all dams experienced total litter loss. RAC considers that the effects on reproduction reported are considered not to be a secondary non-specific consequence of parental toxicity.

RAC supports the DS and is of the opinion that based on the clear evidence of adverse effects reported on sexual function and fertility **classification of penta-PSCA Na-TEA as Repr. 1B; H360F is warranted**.

Developmental toxicity

For the assessment of developmental toxicity following exposure to penta-PSCA Na-TEA the DS included two studies with oral exposure to penta-PSCA Na-TEA. The first study was an OECD TG 422 screening study in Han Wistar rats (11/sex/group) with exposure to 0, 40, 200 and 1000 mg/kg bw/d (> 90% purity). The second study was a developmental toxicity study in Wistar rats (5/females/group) with exposure to 0, 8, 40 and 200 mg/kg bw/d from gestation day 6-20. No historical control data for the developmental effects reported were included in the CLH dossier.

In the OECD TG 422 screening study the incidence of post-implantation loss was statistically significant increased from 40 mg/kg bw/d (0.4, 2.0*, 3.8* and 8.5* in the 0, 40, 200 and 1000

mg/kg bw/d dose-group, respectively). Further, a reduction of litter size was seen at all dose levels (mean number of living pups per dam 11.9, 10.7, 8.8 and 0* in the 0, 40, 200 and 1000 mg/kg bw/d, respectively). All pregnant high dose females lost their litter before first litter check. The birth index was statistically significant reduced in all dose groups (96.7%, 84.3%*, 68.8%*, 0.0%*), while pup mortality on PND0-4 was increased at 40 and 200 mg/kg bw/d (total number: 1, 9**, 27**, 0 in the 0, 40, 200 and 1000 mg/kg bw/d dose group, respectively). Parental toxicity was evident as a reduction in food consumption and body weight gain in the mid- and high-dose animals. For further details of the study see the section RAC assessment of effects on fertility and sexual function.

In the developmental toxicity study (OECD TG 414 in rats), all females survived until scheduled necropsy, and no maternal toxicity was reported. In the high dose group (200 mg/kg bw/d) the food consumption and the body weight gain were slightly reduced, see the table below.

Table: *Food consumption and body weight gain in female rats*

Dose (mg/kg bw/d)	Food consumption, different from control	BW gain during treatment	Corrected BW gain*
0	0.0%	+55%	+17.9%
8	+3.3%	+51%	+12.6%
40	+3.7%	+53%	+13.1%
200	-6.6%	+52%	+14.4%

*corrected for gravid uterus weight

All female rats in the study were pregnant. No differences were reported for control and exposed rats regarding the number of corpora lutea, implantation sites and number of live foetuses, see results in the table below. During necropsy enlarged placentas were found in one control dam and in one high dosed dam and were therefore not considered as treatment related.

Table*: Reproduction data*

Dose (mg/kg bw/d)	0	8	40	200
Corpora Lutea	77	79	75	76
Pre-implantation loss	5	5	5	12
Implantation sites	72	74	70	64
Post-implantation loss	11	5	2	4
Embryonic resorptions	10	4	2	4
Foetal resorptions	1	1	0	0
Foetus total	61	69	68	60

No effects on foetal body weights or differences in the sex ratio were reported at any dose level. The foetal evaluation included external examinations of all pups per litter as well as soft tissue examinations, skeletal examinations and head examinations for half of the pups per litter, see table below:

Table*: Foetal toxicity*

Dose (mg/kg bw/d)		0	8	40	200
Foetuses examined		**N=32**	**N=36**	**N=35**	**N=32**
Spleen	Spleen small* or small severe**	1 (3%)	4 (11%)	17 (49%)	32 (100%)
	Small*	1 (3%)	4 (11%)	17 (49%)	32 (100%)
	Small severe**	0	0	1 (3%)	27 (84%)
Dose (mg/kg bw/d) Foetuses examined		**0 N=29**	**8 N=33**	**40 N=33**	**200 N=28**
Supernumerary ribs	Left	7 (24%)	8 (24%)	26 (79%)	24 (82%)
	Right	8 (28%)	5 (15%)	24 (73%)	25 (89%)

*Small spleen: approx. 75% of expected size

**Severe small spleen: approx. 50% of expected size

In the external examination two foetuses from one litter at 200 mg/kg bw/d exhibited rare abnormalities. One of the foetuses had no lower jaw, small mouth opening and possibly cleft palate and the second foetuses had cleft palate.

