Committee for Risk Assessment

RAC

Annex 1
Background document
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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

8 June 2023

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification:

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

EC Number: **[1] 271-843-1; [2] -; [3] 267-966-5**

CAS Number: **[1] 68609-93-8; [2] - ; [3] 67968-63-2**

Index Number: **N/A**

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ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 9-OCTADECENOIC ACID (Z)-, SULFONATED, POTASSIUM SALTS /REACTION PRODUCTS OF FATTY ACIDS, C18 (UNSATURATED) ALKYL WITH SULFUR TRIOXIDE, POTASSIUM SALTS / 9(OR 10)-SULPHOOCTADECANOIC ACID, POTASSIUM SALT

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1 IDENTITY OF THE SUBSTANCE

1.1 Names and other identifiers of the substances

The scope of the proposed entry covers a substance that has been historically described using different names and identifiers, as follows:

The name "9-Octadecenoic acid (Z)-, sulfonated, potassium salts" describes a substance which composition includes constituents manufactured from "(Z)-9-Octadecenoic acid" (i.e. C18 carbon chains showing one unsaturation). The substance described using the above name and that is actually placed on the market and registered under REACH, is manufactured from a starting material consisting of C18 carbon chains showing one, two and three unsaturations. Such a substance may be more appropriately described by the name "Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts".

Other identifiers used for describing the same substance correspond to the name "9(or 10)-sulphooctadecanoic acid, potassium salt" and EC No. 267-966-5.

Independently from the name used for describing the substance, the hazardous properties described in this document are correlated to the composition of the substance. Therefore, the scope of the proposed entry covers the possible alternative identifiers historically used for describing the substance, having three sets of identifiers:

- 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC No 271-843-1; CAS No 68609-93-8)
- Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (EC -)
- 9(or 10)-sulphooctadecanoic acid, potassium salt (EC 267-966-5; CAS No. 67968-63-2)

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 9-OCTADECENOIC ACID (Z)-, SULFONATED, POTASSIUM SALTS /REACTION PRODUCTS OF FATTY ACIDS, C18 (UNSATURATED) ALKYL WITH SULFUR TRIOXIDE, POTASSIUM SALTS / 9(OR 10)-SULPHOOCTADECANOIC ACID, POTASSIUM SALT

Table 1 -A: Substance identity and information related to molecular and structural formula of the substance 9-Octadecenoic acid (Z)-, sulfonated, potassium salts

Name(s) in the IUPAC nomenclature or other international chemical name(s)	9-Octadecenoic acid (Z)-, sulfonated, potassium salts
Other names (usual name, trade name, abbreviation)	-
ISO common name (if available and appropriate)	Not applicable
EC number (if available and appropriate)	271-843-1
EC name (if available and appropriate)	9-Octadecenoic acid (Z)-, sulfonated, potassium salts
CAS number (if available)	68609-93-8
Other identity code (if available)	-
Molecular formula	A generic formula cannot be provided for this UVCB substance. The alkyl chain length of the sulfonated fatty acids range from C12-C22, however the major alkyl chain is C18
Structural formula	UVCB
SMILES notation (if available)	UVCB
Molecular weight or molecular weight range	UVCB
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	no information available
Description of the manufacturing process and identity of the source (for UVCB substances only)	Confidential information – see confidential annex-IA
Degree of purity (%) (if relevant for the entry in Annex VI)	Not relevant

Table 1-B: Substance identity and information related to molecular and structural formula of the substance Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts*
Other names (usual name, trade name, abbreviation)	
ISO common name (if available and appropriate)	Not applicable
EC number (if available and appropriate)	-
EC name (if available and appropriate)	Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts
CAS number (if available)	-
Other identity code (if available)	-
Molecular formula	(C18H33)nO7K2S, n= 1-2
Structural formula	UVCB
SMILES notation (if available)	UVCB
Molecular weight or molecular weight range	UVCB
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	no information available
Description of the manufacturing process and identity of the source (for UVCB substances only)	Confidential information – see confidential annex-IB
Degree of purity (%) (if relevant for the entry in Annex VI)	Not relevant

** This substance, and hence the test material, was originally identified with EC 267-966-5, i.e. 9 (or 10)-sulphooctadecanoic acid, potassium salt. Based on the analytical data, the substance shall better be described as: "Reaction product of oleic acid with sulfur trioxide and potassium hydroxide". Consequently, a new substance identity has been requested by the registrant. Based on this request, ECHA has assigned a List number 701-179-4 to the substance "Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts". As the manufacturing process of the substance has not changed, the composition of the substance/test material is the same as it was prior the change of the identifiers, and therefore the tests are still relevant for the substance covered by this registration with list entry 701-179-4.*

Table 1-C: Substance identity and information related to molecular and structural formula of the substance 9(or 10)-sulphooctadecanoic acid, potassium salt

Name(s) in the IUPAC nomenclature or other international chemical name(s)	9(or 10)-sulphooctadecanoic acid, potassium salt
Other names (usual name, trade name, abbreviation)	Octadecanoic acid, sulfo-, potassium salt; Agnique® OAS 50 K; Ölsäuresulfonat,KSalz; Disponil® OSS 50 KS
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	267-966-5
EC name (if available and appropriate)	9(or 10)-sulphooctadecanoic acid, potassium salt
CAS number (if available)	67968-63-2
Other identity code (if available)	-
Molecular formula	C18H34K2O5S
Structural formula	UVCB
SMILES notation (if available)	UVCB
Molecular weight or molecular weight range	UVCB
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	no information available
Description of the manufacturing process and identity of the source (for UVCB substances only)	no information available
Degree of purity (%) (if relevant for the entry in Annex VI)	Not relevant

1.2 Composition of the substance

Table 2 -A: Constituents of 9-Octadecenoic acid (Z)-, sulfonated, potassium salts CAS 68609-93-8, EC 271-843-1 (non-confidential information)

Constituent (name and numerical identifier)	**Typical concentration [% (w/w)] (only for legal entity)**	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self- classification and labelling (CLP)**
Potassium oleic acid sulfonate monomers No CAS no. available	Confidential information; see confidential Annex IA	Confidential information; see confidential Annex IA	No harmonised classification available	Not listed in ECHA C&L-inventory (2021)
Potassium	Confidential	Confidential	No harmonised classification	Not listed in ECHA C&L-

Constituent (name and numerical identifier)	**Typical concentration [% (w/w)] (only for legal entity)**	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self- classification and labelling (CLP)**
oleic acid sulfonate dimers No CAS no. available	information; see confidential Annex IA	information; see confidential Annex IA	available	inventory (2021)
Potassium oleic acid sulfonate trimers No CAS no. available	Confidential information; see confidential Annex IA	Confidential information; see confidential Annex IA	No harmonised classification available	Not listed in ECHA C&L-inventory (2021)
Fatty acids, C16-18 and C18-unsatd. CAS no.: 67701-08-0	Confidential information; see confidential Annex IA	Confidential information; see confidential Annex IA	No harmonised classification available	Not self-classified by most notifiers (number of notifiers = 295) Self-classification of some notifiers: Skin Irrit. 2 (H315) Eye Irrit. 2 (H319)
Potassium sulphate CAS no.: 7778-80-5	Confidential information; see confidential Annex IA	Confidential information; see confidential Annex IA	No harmonised classification available	Not self-classified by most notifiers (number of notifiers = 371) Self-classification of some notifiers: Eye Irrit. 2 (H319) or Eye Dam. 1 (H318) or Skin Irrit. (H315)

The following self-classification has been provided by twenty five notifiers for the UVCB 9-octadecenoic acid (Z)-, sulfonated, potassium salts (according ECHA C&L inventory, 2021):

- Eye Irrit. 2 (H319: Causes serious eye irritation)
- Skin. Irrit. 2 (H315: Causes skin irritation)

The following self-classification has been provided by the registrant for the UVCB 9-octadecenoic acid (Z)-, sulfonated, potassium salts (according to the registration dossier*; ECHA Dissemination, 2021):

- Eye Irrit. 2 (H319: Causes serious eye irritation)
- Repr. 1B (H360: May damage fertility or the unborn child)

** it is noted that this self-classification is also included in the C&L inventory as joint entry submitted by one notifier*

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The substance is a UVCB, there are no impurities. Substance is described by its constituents, see Table 2-A. There is no information on additives available.

