Committee for Risk Assessment

RAC

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

8 June 2023

CLH-O-0000007321-83-01/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: **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]**

The proposal was submitted by **The Netherlands** and received by RAC on **8 June 2022.**

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

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands 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 **8 August 2022**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **7 October 2022**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Michal Martínek**

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 **8 June 2023** by **consensus.**

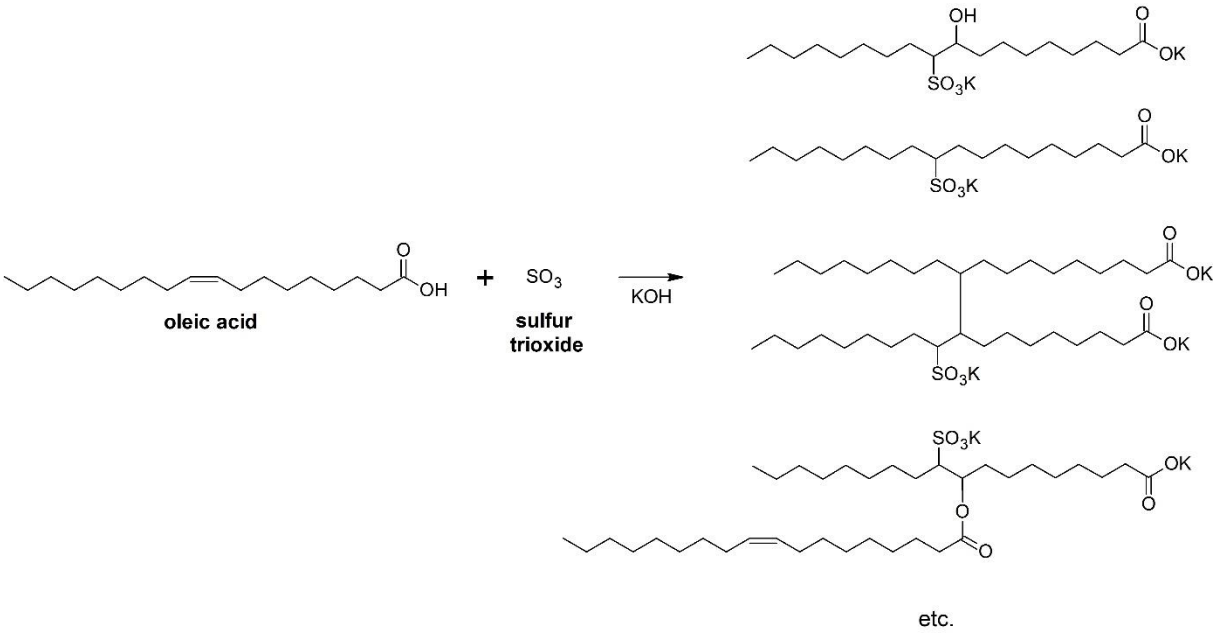
Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	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	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]	271-843-1 [1]; - [2]; 267-966-5 [3]	68609-93-8 [1]; - [2]; 67968-63-2 [3]	Repr. 1B	H360D	GHS08 Dgr	H360D			
RAC opinion	TBD	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]	271-843-1 [1]; - [2]; 267-966-5 [3]	68609-93-8 [1]; - [2]; 67968-63-2 [3]	Repr. 1B	H360D	GHS08 Dgr	H360D			
Resulting Annex VI entry if agreed by COM	TBD	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]	271-843-1 [1]; - [2]; 267-966-5 [3]	68609-93-8 [1]; - [2]; 67968-63-2 [3]	Repr. 1B	H360D	GHS08 Dgr	H360D			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

The substance in the scope of the proposed Annex VI entry corresponds to potassium salts of C18 unsaturated fatty acids sulfonates (hereafter OAS-K). These fatty acid sulfonates are prepared by a reaction of C18 fatty acids showing one, two and three unsaturated bonds with sulfur trioxide and a subsequent neutralisation (in this case with potassium hydroxide). The product is a UVCB substance, whose exact composition depends on the composition of the fatty acids and the manufacturing process. A general scheme of the reaction is presented below. The structures on the right side of the equation are examples of the constituents of OAS-K.



