Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

9-Octadecenoic acid (Z)-, sulfonated, potassium salts [1]; Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts [2]; 9(or 10)-sulphooctadecanoic acid, potassium salt [3]

EC Number: 271-843-1 [1]; - [2]; 267-966-5 [3]
CAS Number: 68609-93-8 [1]; - [2]; 67968-63-2 [3]

CLH-O-0000007321-83-01/F

Adopted

8 June 2023

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 9-OCTADECENOIC ACID (Z)-, SULFONATED, POTASSIUM SALTS [1]; REACTION PRODUCTS OF FATTY ACIDS, C18 (UNSATURATED) ALKYL WITH SULFUR TRIOXIDE, POTASSIUM SALTS [2]; 9(OR 10)-SULPHOOCTADECANOIC ACID, POTASSIUM SALT [3]

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: 9-Octadecenoic acid (Z)-, sulfonated, potassium salts [1]; Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts [2]; 9(or 10)-sulphooctadecanoic acid, potassium salt [3]
EC number: 271-843-1 [1]; - [2]; 267-966-5 [3]
CAS number: 68609-93-8 [1]; - [2]; 67968-63-2 [3]
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2022	Germany		MemberState	1
Comment received				
It is not clear why the EC no. 701-179-4 mentioned on p.3 of the CLH report (c.f. captionof Table 1-B) for "Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts" is not used throughout the CLH dossier, including the title page and Table 3.				
Dossier Submitter's Response				
Number 701-179-4 is not the EC number of "Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts", however it is the List number that is only used by ECHA. List numbers do not have any legal significance and should not be officially used as substance identifiers. See also: see for details https://echa.europa.eu/nl/information-on-chemicals/registered-substances/information and question 143 in https://echa.europa.eu/nl/support/qas Therefore, this number is not used as substance identifier throughout the CLH-dossier.				
RAC's response				
Thank you, noted.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 9-OCTADECENOIC ACID (Z)-, SULFONATED, POTASSIUM SALTS [1]; REACTION PRODUCTS OF FATTY ACIDS, C18 (UNSATURATED) ALKYL WITH SULFUR TRIOXIDE, POTASSIUM SALTS [2]; 9(OR 10)-SULPHOOCTADECANOIC ACID, POTASSIUM SALT [3]

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	France		Individual	2
Comment received				
FR supports the conclusions of no classification for mutagenicity.				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Thank you for your comment, RAC agrees that classification for mutagenicity is not warranted.				

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2022	Germany		MemberState	3
Comment received				
The decision of the DS not to propose a classification for this endpoint is supported, as the endpoint cannot be assessed due to the lack of carcinogenicity studies (and missing indications of carcinogenicity from 90-day studies).				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Thank you for your comment, RAC agrees with no classification due to lack of carcinogenicity studies.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	France		Individual	4
Comment received				
FR supports the conclusions of no classification for carcinogenicity				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Thank you, RAC agrees that classification for carcinogenicity is not warranted.				

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2022	Germany		MemberState	5
Comment received				
Based on six in vitro assays showing negative results and in the absence of in vivo data, the decision of the DS not to propose a classification for this endpoint is supported.				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Thank you, RAC agrees that classification is not warranted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
07.10.2022	France		Individual	6
Comment received				
FR supports the classification Repr 1B H360D using in the study TG 414 and 408 the substance 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (CAS 68609-93-8) and using in the study TG 422 the substance Octadecanoic acid, sulfo-, potassium salt or equivalent (CAS 67968-63-2).				
Dossier Submitter's Response				
Thank you for your support				
RAC's response				
Thank you for your comment. RAC agrees that Repr. 1B; H360D is justified.				

Date	Country	Organisation	Type of Organisation	Comment number
26.09.2022	Germany		MemberState	7
Comment received				
Adverse effects on sexual function and fertility No adverse effects on sexual function and fertility were observed in two repeated dose toxicity studies (NN, 2017a; NN, 2020) as well as in one reproduction/developmental toxicity screening study (NN, 2015c). Thus, DE CA supports the conclusion of the DS not to propose classification for effects on sexual function and fertility. However, we cannot agree that the end point "sexual function and fertility" cannot be assessed (p.28 of the CLH dossier), as key relevant parameters were investigated in the available reliable toxicity studies (e.g. fertility, reproductive organs morphology and weight, spermatogenesis, oestrous cyclicity). Adverse effects on development In the reproduction/developmental toxicity screening study according to OECD TG 422 (NN, 2015c) conducted with octadecanoic acid, sulfo-, potassium salt (CAS no. 67968-63-2) in rats, adverse developmental effects were induced in high dose group at 500 mg/kg bw/d. These effects included reduced viability index (73% vs. 97.9% in control; outside HCD range of 83-100%) corresponding to increased perinatal loss (8/9 litters affected, 36.7% vs. 10% in control) and post-natal pup loss (4 pups found dead and 13 were cannibalised); reduced pup mean body weight on PND1 (-23%) and reduced pup body weight change on PND 1-PND 4 (-28.5%). Presence of runts was as well reported (10 males and 12 females). No marked maternal toxicity was reported, as evident by reduced body weight of dams in the high dose (up to 10%) observed during the lactation phase. Decreased food consumption during premating (up to -9%), gestation (up to -20%) did not result in reduced BW of dams during these phases of the study. In a GLP-compliant PNDT study conducted according to OECD TG 414 (NN, 2017b), 9-octadecenoic acid (Z)-, sulfonated, potassium salts induced a dose dependent increase in skeletal malformations and variations in rats at ≥ 300 mg/kg bw/d. Especially noticeable and statistically significant was the occurrence of skeletal malformation of bent limb bones observed in 41/128 foetuses (32%) at 300 mg/kg bw/d and 111/112 foetuses (99%) at 1000 mg/kg bw/d compared to 0% in control. In the high dose group, one of these foetuses had malrotated limbs. Findings of bent limb bones				