Table 2-B Constituents of Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (non-confidential information)

Constituent (name and numerical identifier)	Typical concentration [% (w/w)] (only for legal entity)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
oleic acid EC: 204-007-1; CAS 112-80-1	Confidential information; see confidential Annex IB	Confidential information; see confidential Annex IB	No harmonised classification available	Not self-classified by most notifiers. However, self-classified by other notifiers as: Skin Irrit. 2 (H315) Eye Irrit. 2 (H319) STOT SE 3 (H335) Aquatic chronic 3 (H412)
9-hydroxy-10-sulfo-octadecanoic acid, di-potassium salt No CAS available	Confidential information; see confidential Annex IB	Confidential information; see confidential Annex IB	No harmonised classification available	Not listed in ECHA C&L-inventory
9(or 10)-sulphooctadecanoic acid, potassium salt CAS 67968-63-2; EC 267-966-5	Confidential information; see confidential Annex IB	Confidential information; see confidential Annex IB	No harmonised classification available	Eye Dam. 1 (H318) Repr. 1B (H360) Aquatic Chronic 3
9-sulfo-octadecanoic acid, di-potassium salt, dimers No CAS available	Confidential information; see confidential Annex IB	Confidential information; see confidential Annex IB	No harmonised classification available	Not listed in ECHA C&L-inventory
9-sulfo-octadecanoic acid, 10-carboxy-octadecenyl ester, dipotassium salt No CAS available	Confidential information; see confidential Annex IB	Confidential information; see confidential Annex IB	No harmonised classification available	Not listed in ECHA C&L-inventory
9-sulfo-octadecanoic acid, 10-carboxy-octadecadienyl ester, dipotassium salt No CAS available	Confidential information; see confidential Annex IB	Confidential information; see confidential Annex IB	No harmonised classification available	Not listed in ECHA C&L-inventory
potassium sulfate CAS 7778-80-5, EC 231-915-5	Confidential information; see confidential Annex IB	Confidential information; see confidential Annex IB	No harmonised classification available	Not listed in ECHA C&L-inventory
Unknown constituents	Confidential information;	Confidential information;	No information	No information

Constituent (name and numerical identifier)	Typical concentration [% (w/w)] (only for legal entity)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
	see confidential Annex IB	see confidential Annex IB		

The following self-classification has been provided by 87 notifiers for the UVCB Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (according ECHA C&L inventory; 2021):

- Eye Dam. 1 (H318: Causes serious eye damage)
- Repr. 1B (H360; May damage the unborn child)
- Aquatic chronic 3 (H412: Harmful to aquatic life with long lasting effects)

The following self-classification has been provided by the registrant for the UVCB Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (according to the registration dossier; ECHA Dissemination - 2021):

- Eye Dam. 1 (H318: Causes serious eye damage)
- Repr. 1B (H360; May damage the unborn child)
- Aquatic chronic 3 (H412: Harmful to aquatic life with long lasting effects)

The substance is a UVCB, there are no impurities. Substance is described by its constituents, see Table 2-B. There is no information on additives available.

Table 2-C Constituents of 9(or 10)-sulphooctadecanoic acid, potassium salt EC 267-966-5, CAS 67968-63-2 (non-confidential information)

Constituent (name and numerical identifier)	Typical concentration [% (w/w)] (only for legal entity)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self- classification and labelling (CLP)
No information; no registration dossier available				

The following self-classification has been provided by 166 notifiers for the UVCB 9-octadecenoic acid (Z)-, sulfonated, potassium salts (according ECHA C&L inventory; 2021):

- Eye Dam. 1 (H318: Causes serious eye damage)
- Repr. 1B (H360; May damage the unborn child)
- Aquatic chronic 3 (H412: Harmful to aquatic life with long lasting effects)

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 3: 9-Octadecenoic acid (Z)-, sulfonated, potassium salts

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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	Not applicable	[1] 9-Octadecenoic acid (Z)-, sulfonated, potassium salts; [2] Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts; [3] 9(or 10)-sulphooctadecanoic acid, potassium salt	[1] 271-843-1; [2] -; [3] 267-966-5	[1] 68609-93-8; [2] -; [3] 67968-63-2	No Annex VI entry						
Dossier submitters proposal	Not applicable	[1] 9-Octadecenoic acid (Z)-, sulfonated, potassium salts; [2] Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts; [3] 9(or 10)-sulphooctadecanoic acid, potassium salt	[1] 271-843-1; [2] -; [3] 267-966-5	[1] 68609-93-8; [2] -; [3] 67968-63-2	**Add:** Repr. 1B	**Add:** H360D	**Add:** GHS08 Dgr	**Add:** H360D			

Resulting Annex VI entry if agreed by RAC and COM	Not applicable	[1] 9-Octadecenoic acid (Z)-, sulfonated, potassium salts; [2] Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts; [3] 9(or 10)-sulphooctadecanoic acid, potassium salt	[1] 271-843-1; [2] -; [3] 267-966-5	[1] 68609-93-8; [2] -; [3] 67968-63-2	Repr. 1B	H360D	GHS08 Dgr	H360D			

Table 4: Reason for not proposing harmonised classification and status under public consultation

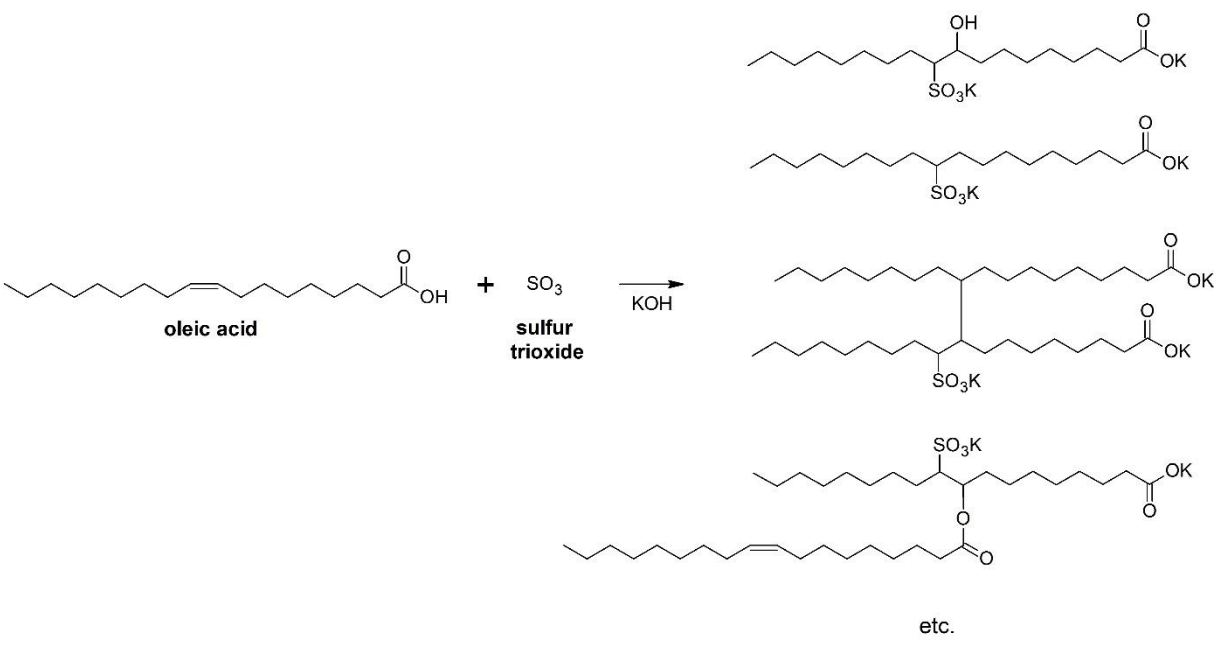
Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	hazard class not assessed in this dossier	No
Oxidising gases	hazard class not assessed in this dossier	No
Gases under pressure	hazard class not assessed in this dossier	No
Flammable liquids	hazard class not assessed in this dossier	No
Flammable solids	hazard class not assessed in this dossier	No
Self-reactive substances	hazard class not assessed in this dossier	No
Pyrophoric liquids	hazard class not assessed in this dossier	No
Pyrophoric solids	hazard class not assessed in this dossier	No
Self-heating substances	hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	hazard class not assessed in this dossier	No
Oxidising liquids	hazard class not assessed in this dossier	No
Oxidising solids	hazard class not assessed in this dossier	No
Organic peroxides	hazard class not assessed in this dossier	No
Corrosive to metals	hazard class not assessed in this dossier	No
Acute toxicity via oral route	hazard class not assessed in this dossier	No
Acute toxicity via dermal route	hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	hazard class not assessed in this dossier	No
Skin corrosion/irritation	hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	hazard class not assessed in this dossier	No
Respiratory sensitisation	hazard class not assessed in this dossier	No
Skin sensitisation	hazard class not assessed in this dossier	No
Germ cell mutagenicity	data conclusive but not sufficient for classification	Yes
Carcinogenicity	data lacking	Yes
Reproductive toxicity	harmonised classification proposed; Repr. 1B (H360D)	Yes
Specific target organ toxicity-single exposure	hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	hazard class not assessed in this dossier	No
Aspiration hazard	hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	hazard class not assessed in this dossier	No
Hazardous to the ozone layer	hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

There is no harmonised classification and labelling available for 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8)/ Reaction products of fatty acid, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (EC -; CAS -) / 9(or 10)-sulphooctadecanoic acid, potassium salt (EC 267-966-5; CAS 67968-63-2). The substance has not been included in former activities on harmonised classification.