Reaction product of oleic acid with sulfur trioxide and potassium hydroxide

The CLH report includes information from two REACH registrations, each with its own substance specification (manufacturing process, composition) and its own toxicological dataset. ECHA substance identity experts evaluated the similarity of the two substance compositions. Based on the information included in the registration dossiers and in particular on the starting material carbon chain distribution the compositions reported have been concluded to correspond to the same substance. The dossier submitter (DS) therefore pooled the studies from both registrations into one common dataset.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

OAS-K was negative in a set of *in vitro* mutagenicity tests consisting of bacterial gene mutation assays, assays for clastogenic activity (chromosomal aberration test, micronucleus test) and assays for gene mutations in mammalian cells. No *in vivo* genotoxicity studies are available. Accordingly, the DS proposed no classification.

Comments received during consultation

Two Member State Competent Authorities (MSCAs) supported no classification.

Assessment and comparison with the classification criteria

The *in vitro* mutagenicity studies are summarised in the following table.

***In vitro* mutagenicity studies**			
Study type; year	**Method**	**Result**	**Remarks**
Ames test; 2014	Plate incorporation method Rat liver S9 Top concentration 5000 µg/plate	Negative ±S9	
Ames test; 1993	Plate incorporation method Rat liver S9 Top concentration 5000 µg/plate (without correction for purity of 51%)	Negative ±S9	TA102 or *E.coli* WP2 not tested Not tested up to the limit concentration (when purity is taken into account) No marked cytotoxicity
Chromosomal aberration test; 2014	Peripheral human lymphocytes Rat liver S9 Top concentration 1000 µg/ml (3-h exposure ±S9) or 400-500 µg/ml (24- and 48-h exposure –S9)	Negative ±S9	Top concentration selection based on precipitation (3-h exposure) or cytotoxicity (24-/48-h exposure)
Micronucleus test; 2015	V79 cells Rat liver S9 Top concentration 250-1000 µg/ml (without correction for purity of 52%)	Negative ±S9	Top concentration selection based on cytotoxicity
Mouse lymphoma assay; 2014	Rat liver S9 Top concentration 185-280 µg/ml Treatment for 3 h (±S9) or 24 h (–S9)	Negative ±S9	Top concentration selection based on cytotoxicity
HPRT test; 2015	CHO cells Rat liver S9 Top concentration 350-800 µg/ml (without correction for purity of 52%)	Negative ±S9	Top concentration selection based on cytotoxicity

A complete battery of *in vitro* mutagenicity tests including assays for:

- bacterial gene mutations,
- structural chromosome aberrations or micronuclei, and
- for gene mutations in mammalian cells) is available.

There is at least one valid study for each endpoint. Since all studies are negative, RAC agrees with the DS's proposal of **no classification**.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

No carcinogenicity studies are available. The DS summarised two 90-day oral studies in rats. Both studies showed target organ toxicity, particularly in the kidneys.

The DS concluded that in the absence of carcinogenicity studies the classification for carcinogenicity cannot be assessed.

Comments received during consultation

Two MSCAs supported the DS's conclusion.

Assessment and comparison with the classification criteria

The effects in the two available 90-day oral rat studies are listed in Table 7 of the CLH report. The main target organ is the kidney, where tubular degeneration was observed in both sexes.

In the absence of carcinogenicity studies, RAC agrees with the DS's proposal of **no classification due to lack of data**.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The available dataset consists of 90-day studies in rats, a prenatal developmental toxicity (PNDT) study in rats and a reproductive toxicity screening study according to OECD TG 422.

The DS proposed classification in Category 1B for developmental toxicity based on skeletal malformations (such as bent limb bones) in the PNDT study and increased stillbirths and early postnatal mortality in the reproductive toxicity screening study.