coincided with observation of bent ribs in all pups with this malformation. However, a skeletal variation of bent ribs is generally not considered to be adverse and it is questionable whether bent limb bones are permanent/irreversible or can remodelled during postnatal development. Besides, three foetuses at the high dose group showed bent pelvic girdle bones.
Other statistically significant skeletal variations included slight to moderate malaligned sternebrae at 1000 mg/kg bw/d. The incidences of the 14th full rib and caudal shift of pelvic girdle exceeded the HCD at ≥ 300 and 1000 mg/kg bw/d, respectively.
Since the observed effects already occurred in the mid dose group, it can be assumed that the effects are unlikely secondary to maternal toxicity. Some maternal toxicity was observed in the high dose group (1000 mg/kg bw/d), as evident by slightly reduced body weight (up to 8%) on day 21 p.c. and reduced food consumption on days 18 - 21 p.c. Moreover, foetal body weight in the high dose group was statistically significantly decreased (up to 13%).
Overall, perinatal loss, reduced viability index, effects on pup body weight in the screening study supported by the additional evidence of high incidence of skeletal malformations in the PNDT study justify the proposed classification as Repr. 1B, H360D.

Of note, during the consultation on the recent classification case of diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide [https://echa.europa.eu/documents/10162/86e7e3f1-725b-2412-59bb-c1fe04529e0c] discussed by the RAC, several publications on significance of bent limb bones were brought to attention of the committee members[https://echa.europa.eu/documents/10162/9c234aed-e027-6c8e-1521-15cb984decf7] :
- Hofmann et al. (2016) Postnatal Fate of Prenatal-induced Fetal Alterations in Laboratory Animals, Reproductive Toxicology, 61, 177–185
- Mitchard and Stewart (2014) Reduced post-natal versus pre-natal incidence of bent long bones and scapulae in a preliminary investigation using the Han Wistar rat, Reproductive Toxicology, 45, 39-44.

Dossier Submitter's Response

Thank you for supporting the proposed classification.

In regards to the "sexual function and fertility assessment": it is agreed that the wording "cannot be assessed" is unclear and confusing. What is meant is that classification for this endpoint is not appropriate.

Thank you for pointing us towards the publications concerning significance of bent limb bones which were also discussed by RAC during the CLH-process of diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide.
RAC considered in that specific advice (https://echa.europa.eu/documents/10162/86e7e3f1-725b-2412-59bb-c1fe04529e0c): "*In the publications by De Schaepdrijver et al. (2014), Mitchard & French (2011) and Kimmel et al. (2014) it has been discussed if bent limb bones should be considered as a temporary variation rather than malformation. All these three publications indicated that the finding of bent limb bones could be transient in nature and should be considered as a variation rather than a malformation. During the general consultation two additional studies by Hofmann et al. (2016) and Mitchard and Stewart (2014) were provided. In the study by Mitchard and Stewart (2014) Wistar Hannover rats were exposed from GD6 to GD17, and it was reported that skeletal abnormalities were evident in the foetuses at GD20, however not in pups assessed at PND21 and concluded that these malformations*

should be regarded as minor rather than major. In the review by Hofmann et al. (2016) it was concluded that the data assessed uniformly show that bent scapulae and bent long bones are transient, and not permanent foetal changes, that are completely repaired postnatally and that they should be classified as variations rather than malformations. RAC notes that all these studies have been performed in relation to the regulation of pharmaceuticals and has to be considered in this context." It is further noted that RAC, in relation to the chemical diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide, considered bent limb bones (observed in absence of maternal toxicity; outside the range of historical control data) as relevant for a classification for adverse effects on development. Also for 9-octadecenoic acid (Z)-, sulfonated, potassium salt, there are no follow up studies available following the pups postnatally, and it is therefore not possible to assess a possible transient nature of the observed effects on limb bones. The effect on limb bones was observed in the mid and high dose group, was outside the range of historical control, and -in case of the mid dose group- was observed in absence of maternal toxicity and in absence of reduced foetal weight. Therefore, this effect is considered relevant for classification.
RAC's response
Thank you for your comments. RAC agrees that Repr. 1B; H360D is justified. As to the bent limb bones in the PNDT study, it is not clear whether these should be considered variations or malformations in this case given the absence of a substance-specific study investigating postnatal reversibility. Nevertheless, this has no impact in terms of category since the stillbirths in the reproductive screening would already be sufficient on their own for classification in Cat. 1B. RAC further agrees that the available evidence related to sexual function and fertility does not warrant classification.