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.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level.

The substance has CMR properties (reproductive toxicity). Harmonised classification and labelling for CMR is a community-wide action under article 36 of the CLP regulation.

5 IDENTIFIED USES

9-Octadecenoic acid (Z)-, sulfonated, potassium salts is used in the following categories of products (both indoor and outdoor) (ECHA Dissemination, 2021): laboratory reagents (processing aid), intermediate use at industrial sites, air care products, biocidal products, polishes and wax blends, machine wash liquids/detergents, metal surface treatment products, adhesives (water-based, 1- or multi-component, reactive, cementitious) and sealants (reactive or otherwise) (ECHA Dissemination, 2021).

6 DATA SOURCES

The REACH registration dossiers for 9-Octadecenoic acid (Z)-, sulfonated, potassium salts and Reaction products of fatty acid, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts publicly available from ECHA's disseminated database (ECHA Dissemination, 2021) has been analysed for study references, which then have been considered as data sources for this CLH report. Additionally, the confidential registration dossier and the original study reports were available for evaluation.

Systematic searches for publications and other relevant data were performed based on the following databases:

- U.S. National Library of Medicine, Pubmed.gov
- TOXNET, ChemIDplus, IPCS , eChemPortal
- Medline, SciSearch, Biosis, PQscitech, Chemical Abstracts (HCA), Embase (at host STN International)

All data sources used in this report are also listed in section 15 or Annex I (references).

7 PHYSICOCHEMICAL PROPERTIES

Table 5 -A: Summary of physicochemical properties of 9-octadecenoic acid (Z)-, sulfonated, potassium salts (CAS 68609-93-8, EC 271-843-1)

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101.3 kPa	Solid, coarse powder	(ECHA Dissemination, 2021)	visual observation
Melting/freezing point	> 318 °C	(ECHA Dissemination, 2021)	measured, at 101.3 kPa
Boiling point	ca. 327 °C	(ECHA Dissemination, 2021)	measured, at 101.6 kPa, boiling and/or thermal decomposition observed
Relative density	1.16	(ECHA Dissemination, 2021)	measured, at 20°C
Vapour pressure	2.1E-5 Pa	(ECHA Dissemination, 2021)	calculated, based on lowest possible boiling point, at 20°C
Surface tension	32.5 mN/m	(ECHA Dissemination, 2021)	measured, at 1 g/L and 20°C
Water solubility	740 g/L	(ECHA Dissemination, 2021)	measured, at 20°C and pH 5.9
Partition coefficient n-octanol/water (log Pow)	< -4.98	(ECHA Dissemination, 2021)	calculated based on solubility in water and n-octanol at 20°C
Flash point	275.5 °C	(ECHA Dissemination, 2021)	measured, at 101.3 kPa
Flammability	non flammable	(ECHA Dissemination, 2021)	measured
Explosive properties	non-explosive	(ECHA Dissemination, 2021)	measured
Self-ignition temperature	< 400 °C	(ECHA Dissemination, 2021)	measured
Oxidising properties	non oxidising	(ECHA Dissemination, 2021)	measured
Granulometry	No data		
Stability in organic solvents and identity of relevant degradation products	No data		
Dissociation constant	1.89 (pKa)	(ECHA Dissemination, 2021)	measured, at 20°C, molecular weight of 700 g/mol used for calculation
Viscosity	No data		

Table 5-B. Summary of physicochemical properties of Reaction products of fatty acid, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
Physical state at 20°C and 101.3 kPa	Solid	(ECHA Dissemination, 2021)	Visual observation
Melting/freezing point	>250°C	(ECHA Dissemination, 2021)	
Boiling point	Substance decomposes before boiling	(ECHA Dissemination, 2021)	
Relative density	1.223	(ECHA Dissemination, 2021)	Relative density at 20°C
Vapour pressure	Not relevant	(ECHA Dissemination, 2021)	
Surface tension	30	(ECHA Dissemination, 2021)	in mN/m at 20°C and concentration in mg/L: 1000
Water solubility	> 80.33 g/L and < 89.96 g/L	(ECHA Dissemination, 2021)	measured, at room temperature
Partition coefficient n-octanol/water (log Pow)	-2	(ECHA Dissemination, 2021)	measured, at 23°C
Flash point	Not applicable	(ECHA Dissemination, 2021)	
Flammability	Non-flammable solid	(ECHA Dissemination, 2021)	
Explosive properties	Non explosive	(ECHA Dissemination, 2021)	
Self-ignition temperature	Not applicable	(ECHA Dissemination, 2021)	
Oxidising properties	No oxidising properties	(ECHA Dissemination, 2021)	
Granulometry	Used in a non-solid or granular form	(ECHA Dissemination, 2021)	
Stability in organic solvents and identity of relevant degradation products	Not considered as critical	(ECHA Dissemination, 2021)	
Dissociation constant	4.35 (pKa)	(ECHA Dissemination, 2021)	Calculated at 25°C
Viscosity	Solid	(ECHA Dissemination, 2021)	

No registration dossier is available for 9(or 10)-sulphooctadecanoic acid, potassium salt EC 267-966-5, CAS 67968-63-2.

8 EVALUATION OF PHYSICAL HAZARDS

Not performed for this substance.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

There are no experimental data on absorption, metabolism, distribution and elimination of 9-octadecenoic acid (Z)-, sulfonated, potassium salts available in the registration dossier. Also for Reaction products of fatty acid, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts, no experimental data on absorption, metabolism, distribution and elimination are available in its registration dossier.

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Registration dossier of 9-octadecenoic acid (Z)-, sulfonated, potassium salts (CAS 68609-93-8, EC 271-843-1):

Based on theoretical considerations it was concluded in the registration dossier of 9-octadecenoic acid (Z)-, sulfonated, potassium salts that the substance has a low bioaccumulation potential. The registrant argued that bioaccumulation of the solid substance is unlikely as all constituents of the UVCB have a molecular weight >500 (this is only true for the dimeric and trimeric constituents but not for Fatty acids, C16-18 and C18-unsatd.), the substance has a water solubility of 740 g/L at 20°C, the vapour pressure is low (2.1 E-5 Pa at 20°C) and the substance has a limited lipophilic character (log Pow: below -4.89).

The following default absorption rates have been assumed in the registration dossier for the different pathways:

- Absorption rate - oral: 50% (default)
- Absorption rate - dermal: 10%
- Absorption rate – inhalation: 100% (default)

In the registration dossier it was discussed that especially the dermal absorption rate might be too high taking into consideration that the substance is very hydrophilic and might therefore be too hydrophilic to cross the lipid rich stratum corneum. as Also, a molecular weight of > 500 for the majority of the constituents, especially the dimeric and trimeric constituents, might hamper their dermal uptake. Assumption of a limited dermal uptake is further supported, according to the registrant, by the observation that the substance is not a skin irritant, was not skin sensitising and did not cause acute toxicity after dermal exposure.

No information is provided in the registration dossier on the likelihood or velocity of hydrolysis of the compound under physiological or environmental conditions.

Registration dossier of Reaction products of fatty acid, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts:

The following was considered by the registrant: Based on the physicochemical properties and the results obtained in the toxicity tests, the substance will most likely be absorbed via the GI tract and become systemically available.

Uptake into the systemic circulation following dermal exposure is very limited due to high water solubility of the substance at room temperature. Also, based on the high water solubility and the results obtained in the respective toxicological investigation, it is unlikely that relevant amounts of the reaction mass will become systemically bioavailable via inhalation.

After becoming bioavailable, it is assumed that the substance will circulate within the blood stream and will finally be transported to the liver where Phase I and Phase II metabolism may occur. Ultimately the metabolism products will be excreted via the kidney in the urine.

Based on its PC values the constituents of the reaction mass are not considered to be bioaccumulative.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Evaluation not performed for this substance.

10.2 Acute toxicity - dermal route

Evaluation not performed for this substance.

10.3 Acute toxicity - inhalation route

Evaluation not performed for this substance.

10.4 Skin corrosion/irritation

Evaluation not performed for this substance.

10.5 Serious eye damage/eye irritation

Evaluation not performed for this substance.

10.6 Respiratory sensitisation

Evaluation not performed for this substance.

10.7 Skin sensitisation

Evaluation not performed for this substance.