Visceral abnormalities were seen in all foetuses in the 200 mg/kg bw/d. These included small spleen and, in seven foetuses incomplete fusion of nasal septum to palate was observed. Small spleen was found from 8 mg/kg bw/da (see the table above).

Skeletal abnormalities were reported in all examined foetuses (n=28) at 200 mg/kg bw/d, comprising thin skull zygomatic jugal arch, abnormal curvature of pectoral girdle clavicle. Additional findings were absent humerus deltoid tuberosity in forelimb in 24 foetuses, short mid region of rib cage in 17 foetuses, abnormal curvature of hyoid body in 14 foetuses and abnormal spacing of zygomatic arch structures in 6 foetuses.

Variations were also noted in the 200 mg/kg bw/d dose group. These included an increased incidence of ossification/thick tympanic ring in 28 foetuses, fusion of zygomatic arch in 22 foetuses, increased ossification of scapula in pectoral gridle in 13 foetuses and slight curved or slightly bent forelimb radius in 10 foetuses.

Further, and increased number of supernumerary ribs was reported from 40 mg/kg bw/d (see table above).

In this study clear signs of developmental toxicity were reported at doses that were not associated with maternal toxicity.

Summary

In the OECD TG 422 screening study penta-PSCA Na-TEA induced adverse effects on development including a statistically significant increase in post-implantation losses at all dose levels as well as postnatal mortality (days 0-4) at 40 and 200 mg/kg bw/d and complete litter loss at 1000 mg/kg bw/d. These effects were not considered to be a secondary non-specific consequence of parental toxicity. In the developmental toxicity study (OECD 414) foetotoxic effects such as cleft palate formation, visceral abnormalities (small spleen) and skeletal abnormalities were observed from the lowest dose tested (8 mg/kg bw/d). These effects were seen at doses that were not associated with maternal toxicity.

RAC supports the DS and is of the opinion that based on the clear evidence of adverse foetotoxic effects reported on the developing foetuses **classification of penta-PSCA Na-TEA as Repr. 1B; H360D is warranted.**

Adverse effects on lactation

No data was available, therefore no assessment of adverse effects on lactation has been performed by RAC.

Setting of specific concentration limits (SCLs)

RAC supports the DS assessment for the setting of concentration limits from the OECD TG 422 screening reproductive toxicity study and the developmental toxicity study in rats following exposure to penta-PSCA Na-TEA. 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. Overall, RAC did not propose a SCL.

Concentration limit for effects on sexual function and fertility

The most sensitive effects on fertility and sexual function reported in the OECD TG 422 study with penta-PSCA Na-TEA was considered to be a 10% decrease in the fertility index at 40 mg/kg bw/d, with a corresponding ED_{10} at 40 mg/kg bw/d. The DS used the decrease in post-

implantation loss for deriving an ED_{10} for reproductive toxicity. RAC is however of the opinion that this effect should be used for setting SCL for developmental toxicity, since effects on post-implantation loss is considered for a classification for developmental toxicity (CLP Guidance on setting of SCL, example No. 1). RAC considers that an assessment of the modifying factors is not relevant for setting a SCL for effects on sexual function and fertility. Due to the ED_{10} value obtained (well within the medium potency values), it is not relevant to modify the potency group (CLP Guidance, ECHA 2017, Version 5 point 3.7.2.6.5). RAC concludes that based on the ED_{10} at 40 mg/kg bw/d the GCL should be applied for penta-PSCA Na-TEA for sexual function and fertility.

Concentration limit for developmental toxicity

Post-implantation loss and small spleen were considered as the main effects for reproductive toxicity, with the resulting ED_{10} values shown in the table above in the summary of the DS proposal. Decreased expected spleen weights were not associated at low dose levels with effects on foetal body weights or at any dose level with histopathological changes. The mechanism for this effect is unknown but it may be ascribed to immunotoxicity, as proposed by the DS.

As regards to the assessment of the modifying factors, RAC agrees with the DS that based on the reported effects on the spleen, penta-PSCA Na-TEA could be considered as a borderline between the medium and high potency group. However, as the other adverse effects in the foetuses in the developmental toxicity study and on fertility in the OECD TG 422 were reported from doses of 40 mg/kg bw/d, RAC concludes that the GCL should be applied for penta-PSCA Na-TEA.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).