CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

sodium 3-(allyloxy)-2-hydroxypropanesulphonate

EC Number: 258-004-5

CAS Number: 52556-42-0

Index Number: NA

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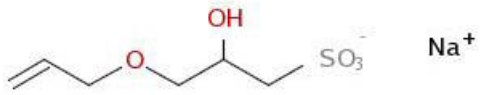
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Sodium 3-(allyloxy)-2-hydroxypropanesulphonate
Other names (usual name, trade name, abbreviation)	
ISO common name (if available and appropriate)	*none*
EC number (if available and appropriate)	258-004-5
EC name (if available and appropriate)	sodium 3-(allyloxy)-2-hydroxypropanesulphonate
CAS number (if available)	52556-42-0
Other identity code (if available)	/
Molecular formula	C6H12O5S.Na
Structural formula	
SMILES notation (if available)	/
Molecular weight or molecular weight range	218.203
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	*[If the substance structure demonstrates stereo-isomerism the ratio of these stereo-isomers should be specified. If the ratio is unknown it should be stated as such. For optical isomers a measure of optical activity (specific rotation) should be specified.]*
Description of the manufacturing process and identity of the source (for UVCB substances only)	*[In the case of UVCB substance a full manufacturing process description should be provided including the identity of the source or starting materials and their ratio. Any relevant process parameters should also be specified.]*
Degree of purity (%) (if relevant for the entry in Annex VI)	> 80% w/w

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**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)**

Constituent (Name and numerical identifier)	**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)**
Sodium 3-(allyloxy)-2-hydroxypropanesulphonate	>80 % (w/w)	No harmonised classification	Skin Irrit. 2 – H315 Eye. Dam. 1 – H318 Repro. 2 – H361 STOT SE 3 – H335

Impurities (non-confidential information) if relevant for the classification of the substance

Confidential information

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 3:

	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	No harmonised classification										
Dossier submitters proposal	tbd	Sodium 3-(allyloxy)-2-hydroxypropanesulphonate	258-004-5	52556-42-0	Eye Dam. 1 Repr. 1B	H318 H360F	GHS08 Danger	H318 H360F			
Resulting Annex VI entry if agreed by RAC and COM	tbd	Sodium 3-(allyloxy)-2-hydroxypropanesulphonate	258-004-5	52556-42-0	Eye Dam. 1 Repr. 1B	H318 H360F	GHS08 Danger	H318 H360F			

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	data conclusive but not sufficient for classification	No
Flammable gases (including chemically unstable gases)	hazard class not applicable	No
Oxidising gases	hazard class not applicable	No
Gases under pressure	hazard class not applicable	No
Flammable liquids	hazard class not applicable	No
Flammable solids	data conclusive but not sufficient for classification	No
Self-reactive substances	data conclusive but not sufficient for classification	No
Pyrophoric liquids	hazard class not applicable	No
Pyrophoric solids	data conclusive but not sufficient for classification	No
Self-heating substances	data conclusive but not sufficient for classification	No
Substances which in contact with water emit flammable gases	data conclusive but not sufficient for classification	No
Oxidising liquids	hazard class not applicable	No
Oxidising solids	data conclusive but not sufficient for classification	No
Organic peroxides	hazard class not applicable	No
Corrosive to metals	Data lacking	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	**harmonised classification proposed: Eye Dam. 1 – H318**	Yes
Respiratory sensitisation	hazard class not assessed in this dossier	No
Skin sensitisation	hazard class not assessed in this dossier	No
Germ cell mutagenicity	hazard class not assessed in this dossier	No
Carcinogenicity	hazard class not assessed in this dossier	No
Reproductive toxicity	**harmonised classification proposed: Repr. 1B – H360F**	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 for this substance.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Concerning classification for toxicity on reproduction:

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

Concerning classification for Eye damage:

Justification that action is needed at Community level is required.

There are differences in self-classification for this endpoint according to ECHA website (25 June 2020):

- Eye Dam 1 – H318: 6/53 self-classifications
- Eye Irrit. 2 – H315: 38/53 self-classifications
- Not classified for this endpoint: 9/53 self-classifications

5 IDENTIFIED USES

The substance is manufactured and/or imported in the European Economic area in 1000 – 10 000 tonnes per year. It is used in formulation or re-packing, at industrial sites and in manufacturing (ECHA, 2020). According to US-EPA, the substance is included in the following product or use categorisations: “manufacturing, chemical”, “consumer use”, “manufacturing, plastics”, “manufacturing, raw material”, “paint”, surface treatment”. Industrials uses consists in corrosion inhibitors and anti-scaling agent, intermediate and solid separation agent. Consumer uses consist in adhesives and sealants, paints and coatings, resin products and water treatment product (EPA dashboard, 2020; Pubchem, 2020).

6 DATA SOURCES

Data are issued from the registration dossier (public ECHA website, IUCLID ECHA and CSR) and from literature research (June 2020). Lead registrant was contacted in July 2020 in order to obtain the study reports for the endpoints concerned. Study reports for the BCOP study (Anonymous, 2012a), the 28-day study (Anonymous, 2007), the 90-day study (Anonymous, 2016b), the OECD 414 study (anonymous, 2017a) and the OECD 421 study (without the individual data) (Anonymous, 2013) were obtained between February and March 2021.