10.8 Germ cell mutagenicity

Table 6: Summary table of mutagenicity/genotoxicity tests *in vitro*

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
Bacterial gene mutation OECD TG 471 Deviations: no Ames Test GLP: yes RL1[#] (according to the Dossier Submitter)	9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8) (Analytical Purity: 100%) Vehicle: Milli-Q water	Salmonella typhimurium TA 1535, TA 1537, TA 98, TA 100 and E.coli WP2uvrA Plate incorporation-Range finding test (only TA 100 and WP2uvrA) 10, 33, 100, 333, 1000, 3300, 5000 µg/plate with or without 5% (v/v) S9-mix Plate incorporation-Initial test (TA 1535, TA1537, TA 98): 100, 333, 1000, 3330, 5000 µg/plate with or without 5% (v/v) S9-mix Plate incorporation – confirmation (all strains): 100, 333, 1000, 3330, 5000 µg/plate with or without 10% (v/v) S9-mix Tested up to limit concentration Vehicle: Milli-Q water +/- S9 mix from rat liver Positive controls: yes	Negative (+/- S9 mix) for all strains tested	NN[##], 2014a
Chromosome aberration study in mammalian	9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS	Peripheral human lymphocytes Assay 1:	Negative (+/- S9 mix) Number of polyploid cells and cells with endoreduplicated chromosomes	NN, 2014b

Method, guideline, deviations if any	**Test substance,**	**Relevant information about the study including rationale for dose selection (as applicable)**	**Observations**	**Reference**
cells OECD TG 473 Deviations: no GLP: yes RL1 (according to the Dossier Submitter)	68609-93-8) (Analytical Purity: 100%) Vehicle: Milli-Q water	3-h treatment with and without S9-mix, 24 h fixation time: concentrations: 10, 100, 1000 µg/mL Assay 2: 24-h and 48 h treatment without S9-mix, 24 h and 48 h fixation time: concentrations: 10, 30, 100, 200, 300, 400, 500 µg/mL 3-h treatment with S9-mix, 48 h fixation time: concentrations: **10**, **100**, **1000** µg/mL Assay 2a (repeat experiment as in the absence of S9-mix no appropriate dose levels could be selected for scoring of chromosome aberrations): 24-h treatment without S9-mix, 24 h fixation time: concentrations: **10**, **100**, **300**, 325, 350, 375, 400, 450 µg/mL 48-h treatment without S9-mix, 48 h fixation time: concentrations: **10**, **100**, **250**, **300**, 325, 350, 375, 400 µg/mL +/- S9 mix from rat liver Positive controls: yes No cytotoxicity in first and second cytogenetic assay (with MA, but	not affected.	

Method, guideline, deviations if any	**Test substance,**	**Relevant information about the study including rationale for dose selection (as applicable)**	**Observations**	**Reference**
		tested up to precipitating concentrations. Cytotoxicity visible in second cytogenetic assay (without MA) at concentrations ≥300 µg/mL (concentrations marked in bold were evaluated, other concentrations were too cytotoxic)		
Gene mutation study in mammalian cells OECD TG 476 Deviations: no GLP: yes RL1 (according to the Dossier Submitter)	9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8) (Analytical Purity: 100%)	Mouse lymphoma L5178Y cells Target gene: Thymidine kinase (TK) Dose range finding test (3-hour treatment with and without MA[###] and 24 h treatment without MA): 0, 33, 100, 333, 666 and 1,000 µg/mL Assay 1: 3 h treatment with (4%) v/v S9-mix: **0, 10,** 33, **100,** 150, **170, 200, 225, 235, 250, 265** µg/mL; 3 h treatment without MA: **0, 1, 3, 10, 33,** 66, **100, 125, 150, 160**, 170, 180, 190 µg/mL µg/mL Assay 2: 3 h treatment with (8% v/v) S9-mix: **0,** 10, **33, 100, 150,** 200, **225, 235, 250, 265, 280** µg/mL; 24 h treatment without MA: **0, 3, 10, 33, 50,** 65, 85, **100,** 115, 130, **150, 170, 185** µg/mL Test substance concentrations were selected based on cytotoxicity: without S9-mix: 170 µg/mL and above; with 4% (v/v)	Negative (+/- S9 mix)	NN, 2014c

Method, guideline, deviations if any	**Test substance,**	**Relevant information about the study including rationale for dose selection (as applicable)**	**Observations**	**Reference**
		S9-mix: 250 µg/mL and above; with 8% (v/v) S9-mix: 200 µg/mL and above (concentrations marked in bold were evaluated) Vehicle test material: RPMI 1640 (exposure medium, Hepes buffered medium (Dutch modification) Vehicle positive control: DMSO (methyl methane sulfonate) or Hanks' balanced salt solution (cyclophosphamide)		
Bacterial gene mutation OECD 471 Deviations: not mentioned GLP: yes	Sykanol Ke 2780 (Analytical Purity: 50.8%) Vehicle: Bidist water	Salmonella typhimurium TA 1535, TA 1537, TA1538, TA 98, and TA 100 Plate incorporation-Range finding test 8; 40; 200; 1000, and 5000 µg/plate with or without S9-mix Vehicle: Bidist water +/- S9 mix from rat liver Positive controls: yes	Negative (+/- S9 mix) for all strains tested	NN, 1993
In vitro gene mutation testing CHO cells (HPRT locus assay) OECD No. 476 Deviations: not mentioned	Octadecanoic acid, sulfo-, potassium salt (CAS 67968-63-2)* (purity: 51.92% test item)	CHO cells 1st Experiment without S9 mix 0; 21.9; 43.8; 87.5; 175.0; 350.0; 700.0 µg/mL with S9 mix 0; 10.9; 21.9; 43.8; 87.5; 175.0; 350.0 µg/mL	Negative (+/- S9 mix) in the HPRT assay in CHO cells. In this study, in the 1st and 2nd Experiment, at least the highest concentrations evaluated for gene mutations were clearly cytotoxic in the absence and the presence of metabolic activation.	NN, 2015a

Method, guideline, deviations if any	**Test substance,**	**Relevant information about the study including rationale for dose selection (as applicable)**	**Observations**	**Reference**
GLP: yes		2nd Experiment without S9 mix 0; 25.0; 50.0; 100.0; 200.0; 400.0; 800.0 µg/mL with S9 mix 0; 12.5; 25.0; 50.0; 100.0; 200.0; 400.0 µg/mL Vehicle: aqueous culture medium (Ham's F12) Positive controls: yes		
In vitro micronucleus assay in V79 cells (cytokinesis block method) OECD 487 Deviations: not mentioned GLP: yes	Octadecanoic acid, sulfo-, potassium salt (CAS 67968-63-2)* (purity: 51.92% test item)	V79 cells 1st Experiment 4 hours exposure, 24 hours harvest time, without S9 mix 0; 31.3; 62.5; 125.0; 250.0; 500.0; 1000.0 µg/mL 4 hours exposure, 24 hours harvest time, with S9 mix 0; 31.3; 62.5; 125.0; 250.0; 500.0; 1000.0 µg/mL 2nd Experiment 24 hours exposure, 24 hours harvest time, without S9 mix 0; 7.8; 15.6; 31.3; 62.5; 125.0; 250.0 µg/mL 4 hours exposure, 44 hours harvest time, with S9 mix 0; 15.6; 31.3; 62.5; 125.0; 250.0; 500.0 µg/mL Vehicle: culture medium (MEM)	Negative (+/- S9 mix) in the micronucleus assay in V79 cells. Cytotoxicity indicated by clearly reduced relative cell count (given as relative population doubling [RPD]) or proliferation index (CBPI) or low slide quality was observed at least at the highest applied test substance concentration in all experimental parts of this study.	NN, 2015b

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
		Positive control: yes		

[#] RL = Klimisch reliability score

[##] NN = Nomen Nescio

[###] MA = metabolic activation

** The substance, and hence the test material, was originally identified with EC 267-966-5, i.e. 9 (or 10)-sulphooctadecanoic acid, potassium salt. Based on the analytical data, the substance shall better be described as: "Reaction product of oleic acid with sulfur trioxide and potassium hydroxide". Consequently, a new substance identity has been requested by the registrant. Based on this request, ECHA has assigned the new List number 701-179-4 to the substance "Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts". As the manufacturing process of the substance has not changed, the composition of the substance/test material is the same as it was prior the change of the identifiers, and therefore the tests are still relevant for the substance covered by the registration with list entry 701-179-4.*

There are no studies investigating mutagenicity/genotoxicity in mammalian somatic or germ cells *in vivo* available.

There are no human data relevant for germ cell mutagenicity available.

10.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

There are only *in vitro* data available for the assessment of germ cell mutagenicity. No *in vivo* data and no human data were identified.