The DS noted that no effects related to sexual function or fertility were detected in the 90-day studies or in the reproductive toxicity screening study. The initial DS's conclusion was that classification for effects on sexual function and fertility cannot be assessed since the available studies are not sufficient for a comprehensive evaluation of this hazard. Later, in response to a comment from the consultation of the CLH report, the DS clarified that their proposal for fertility was no classification.

The DS further proposed no classification for effects on or via lactation due to lack of data.

Comments received during consultation

Comments were received from 2 MSCAs. Both supported the DS's proposal of Repr. 1B; H360D. One of the MSCAs noted that the skeletal variation of bent ribs is generally not considered adverse and that it is not clear whether bent limb bones are irreversible or can be remodelled during postnatal development. They referred to publications discussed in the RAC opinion on diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (RAC, 2021). The DS replied that there are no follow-up studies investigating postnatal reversibility, and it is therefore not possible to assess a possible transient nature of the observed effects on limb bones.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

Parameters related to sexual function and fertility were examined in a reproductive screening study conducted according to OECD TG 422 and in 90-day studies. All studies were conducted in rats.

Reproductive screening study in rats (2015)

Wistar rats (10/sex/group) were administered OAS-K in water via gavage at dose levels of 0, 50, 150 and 500 mg/kg bw/d. Males were treated for 43 days (two weeks prior to mating, throughout mating and until termination), females for 56 days (two weeks prior to mating, throughout mating and gestation and until termination). Pups were sacrificed on postnatal day 4 (corresponding to study day 40 or later). Top dose selection was based on a range-finding experiment, where 1000 mg/kg bw/d caused a moribund state of animals of both sexes within 4 days.

General toxicity at the top dose of 500 mg/kg bw/d was limited to salivation in both sexes and a reduction in food consumption and body weight in females (body weight decreased by 9% on lactation day 0). No effects related to sexual function or fertility were detected in this screening study. In particular, there was no effect on mating index, fertility index, number of implantation sites, gestation length, reproductive organ weight or histopathology. Effects related to developmental toxicity are described in the respective section.

90-day oral study in rats (2020)

Wistar rats (10/sex/group) were administered OAS-K in water via gavage at dose levels of 0, 79, 236 and 735 mg/kg bw/d. General toxicity at the top dose included renal lesions and respiratory tract effects. The latter finding was probably secondary to gavage-related reflux. There was no effect on reproductive organs (weight, histopathology) or oestrous cycle.

90-day oral study in rats (2017)

Wistar rats (10/sex/group) were administered OAS-K in water via gavage at dose levels of 0, 100, 300 and 1000 mg/kg bw/d. General toxicity at the top dose included mortality (1 out of 10 males), diarrhoea, renal lesions (e.g. tubular degeneration and regeneration) and increased liver weight. No effects were observed in reproductive organs except a few testicular changes of minimal severity in several top dose males (tubular atrophy, disorganisation, sperm stasis, degenerating germ cells – each of the four diagnoses limited to one animal, i.e. four animals affected in total). Reproductive organ weights and oestrous cycle remained unaffected.

Conclusion on sexual function and fertility

Noting the absence of a full generational study, RAC agrees with the DS that the available information on sexual function and fertility does not warrant classification.

Adverse effects on development

Developmental toxicity of OAS-K was investigated in a reproductive screening according to OECD TG 422 and in a rat PNDT study.

Reproductive screening in rats (2015)

This OECD TG 422 screening study via the oral route employed dose levels of 0, 50, 150 and 500 mg/kg bw/d. Pups were sacrificed on postnatal day 4.

Maternal toxicity was limited to salivation and a modest body weight reduction (by 9% at the beginning of lactation). Post-implantation loss was comparable across groups. There was a dramatic increase in stillbirths at 500 mg/kg bw/d (43 out of 120 pups vs 1 pup in the control). In addition, a number of liveborn top dose pups died shortly after birth (17 out of 77, mostly on PND 1). Pup weight at the high dose was decreased by 24% (PND 1).