Gene mutation *in vitro* was assessed in 2 bacterial reverse mutation assays according to OECD guideline 471 and GLP (NN, 2014a, NN, 1993). First bacterial assay was performed with 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8), tested at five concentrations in the range of 100 to 5,000 µg/plate, was negative in all strains, both in the plate incorporation assay and the pre-incubation assay in the presence and absence of metabolic activation (NN, 2014a). According to the information provided in the registration dossier "the negative control values were within the laboratory historical control data ranges, except for TA1535 in the absence of S9-mix" in the pre-incubation assay. "Since this value was just outside the limit of the range" it is concluded that this has no impact on the validity of the test. Positive controls provided adequate results (three times the concurrent vehicle control group mean) indicating that the test conditions were adequate.
The second bacterial assay was performed with Sykanol Ke 2780 (o1eic acid sulfonate -di-potassium-salt / 9-octadecenoic acid, sulfo-K-salt), tested at five concentrations in the range 8-5000 µg/plate (NN, 1993). Two independent experiments were conducted and were both negative in all strains in presence of absence of metabolic activation. However, slightly toxic effects at 5000 µg/plate were noted as indicated by a slightly reduced revertant rate in the presence of S9-mix.

A chromosome aberration assay in cultured peripheral human lymphocytes according to OECD Guideline 473 and in compliance with GLP has been performed with 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8) (NN, 2014b). Two independent experiments were conducted. The test substance did not induce a statistically significant or biologically relevant increase in the number of cells with chromosome aberrations in the presence or absence of metabolic activation. No biologically relevant effect on number of polyploid cells and cells with endoreduplicated chromosomes was observed.

Further, gene mutation in L5178Y mouse lymphoma cells according to OECD Guideline 476, in compliance with GLP has been investigated with 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8) (NN, 2014c). Neither in the absence nor in the presence of S9-mix a significant increase in the mutation frequency at the TK locus was observed. The numbers of small and large colonies did not show relevant differences between treated cultures and solvent controls.

Based on the results of the HPRT locus assay with Octadecanoic acid, sulfo-, potassium salt (CAS 67968-63-2), the test substance did not cause any dose dependent increase in the mutant frequencies both without S9 mix and after the addition of a metabolizing system in two experiments performed independently of each other (NN, 2015a). Thus, under the experimental conditions of this study, the test substance Octadecanoic acid, sulfo-, potassium salt is not mutagenic in the HPRT locus assay under *in vitro* conditions in CHO cells in the absence and the presence of metabolic activation.

On the basis of the results of the present micronucleus study with Octadecanoic acid, sulfo-, potassium salt (CAS 67968-63-2), the test substance did not cause any biologically relevant increase in the number of cells containing micronuclei either without S9 mix or after adding a metabolizing system (NN, 2015b). Thus, under the experimental conditions described, Octadecanoic acid, sulfo-, potassium salt is considered not to have a chromosome-damaging (clastogenic) effect nor to induce numerical chromosomal aberrations (aneugenic activity) under in vitro conditions in V79 cells in the absence and the presence of metabolic activation.

In summary, all six *in vitro* assays, which were reliable and relevant, provide consistently negative results.

10.8.2 Comparison with the CLP criteria

There are no epidemiological data to support classification in Category 1A.

In the absence of any *in vivo* germ cell or somatic cell mutagenicity tests there is no evidence that the substance has the potential to cause germ cell mutations. Classification in Category 1B is not justified.

In the absence of any *in vivo* somatic cell genotoxicity data and with only negative results from *in vitro* assays there is no evidence that the substance has the potential to cause somatic cell mutations. Thus, classification in Category 2 is not justified.

10.8.3 Conclusion on classification and labelling for germ cell mutagenicity

As outlined in section 10.8.1 only negative results were obtained in *in vitro* assays and no *in vivo* or epidemiological data are available. Therefore, none of the criteria for classification for germ cell mutagenicity is fulfilled.

Therefore, no classification as germ cell mutagen is proposed for 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8)/ Reaction products of fatty acid, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (EC -; CAS -) / 9(or 10)-sulphooctadecanoic acid, potassium salt (EC 267-966-5; CAS 67968-63-2).

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**.

10.9 Carcinogenicity

There are no carcinogenicity data available, neither in animals nor in humans.

Table 7: Summary table of other studies relevant for carcinogenicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Repeated Dose Toxicity Study According to OECD TG 408 Deviations: no GLP: yes Wistar Han rats (SPF-bred; 10 animals/sex/dose group) RL1 (according to the Dossier Submitter)	9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8) (Purity/Composition UVCB: 100%)	Oral Gavage 0, 100, 300, 1000 mg /kg bw/d Vehicle: water	NOAEL: 300 mg/kg bw/d (according to registration dossier) Relevant effects at 1000 mg/kg bw/d: spontaneous death of one male; increased kidney weights, morphologic alterations in the kidneys of males and females which consisted of the accumulation of pigmented material in vacuolar structures in the cortical tubules; degeneration of the tubules and regenerative changes of the tubules; increased liver weight, increased levels of alanine aminotransferase and aspartate transaminase, glucose and cholesterol levels decreased, no histopathological changes of the liver; no neoplastic changes observed Foregrip strength was reduced in 300 and 1000 mg/kg bw/d males and 1000 mg/kg bw/d females in a statistically significant manner. Not regarded as adverse since in the absence of any clear correlation of clinical signs or morphological changes. Slight histological changes of kidney in 300 mg/kg bw/d animals not regarded as adverse in the registration dossier.	NN (2017a) See section 3.12.1 of Annex I
Repeated Dose Toxicity Study	Reaction products of fatty acids, C18 (unsaturated) alkyl	Oral Gavage 0, 150, 450, 1400 mg /kg	NOAEL: 450 mg/kg bw/d for systemic toxicity corresponding to 236 mg/kg bw/d of the active ingredient,	NN, 2020

Type of study/data	**Test substance,**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
According to OECD TG 408 GLP: yes Wistar Han rats (SPF-bred: 10 animals/sex/dose group) RL1 (according to the Dossier Submitter)	with sulfur trioxide, potassium salts (CAS 67968-63-2, EC -)* # (Purity/Composition UVCB: 52.5%)	bw/d Dose based ingredient: 0, 79, 263, 735 mg /kg bw/d Vehicle: deionised water	NOAEL of <150 mg/kg bw/day for local toxicity corresponding to 79 mg/kg bw/day of the active ingredient. Relevant effects at 1400 mg/kg bw/d (corresponds to 735 mg/kg bw/d active ingredient) *Clinical Examinations* • Soft faeces in 10/10 males from study day 66 onwards • Respiration sounds in 3/10 males and females on each one or two days after treatment • Semi-closed eyelids in 1/10 males and 2/10 females on each one day after treatment • Nose discharge in 1/10 males on one day • Decreased motor activity in females during two intervals (1 and 2) and the overall interval *Clinical Pathology* • Decreased haemoglobin and haematocrit values in both sexes • Decreased red blood cell (RBC) counts in females • Decreased absolute reticulocyte counts in males • Increased absolute neutrophil counts in females • Increased LDL-cholesterol and total bilirubin values in both sexes • Decreased HDL-cholesterol values in males • Increased inorganic phosphate levels in males • Increased incidences of transitional epithelial cells and blood (erythrocytes) in the urine of females *Pathology* • Increase in absolute and relative kidney weight in male (+9%/+18%) and female (+20%/+20%) animals • Minimal to severe degeneration/regeneration and pigment storage (all animals) in kidney tubules in 9 males and 9 females	See section 3.12.1 of Annex I

 # As presented in study report. The Dossier submitter notes that, according to ECHA, CAS 67968-63-2/EC 267-966-5 corresponds to "9(or 10)-sulphooctadecanoic acid, potassium salt" and CAS - /EC - corresponds to "Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts"

** The substance, and hence the test material, was originally identified with EC 267-966-5, i.e. 9 (or 10)-sulphooctadecanoic acid, potassium salt. Based on the analytical data, the substance shall better be described as: "Reaction product of oleic acid with sulfur trioxide and potassium hydroxide". Consequently, a new substance identity has been requested by the registrant. Based on this request, ECHA has assigned the new List number 701-179-4 to the substance "Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts". As the manufacturing process of the substance has not changed, the composition of the substance/test material is the same as it was prior the change of the identifiers, and therefore the tests are still relevant for the substance covered by the registration with list entry 701-179-4.*

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

There are no carcinogenicity studies available.

No neoplastic or pre-neoplastic lesions were reported in a 90-day repeated dose toxicity study with rats up to the highest dose of 1000 mg/kg bw/d 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8) (NN, 2017A; see section 3.12.1 of Annex I for a detailed description of this study). Major findings in this subchronic study were histopathological but no neoplastic changes in the kidney and increased kidney and liver weights. A NOAEL of 300 mg/kg bw/d based on the findings in kidney and liver was reported for this study. Neurobehavioural effects (reduced foregrip strength) observed at 300 mg/kg bw/d were not regarded as adverse since there was no correlation to clinical signs or morphological changes.

In another 90-day repeated dose study with rats exposed to 0, 150, 450, 1400 mg /kg bw/d (Dose based ingredient: 0, 79, 263, 735 mg /kg bw/d) of reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (CAS: 67968-63-2, EC -) (NN, 2020; see section 3.12.1 of Annex I for a detailed description of this study) neoplastic or pre-neoplastic lesions were reported in the highest dose 1400 mg/kg bw/d (corresponding to 735 mg/kg bw/d of active ingredient). Minimal to severe degeneration/regeneration and pigment storage (all animals) in kidney tubules in 9 males and 9 females were observed. Additionally, other finding were noted such as an increase in absolute and relative kidney weight in male (+9%/+18%) and female (+20%/+20%) animals. Therefore, the NOAEL for systemic toxicity was 450 mg/kg bw/d for male and female rats corresponding to 236 mg/kg bw/d of the active ingredient. The NOAEL for local toxicity was <150 mg/kg bw/day corresponding to <79 mg/kg bw/day of the active ingredient.

10.9.2 Comparison with the CLP criteria

In the absence of relevant and reliable studies on possible carcinogenic effects in humans and experimental animals and in the absence of any indications of carcinogenic effects from a repeated dose toxicity study the criteria are not applicable and classification for 9-octadecenoic acid (Z)-, sulfonated, potassium salt as a carcinogen cannot be assessed.

10.9.3 Conclusion on classification and labelling for carcinogenicity

In the absence of relevant and reliable studies on potential carcinogenic effects of 9-octadecenoic acid (Z)-, sulfonated, potassium salt the classification for carcinogenicity cannot be assessed.

Therefore, no classification as a carcinogen is proposed for 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8)/ Reaction products of fatty acid, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (EC -; CAS -) / 9(or 10)-sulphooctadecanoic acid, potassium salt (EC 267-966-5; CAS 67968-63-2).

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

2 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**.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 8: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Repeated Dose Toxicity Study According to OECD TG 408 Deviations: no GLP: yes Wistar Han rats (SPF-bred; 10 animals/sex/dose group) RL1 (according to the Dossier submitter)	9-Octadecenoic acid (Z)-, sulfonated, potassium salts (Purity/Composition UVCB: 100%) 0, 100, 300, 1000 mg /kg bw/d Oral, via gavage Vehicle: water Parameters relevant for sexual function	NOAEL reproduction/fertility: 1000 mg/kg bw/d No adverse effects on oestrous cycle regularity, spermatogenesis staging and morphology and weight of gonads and accessory reproductive organs	NN (2017a) See section 3.12.1 of Annex I

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
	and fertility examined: Organ weights of thyroid, adrenal glands, epididymides, ovaries, prostate, seminal vesicles including coagulating glands, testes, uterus including cervix. Histopathology of ovaries, adrenal gands, pituitary gland, preputial gland, cervix, prostate gland, clitoral gland seminal vesicles, mammary gland, testes, epididymis, thyroid including parathyroid, uterus, vagina, all gross lesions. Histopathologic investigation of spermatogenesis staging. Estrous cycle determination: All females had a daily lavage from Day 70 up to and including Day 90 to determine the stage of estrous		
Reproduction/developmental toxicity screening study According to OECD TG 422 Deviations: not mentioned GLP: yes Wistar Han rats (SPF-bred; 10 animals/sex/dose group) RL1 (according to the Dossier Submitter)	Octadecanoic acid, sulfo-, potassium salt (CAS 67968-63-2)* (Purity/Composition UVCB: 51.92%) 0, 96, 289 and 963 mg/kg bw/d of the test item corresponding to 0, 50, 150, and 500 mg/kg bw/d	NOAEL for reproductive performance and fertility was 500 mg/kg bw/d in male and female Wistar rats. No adverse effects on fertility noted in males and females. See section 10.10.4/10.10.5 for adverse effects on development.	NN, 2015c

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
	octadecanoic acid, sulfo-, potassium salt Oral, via gavage Vehicle: water Duration of treatment covered a 2 week premating period and mating in both sexes (mating pairs were from the same dose group) as well as entire gestation and 4 days of lactation period in females up to one day prior to the day of schedule sacrifice of the animals		
Repeated Dose Toxicity Study According to OECD TG 408 GLP: yes Wistar Han rats (SPF-bred: 10 animals/sex/dose group) RL1 (according to the Dossier Submitter)	Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (CAS 67968-63-2, EC -)*# (Purity/Composition UVCB: 52.5%) Oral Gavage 0, 150, 450, 1400 mg /kg bw/d Dose based ingredient: 0, 79, 263, 735 mg /kg bw/d Vehicle: deionised water	NOAEL: 450 mg/kg bw/d for systemic toxicity corresponding to 236 mg/kg bw/d of the active ingredient, NOAEL of <150 mg/kg bw/day for local toxicity corresponding to <79 mg/kg bw/day of the active ingredient *Clinical Examinations* • Special attention was given for the synchrony of the morphology of the oestrous cycle in ovaries, uterus, cervix, and vagina. • Special attention was given for the male reproductive organs, especially the stage of seminiferous tubules. *Pathology* • No effects on reproduction organs were noted in males and females.	NN (2020) See section 3.12.1 of Annex I

 # As presented in study report. The Dossier submitter notes that, according to ECHA, CAS 67968-63-2/EC 267-966-5 corresponds to "9(or 10)-sulphooctadecanoic acid, potassium salt" and CAS - /EC - corresponds to "Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts"

** The substance, and hence the test material, was originally identified with EC 267-966-5, i.e. 9 (or 10)-sulphooctadecanoic acid, potassium salt. Based on the analytical data, the substance shall better be described as: "Reaction product of oleic acid with sulfur trioxide and potassium hydroxide". Consequently, a new substance identity has been requested by the registrant. Based on this request, ECHA has assigned the new List number 701-179-4 to the substance "Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts". As the manufacturing process of the substance has not changed, the composition of the substance/test material is the same as it was prior the change of the identifiers, and therefore the tests are still relevant for the substance covered by the registration with list entry 701-179-4.*

There are no human data on adverse effects on sexual function and fertility or other studies relevant for toxicity on sexual function and fertility available.

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

One study from an oral subchronic toxicity study in rats (NN, 2017a) which investigated effects of 9-octadecenoic acid (Z)-, sulfonated, potassium salt on the weight and histopathology of reproductive organs as well as spermatogenesis staging in male rats and oestrous cycle in female rats. No adverse effects on these endpoints were observed up to the limit dose of 1000 mg/kg bw/d.

Results of Reproduction/developmental toxicity screening study according OECD 422 in rats with Octadecanoic acid, sulfo-, potassium salt (CAS 67968-63-2) (NN, 2015c) indicate adverse effects on the combined occurrence of clinical signs and effects on food consumption as well as on body weight at a dose of 500 mg/kg bw/day. Fertility indices for male and female animals were not impaired by test-substance administration up to the highest dose tested 500 mg/kg bw/d. The live birth indices of pups in at a dose of 50 and 150 mg/kg bw/d were not influenced. Concerning clinical pathology no treatment-related, adverse effects were observed up to a dose of the test item of 500 mg/kg bw/d. Regarding pathology, all findings occurred either individually or were biologically equally distributed over control and treatment groups. They were considered to be incidental or spontaneous in origin and without any relation to treatment. See also section 10.10.4 for a description of the adverse effects on development.

In another 90-day repeated dose study with rats exposed to 0, 150, 450, 1400 mg /kg bw/d (Dose based ingredient: 0, 79, 263, 735 mg /kg bw/d) of reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (CAS: 67968-63-2, EC -) (NN, 2020; see section 3.12.1 of Annex I for a detailed description of this study), special attention was given for the synchrony of the morphology of the oestrous cycle in ovaries, uterus, cervix, and vagina. Additionally, special attention was given for the male reproductive organs, especially the stage of seminiferous tubules. No effects on reproduction were noted in males and females. Based on other pathological findings, the NOAEL for systemic toxicity was 450 mg/kg bw/d for male and female rats corresponding to 236 mg/kg bw/d of the active ingredient. The NOAEL for local toxicity was <150 mg/kg bw/day corresponding to <79 mg/kg bw/day of the active ingredient.

10.10.3 Comparison with the CLP criteria

There are no epidemiological data to support classification of 9-octadecenoic acid (Z)-, sulfonated, potassium salt in Category 1A.

Results of a repeated dose toxicity study in rats with 9-octadecenoic acid (Z)-, sulfonated, potassium salt did not indicate any adverse effects on reproductive organs, neither weight nor histopathological changes, oestrous cycle and spermatogenesis up to the limit dose of 1000 mg/kg bw/d, which caused severe general toxicity (one spontaneous death, liver and kidney toxicity). Results of a repeated dose study with rats exposed to 0, 150, 450, 1400 mg /kg bw/d (Dose based ingredient: 0, 79, 263, 735 mg /kg bw/d) of reaction

products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (CAS: 67968-63-2, EC -) (NN, 2020; see section 3.12.1 of Annex I for a detailed description of this study) did not indicate any adverse effects on reproductive organs, oestrous cycle, and spermatogenesis. Based on other pathological findings (Kidney toxicity at 1400 mg/kg bw/d (corresponds to 735 mg/kg bw/d active ingredient)), the NOAEL for systemic toxicity was 450 mg/kg bw/d for male and female rats corresponding to 236 mg/kg bw/d of the active ingredient.