Reproductive screening in rats (2015)				
Dose (mg/kg bw/d)	**0**	**50**	**150**	**500**
Females mated	10	10	10	10
Not pregnant (mated, no implants)	0	0	1	1
Pregnant without delivery (implants, no pups)	0	1	0	0
Females delivering	10	9	9	9
Mean no. of implantation sites	11.0	12.6	13.4	14.3
Mean litter size	9.8	11.3	12.6	13.3
Postimplantation loss (%)	13.9	15.3	6.6	6.9
No. of pups delivered	98	113	113	120
Stillborn: pups (litters); % of affected pups per litter	1 (1) 10%[a]	1 (1) 0.6%	0 0%	43 (8**) 37%**
Liverborn: pups (litters)	97 (9)	112 (9)	113 (9)	77 (9)
Litters with all pups pups stillborn	1	0	0	0
Pups found dead or missing (cannibalized) between PND 1 and 4: pups (litters); % of affected pups per litter	2 (2) 2.1%	1 (1) 0.7%	1 (1) 0.7%	17 (6) 27.0%
Pups alive at termination on PND 4	95	111	112	60
Viability index (PND 1-4)	97.9%	99.3%	99.3%	73.0%
Mean weight of live pups PND 1 (g)	6.8	6.7	6.5	5.2**
Mean weight of live pups PND 4 (g)	10.8	10.5	10.4	8.1**
Maternal bw GD 0 (g)	232	227	227	228
Maternal bw LD 0 (g)	269	266	257	244*
Maternal bw LD 4 (g)	275	278	270	253*

Statistically significant difference from control: *, $p \leq 0.05$; **, $p \leq 0.01$

[a] Although only 1 control pup was stillborn, it was the only pup of the affected dam (no. 109), resulting in 100% stillbirths in that dam and 10% when averaged over the whole group

PNDT study in rats (2017)

Pregnant Wistar rats (22/group) were administered OAS-K in water via gavage at dose levels of 0, 100, 300 and 1000 mg/kg bw/d from GD 6 to 20. The study was terminated on GD 21. Approximately half of the foetuses were examined for visceral anomalies, the other half were processed for skeletal examination.

One top dose female was sacrificed moribund on GD 14 (signs of ill health from GD 11 included marked body weight loss, hunched posture, piloerection, rales and diarrhoea). General toxicity in the rest of the top dose dams was limited to post-dosing salivation and a slight reduction in body weight and food consumption. No maternal toxicity was observed at 300 mg/kg bw/d.

Post-implantation loss was comparable across groups and there were no dead foetuses in any group. Foetal weight was reduced by 13% at the top dose. Skeletal examination revealed increased incidence of several skeletal anomalies: bent limb bones, bent ribs, bent pelvic girdle bones (iliaca), 14th full ribs, caudal shift of pelvic girdle and malaligned sternebrae (slight to moderate). The incidence of bent ribs and bent limb bones was markedly increased already from 300 mg/kg bw/d, and virtually all examined foetuses were affected at 1000 mg/kg bw/d. As to the individual bones, all foetuses with bent limb bones had bent spatula. Other limb bones were rarely affected at the mid-dose, while ca. 90% of high-dose foetuses had bent forelimb bones (humerus, radius, ulna) and about 60% also had bent hindlimb bones (femur, fibula, tibia). The skeletal anomalies were not apparent on external examination except one top dose foetus with malrotated limbs (all four limbs affected).

PNDT study in rats (2017)					
Dose (mg/kg bw/d)	**0**	**100**	**300**	**1000**	**HCD[a]**
Females on study	22	22	22	22	-
Not pregnant	0	2	0	1	-
Mortality	0	0	0	1	-
No. of pregnant females on GD 21	22	20	22	20	-
Final body weight (g)	342	339	334	315**	-
Corrected body weight (g)	260	261	254	246	-
Food consumption GD 6-21 (g/day)[b]	22	23	22	20	-
Mean litter size	11.6	11.0	11.5	11.1	-
Post-implantation loss (%); (±SD)	3.9 (±5.9)	9.2 (±10.8)	5.5 (±7.6)	4.8 (±8.4)	-
Foetal weight (g)	5.3	5.3	5.2	4.6**	-
No. of foetuses (litters) for external examination	255 (22)	220 (20)	254 (22)	222 (20)	-
Malrotated limb(s): foetuses (litters); % affected foetuses/litter	0	0	0	1 (1) 0.4%	No cases
No. of foetuses (litters) for skeletal examination	129 (22)	112 (20)	128 (22)	112 (20)	-
Bent limb bone(s): foetuses (litters); % affected foetuses/litter	0	0	41 (13) 32.1%**	111 (20) 99.3%**	Mean±SD 0.8%±1.0 Range 0.0-4.5%

Bent pelvic girdle: foetuses (litters); % affected foetuses/litter	0	0	0	3 (3) 2.8%	No cases
Bent rib(s): foetuses (litters); % affected foetuses/litter; [mean severity][c]	10 (7) 7.7% [1.0]	15 (9) 12.2% [1.0]	76 (21) 60.7%** [1.2]	111 (20) 99.3%** [2.5]	Mean±SD 14.3%±7.1 Range 0.8-27.4%
14th full rib(s): foetuses (litters); % affected foetuses/litter	14 (8) 11.3%	4 (4) 3.3%	21 (11) 16.4%	25 (11) 21.2%	Mean±SD 6.5%±3.9 Range 0.0-13.1%
Pelvic girdle – caudal shift: foetuses (litters); % affected foetuses/litter	7 (4) 6.1%	5 (3) 3.8%	15 (9) 12.0%	22 (12) 18.9%*	Mean±SD 6.2%±3.0 Range 1.7-13.0%
Sternebra(e) malaligned (slight or moderate): foetuses (litters); % affected foetuses/litter	27 (18) 22.4%	23 (15) 20.2%	27 (16) 21.7%	41 (18) 40.0%*	Mean±SD 18.0%±9.1 Range 4.4-43.8%

Statistically significant difference from control: *, $p \leq 0.05$; **, $p \leq 0.01$

[a] 35 studies, the same laboratory, strain and source, within 3 years before the current study

[b] Statistical analysis not performed

[c] Severity grades: 1 = slight; 2 = moderate; 3 = marked

Two of the skeletal findings were considered malformations by the authors of the study: bent limb bones and bent pelvic girdle. RAC notes the published studies showing postnatal reversibility of chemical-induced bent limb bones in rats (in particular De Schaepdrijver *et al.*, 2014). Such studies generally reduce the concern about this finding. On the other hand, no substance-specific study demonstrating postnatal reversibility of bent limb bones is available for OAS-K.

Conclusion on development

A strong increase in stillbirths was observed in the reproductive screening in rats (2015) in the absence of marked maternal toxicity. Based on this finding classification in Category 1B for developmental toxicity is warranted. The associated increase in early postnatal mortality, although not statistically significant, also contributes to the classification conclusion.

The PNDT study in rats (2017) reported a high incidence of skeletal anomalies in the absence of maternal toxicity. Although it is debatable whether bent limb bones represent a permanent change or not, the finding is of concern and provides additional support for classification.

Effects on or via lactation

No relevant human or animal information is available.

The only generational study with OAS-K, the reproductive screening in rats (2015), was terminated on PND 4, so it did not cover the whole period of lactation. The observed increase in early postnatal mortality (occurring mostly on PND 1) is considered to support classification for developmental toxicity.

Classification for effects on or via lactation is not warranted.

Overall conclusion on reproductive toxicity

RAC agrees with the DS's classification proposal as **Repr. 1B; H360D**.

Additional references

De Schaepdrijver et al. (2014) In vivo longitudinal micro-CT study of bent limb bones in rat offspring. Reproductive Toxicology 46:91-97

RAC (2021) Opinion proposing harmonised classification and labelling at EU level of diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide. CLH-O-0000007023-85-01/F. Adopted 16 September 2021

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).