Results of a reproduction study, a combined oral repeated dose toxicity study with the reproduction/developmental toxicity screening test in Wistar rats investigated effects of an equivalent of 9-octadecenoic acid (Z)-, sulfonated, potassium salt on reproductive performances, clinical pathology, functional battery, motor activity, pup viability/mortality. NOAEL for reproductive performance and fertility was 500 mg/kg bw/d in male and female Wistar rats. NOAEL for developmental toxicity in the F1 progeny was 150 mg/kg bw/d.

There are no other studies available investigating certain endpoints which are also relevant for the evaluation of effects on sexual function and fertility as effects on onset of puberty, sexual behaviour, parturition, or premature reproductive senescence.

In the absence of relevant information on possible effects on sexual function and fertility in humans and experimental animals the classification criteria are not applicable and classification for effects on sexual function and fertility cannot be assessed.

10.10.4 Adverse effects on development

Table 9: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Prenatal Developmental Toxicity Study According to OECD TG 414 Deviations: no GLP: yes Female Crl:WI(Han) (outbred, SPF quality) rats (22 animals/dose group) RL1 (according to registration dossier and the authors of this document)	9-Octadecenoic acid (Z)-, sulfonated, potassium salts (Purity/Composition UVCB: 100%) 0, 100, 300, 1000 mg /kg bw/d) from GD 6 to GD 20 GD 21: females underwent caesarean section, ½ of the foetuses were examined for visceral anomalies and ½ for skeletal anomalies. Application via gavage Vehicle: water	Dams: NOAEL: 300 mg/kg bw/d (high dose: mortality in 1/22 dams (sacrifice in extremis on GD 14: piloerection, hunched posture, rales and diarrhea from GD11 onwards; marked weight loss, yellow discoloration of urine and emaciation, tan colored pasty content in the caecum at macroscopy); reduced food consumption, reduced body weight (ca. -8% on Day 21) and body weight gain (6.4% vs. 11.3% body weight gain (corrected for gravid uterine weight) from Day 6-21 in high dose vs. control females, respectively) in surviving females of high dose group but no macroscopic abnormalities) Offspring: NOAEL: 100 mg /kg bw/d (increased number of foetuses with bent limb bones in mid and high dose group; three foetuses of the high dose group showed bent pelvic girdle bones (iliaca); a rarely observed malformation not seen previously in historical controls; bent ribs were seen in all foetuses with bent limb bones). External examination of the high dose foetuses revealed malrotated limbs in one foetus. This malformation correlated to the skeletal malformation of bent limb bones in high dose foetuses, which was observed in all foetuses that were skeletally examined (i.e. 50% of foetuses), including the foetus with the	NN (2017b)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
		malrotated limbs. Other malformations as cleft palate and anasarca occurred only in single foetuses and are not considered treatment related. The mean litter proportions for the skeletal variation of bent ribs were 7.7%, 12.2%, 60.7% and 99.3% per litter in control, low, mid and high dose animals, respectively (statistically significant in mid and high dose). Mean litter proportions of slight to moderate malaligned sternebrae were 22.4%, 20.2%, 21.7%, 40.0% in control, low, mid and high dose animals, respectively, i.e. statistically significant difference to control only in high dose group. The litter incidences of 14th full ribs and caudal shift of pelvic girdle showed a dose-related increase in mid and high dose group. Mean litter proportions of these respective variations were 11.3%, 3.3%, 16.4%, 21.2% and 6.1%, 3.8%, 12.0%, 18.9% per litter in control, low, mid and high dose groups, respectively. Both the mid and high dose group incidences of these two related findings were nearby or above their historical control maximum value (13.1% for 14th full ribs and 12.8% for caudal shift of pelvic girdle) and considered to be related to treatment. Visceral variations were observed in 14.0%, 10.2%, 10.0% and 8.2% of foetuses per litter in control, low, mid and high dose groups, respectively. The individual variations all occurred in the absence of a dose-related trend, infrequently and/or at frequencies that were within the range of available historical control data. Significantly reduced foetal body weights in the high dose (5.4, 5.5, 5.3, 4.7 g in control, low, mid and high dose males, respectively; 5.2, 5.2, 5.1, 4.4 g in control, low, mid and high dose females, respectively).	
Reproduction/developmental toxicity screening study According to OECD TG 422 Deviations: not mentioned GLP: yes Wistar Han rats (SPF-bred; 10 animals/sex/dose group) RL1 (according to the Dossier Submitter)	Octadecanoic acid, sulfo-, potassium salt (CAS 67968-63-2) * (Purity/Composition UVCB: 51.92%) 0, 96, 289 and 963 mg/kg bw/d of the test item corresponding to 0, 50, 150, and 500 mg/kg bw/d octadecanoic acid, sulfo-, potassium salt	NOAEL) for reproductive performance and fertility was 500 mg/kg bw/d in male and female Wistar rats. NOAEL for developmental toxicity in the F1 progeny was 150 mg/kg bw/d. Adverse effect on development were observed at 963 mg/kg bw/d (corresponding to 500 mg/kg bw/d octadecanoic acid, sulfo-, potassium salt). <u>F0 parental animals</u> *Clinical Examinations* • Decreased food consumption during premating (up to -9%), gestation (up to -20%), and lactation (not statistically significant -10%) in females • Decreased body weight during lactation (up to -10%) • Piloerection shown by 3 females during lactation	NN, 2015c

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
	Oral, via gavage Vehicle: water Duration of treatment covered a 2 week premating period and mating in both sexes (mating pairs were from the same dose group) as well as entire gestation and 4 days of lactation period in females up to one day prior to the day of schedule sacrifice of the animals	<u>F1 pups</u> *Clinical Examinations/ Gross Findings* • Decreased live birth index (64.2%) • Increase number of stillborn pups (35.8%) leading to 88.9% dams with stillborn pups • Increased perinatal loss (36.7%) • Decreased viability index (73%) • Increased number of pups found dead (4 pups) • Increased number of pups missing (cannibalized, 13 pups) • Decreased pup weights of both sexes at postnatal day 1 (-23.0%) • Decreased pup weight change between postnatal day 1 and 4 in pups of both sexes (-28.5%) were based on a decreased pup weight change in male pups of -25.4%, and in female pups of -24.1% (not statistically significant) • Increased number of runts (10 males and 12 females) • Increased number of pups with *post mortem* autolyzes • Increased number of pups with discolored liver • Increased number of pups with empty stomach See section 10.10.2 for adverse effects on fertility/sexual function.	

** The substance EC -, and hence the test material, was originally identified with EC 267-966-5, i.e. 9 (or 10)-sulphooctadecanoic acid, potassium salt. Based on the analytical data, the substance shall better be described as: "Reaction product of oleic acid with sulfur trioxide and potassium hydroxide". Consequently, a new substance identity has been requested by the registrant. Based on this request, ECHA has assigned the new List number 701-179-4 to the substance "Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts". As the manufacturing process of the substance has not changed, the composition of the substance/test material is the same as it was prior the change of the identifiers, and therefore the tests are still relevant for the substance covered by the registration with list entry 701-179-4.*

There are no human data on adverse effects on development or other studies relevant for developmental toxicity available.

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

There is only one developmental toxicity study with 9-octadecenoic acid (Z)-, sulfonated, potassium salts available (NN, 2017b). This OECD TG 414 study (according to GLP) was performed in rats, which received 0, 100, 300 and 1000 mg/kg bw/d once daily by oral gavage on GD 6 to 20. In pregnant females at 1000 mg/kg bw/d, reduced body weight and food consumption were observed shortly before scheduled caesarean

section on Day 21 post-coitum. Body weight gain was decreased in females at 1000 mg/kg over Days 18-21 post-coitum resulting in lower mean body weights in these females on Day 21, reaching statistical significance for both parameters in comparison with controls (ca. -8% reduced body weight on Day 21; 6.4% vs. 11.3% body weight gain (corrected for gravid uterine weight) from Day 6-21 in high dose vs. control females, respectively). One female of the high dose group was sacrificed on Day 14 post-coitum because of a bad health status which was possible related to treatment. No maternal toxicity was observed in the 300 and 100 mg/kg bw/d groups. The maternal NOAEL was 300 mg/kg bw/d.

Foetuses of both sexes of the high dose group revealed reduced body weights. Foetal body weight was not affected in the low and mid dose group (5.4, 5.5, 5.3, 4.7 g in control, low, mid and high dose males, respectively; 5.2, 5.2, 5.1, 4.4 g in control, low, mid and high dose females, respectively).

External examination of the high dose foetuses revealed malrotated limbs in one foetus. This malformation correlated to the skeletal malformation of bent limb bones in high dose foetuses. Bent limb bones were also observed in all other foetuses of the high dose group, that were skeletally examined (i.e. one half of the total number of foetuses), including the foetus with the malrotated limbs. A statistical significant increase in bent limb bones was also observed in the mid dose whereas no such malformations were observed in any of the foetuses of the control and low dose group. Other malformations as cleft palate and anasarca occurred only in single foetuses and are not considered treatment related. The mean litter proportions for the skeletal variation of bent ribs were 7.7%, 12.2%, 60.7% and 99.3% per litter in control, low, mid and high dose animals, respectively (statistically significant in mid and high dose). Mean litter proportions of slight to moderate malaligned sternebrae were 22.4%, 20.2%, 21.7%, 40.0% in control, low, mid and high dose animals, respectively; changes compared to controls and reached statistical significance only in the high dose group. Litter incidences of 14th full ribs and caudal shift of pelvic girdle showed a dose-related increase in mid and high dose groups. Incidences for these two findings in the mid and high dose groups were nearby or above their historical control maximum value (13.1% for 14th full ribs and 12.8% for caudal shift of pelvic girdle). No treatment related effects on visceral variations were observed. Based on retardation of male and female foetal body weight at 1000 mg/kg bw/d and dose related increases in the incidence of several skeletal malformations and variations at 300 and 1000 mg/kg bw/d the developmental NOAEL of this study is 100 mg/kg bw/d.

Results of Reproduction/developmental toxicity screening study according OECD 422 in rats with Octadecanoic acid, sulfo-, potassium salt (CAS 67968-63-2) (NN, 2015c) indicate adverse effects on the combined occurrence of clinical signs and effects on food consumption as well as on body weight at a dose of 500 mg/kg bw/day. Fertility indices for male and female animals were not impaired by test-substance administration up to the highest dose tested 500 mg/kg bw/d. The live birth indices of pups at a dose of 50 and 150 mg/kg bw/d were not influenced. However, the test compound caused an increase of stillborn pups (36%) at a dose of 500 mg/kg bw/d. The viability index as indicator for pup mortality was not impaired by test-substance administration at a dose of 50 and 150 mg/kg bw/d. At a dose of 500 mg/kg bw/d an increased number of pups found dead and being cannibalized result in a significant decreased viability index of 73% in comparison to control (98%). The body weights of pups at a dose of 50 and 150 mg/kg bw/d were comparable with control, but at a dose of 500 mg/kg bw/d a decreased body weight of pups were observed from postnatal day 1 to 4. Concerning clinical pathology no treatment-related, adverse effects were observed up to a dose of the test item of 500 mg/kg bw/d. Regarding pathology, all findings occurred either individually or were biologically equally distributed over control and treatment groups. They were considered to be incidental or spontaneous in origin and without any relation to treatment. See also section 10.10.2 for a description of the adverse effects on sexual function and fertility. The NOAEL for adverse effects on development is 150 mg/kg bw/d.

10.10.6 Comparison with the CLP criteria

There are no epidemiological data to support classification of 9-octadecenoic acid (Z)-, sulfonated, potassium salts in Category 1A.

Results from a single developmental toxicity study in rats with 9-octadecenoic acid (Z)-, sulfonated, potassium salt according to OECD TG 414 and GLP revealed severe effects on offspring (NN, 2017b). Foetuses showed bent limb bones and bent pelvic girdle bones (iliaca), which is a rarely observed malformation in historical controls. Additional variations (bent ribs) were observed after treatment. Other single malformations like cleft palate and anasarca were not regarded as treatment related. Treatment related developmental effects were observed in high dose animals as well as in mid dose animals. Maternal animals of the high dose group showed reduced body weight and body weight gain at the end of the treatment period (Day 21), an effect not observed in mid dose females. Since developmental effects already occurred in mid dose foetuses, i.e. in a dose group without maternal toxicity, and in the absence of unequivocal evidence that the developmental effects in the high dose group foetuses are secondary to maternal toxicity, it is concluded that the developmental effects are direct effects and not secondary to maternal toxicity.

In a reproduction/development toxicity screening study in rats with Octadecanoic acid, sulfo-, potassium salt (CAS 67968-63-2) (NN, 2015c) according to OECD TG 422 and GLP revealed no effects on fertility indices for male and female animals by test-substance administration up to the highest dose tested 500 mg/kg bw/d. The live birth indices of pups at a dose of 50 and 150 mg/kg bw/d were not influenced. At a dose of 500 mg/kg bw/d an increased number of pups found dead and being cannibalized result in a significant decreased viability index of 73% in comparison to control (98%). With regards to the effects observed, The NOAEL for developmental toxicity in the F1 progeny was 150 mg/kg bw/d.

There is no information on a possible mode of action underlying the observed effects. In the absence of any information on a species specific mode of action the effects are regarded as relevant for humans.

Although there is only information from two developmental toxicity studies, due to the severity of effects and assuming relevance of the underlying mode of action for humans in the absence of any other information, the observed adverse effects (bent limb bones, bent, pelvic girdle bones, bent ribs, malaligned sternebrae, 14th full ribs, decreased viability index) are considered clear evidence of an adverse effect on development. Therefore, classification for developmental toxicity in Category 1B is proposed.

10.10.7 Adverse effects on or via lactation

There are neither animal studies nor human data on effects on or via lactation or other studies relevant for effects on or via lactation available.

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

There are no human or experimental data available with respect to effects via lactation.

10.10.9 Comparison with the CLP criteria

In the absence of any data on possible effects on or via lactation this endpoint cannot be assessed.

10.10.10 Conclusion on classification and labelling for reproductive toxicity

Available information from two repeated dose toxicity studies which did not indicate any adverse effects on reproductive organs (weight and histopathology), oestrous cycle and spermatogenesis are not regarded as sufficient for a comprehensive evaluation of effects on sexual function and fertility. Additionally, a reproduction/developmental toxicity study indicate no impairment in the fertility indices for male and female animals. In the absence of human data and relevant information from experimental studies on possible effects on certain parameters influencing sexual function and fertility this endpoint cannot be assessed.

Therefore, no classification for effects on sexual function and fertility is proposed for 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8)/ Reaction products of fatty acid,

C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (EC -; CAS -) / 9(or 10)-sulphooctadecanoic acid, potassium salt (EC 267-966-5; CAS 67968-63-2).

Based on the relevant and severe effects in foetuses (bent limb bones, bent, pelvic girdle bones, bent ribs, malaligned sternebrae, 14th full ribs, decreased viability index) in two reproduction/developmental toxicity studies observed after gestational exposure in the absence of maternal toxicity classification for developmental toxicity in Category 1B is proposed.

Therefore, classification for effects on development (Repr. 1B, H360D) is warranted for 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8)/ Reaction products of fatty acid, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (EC -; CAS -) / 9(or 10)-sulphooctadecanoic acid, potassium salt (EC 267-966-5; CAS 67968-63-2).

In the absence of relevant and reliable studies no classification is proposed for effects of 9-octadecenoic acid (Z)-, sulfonated, potassium salt on or via lactation due to a lack of data.

Therefore, no classification for effects on or via lactation is warranted for 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (EC 271-843-1; CAS 68609-93-8)/ Reaction products of fatty acid, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (EC -; CAS -) / 9(or 10)-sulphooctadecanoic acid, potassium salt (EC 267-966-5; CAS 67968-63-2).

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**.

10.11 Specific target organ toxicity-single exposure

Evaluation not performed for this substance.

10.12 Specific target organ toxicity-repeated exposure

Evaluation not performed for this substance. However, an evaluation of the 90-day repeated dose toxicity studies (see section 5.12 of Annex I for a detailed description of these studies) is included in the overall assessment of the endpoints carcinogenicity and reproductive toxicity in sections 10.9 and 10.10, respectively.

10.13 Aspiration hazard

Evaluation not performed for this substance.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Evaluation not performed for this substance.

12 EVALUATION OF ADDITIONAL HAZARDS

Evaluation not performed for this substance.

13 ADDITIONAL LABELLING

Not applicable for this evaluation.

14 ANNEXES

Please see separate documents for:

- Non-confidential Annex I
- Confidential Annex IA (with confidential information concerning the manufacturing process and substance identity of 9-Octadecenoic acid (Z)-, sulfonated, potassium salts (CAS 68609-93-8; EC 271-843-1))
- Confidential Annex 1B (with confidential information concerning the manufacturing process and substance identity of Reaction products of fatty acids, C18 (unsaturated) alkyl with sulfur trioxide, potassium salts (CAS -, EC -))

15 REFERENCES

See confidential Annexes for a detailed list of study reports.

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