7 PHYSICOCHEMICAL PROPERTIES

Table 5: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	solid at 20°C and 101.3 kPa	ECHA (2020)	

Property	Value	Reference	Comment (e.g. measured or estimated)
Melting/freezing point	No melting point or melting range of the test item sodium	ECHA (2020)	The substance decomposes (177°C) before melting
Boiling point	The key value cannot be determined	ECHA (2020)	The substance decomposes (177°C) before boiling
Relative density	1.5 at 20°C	ECHA (2020)	OECD 109 guideline study
Vapour pressure	0.0002 Pa at 20°C	ECHA (2020)	EU A.4 using the effusion method (weight loss).
Surface tension	71.31 mN/m at 20°C at 1 mg/L	ECHA (2020)	OECD 115 guideline study. Plate method
Water solubility	781.1g/L at 20°C	ECHA (2020)	OECD Guideline 105 Measured with HPLC-UV
Partition coefficient n-octanol/water	Log Kow (Log Pow): -1.51 at 25°C at pH of 0	ECHA (2020)	OECD 107 guideline study. Shake flask at 20°C and then quantification by ion chromatography.
Flash point	Not relevant	ECHA (2020)	Substance is a solid
Flammability	non flammable	ECHA (2020)	OECD 107 guideline study
Explosive properties	no chemical groups associated with explosive properties present in the molecule	ECHA (2020)	statement
Self-ignition temperature	The study has not to be conducted, for solids, if the substance has a melting point < 160°C. The test item decomposed at 177 °C before melting. Therefore it could be expected that sodium 3-(alloxy)-2-hydroxypropane-1-sulfonate is not self igniting and a testing is not necessary.	ECHA (2020)	statement
Oxidising properties	Based on structural considerations for sodium 3-(alloxy)-2-hydroxypropane-1-sulfonate, oxidizing properties are expected to be highly unlikely based on the chemical structure.	ECHA (2020)	statement
Granulometry	the study does not need to be conducted because the substance is marketed or used in a non solid or granular form: substance is usually used and sold in aqueous formulation	ECHA (2020)	statement
Stability in organic solvents and identity of relevant degradation products	No data	ECHA (2020)	Not critical
Dissociation constant	pKa at 20°C: 11.004	ECHA	OECD 112.

Property	Value	Reference	Comment (e.g. measured or estimated)
		(2020)	
Viscosity	Not relevant	ECHA (2020)	Substance is a solid

8 EVALUATION OF PHYSICAL HAZARDS

Not performed for this substance

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

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

There is no experimental toxicokinetics study available for the substance.

Information can be estimated from structure and physicochemical properties. The substance contains sulphonate group which is potentially ionisable. The molecular weight is 218.21 g/mol and the substance is soluble (moderate to high) in water (781.1 g/L). These properties are favourable for absorption. In contrast, the log Pow is not very favourable for absorption (-1.51). The substance has a low volatility with a vapour pressure of about $2x10^{-4}$ Pa.

According to the DK QSAR Toolbox (June 2020), the absorption from the gastrointestinal tract for 1 mg and 1000 mg doses is estimated at 5%. The skin absorption is estimated to be 0.00382 mg/cm^2/event. The log brain/blood partition coefficient is -1.3463. It is not estimated to be a substrate of CYP2C9 and 2D6.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity

Not assessed in this report.

10.2 Skin corrosion/irritation

Not assessed in this report.

10.3 Serious eye damage/eye irritation

Table 6: Summary table of other studies relevant for serious eye damage/eye irritation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
BCOP test OECD 437 GLP	Sodium 3-(allyloxy)-2-hydroxypropanesulphonate (HAPS) Aqueous solution (see confidential annex for composition)	Undiluted test item incubated on the cornea for 10 minutes Negative and positive controls included.	IVIS = 150.293	Anonymous (2012a) Disseminated registration dossier (2020)

10.3.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

A Bovine Corneal Opacity and Permeability (BCOP) Test (OECD TG 437) is available with Sodium 3-(allyloxy)-2-hydroxypropanesulphonate (HAPS) (Anonymous, 2012a). Aqueous solution of HAPS, was incubated on the cornea for 10 minutes at 32±1 °C. According to study report, since the test item is a non-surfactant liquid, it was tested directly, without dilution or preparation of a solution. After removal of the test item and two hours post-incubation, opacity and permeability values were measured. Three replicates were included for each treatment groups: negative control (physiological sodium chloride solution: 0.9% NaCl), positive control (sodium hydroxide, 10% NaOH dissolved in 0.9% sodium chloride solution) and test item.

The *in vitro* irritancy score (IVIS) (defined in the study report as opacity difference + (15 x corrected OD_{490} value)) was calculated to be 150.293. The negative and positive controls were considered valid.

Other data regarding irritative potential of sodium 3-(allyloxy)-2-hydroxypropanesulphonate are available:

The substance (applied as powder in water) was tested in an *in vitro* skin corrosion assay on human skin model Epiderm™ (OECD TG 431: In vitro skin corrosion: reconstructed human epidermis (RhE) test method). Based on the absorbance values reported, the substance is not considered corrosive to skin in this *in vitro* assay (Anonymous, 2012b).

The substance (applied as powder wetted with DPBS-buffer) was tested in an *in vitro* skin irritation assay on human skin model Epiderm™ (OECD TG 439: In vitro skin irritation: reconstructed human epidermis (RhE) test method). Based on tissue viability reported, the substance is not considered irritant to skin in this *in vitro* assay (Anonymous, 2012c).

In an *in vivo* acute dermal toxicity study (OECD TG 402), erythema was noted from 24 hours post-dose in all tested rats (semi-occlusive; substance applied as aqueous solution) and was fully reversible within 7 days. Scabs were noted in all animals from 48 hours post-dose and remained on day 14 in all animals. (Anonymous, 2012d).

10.3.2 Comparison with the CLP criteria

According to OECD TG 437, a substance needs to be classified as Eye Damage category 1 if the IVIS is ≥ 55. Since the IVIS of sodium 3-(allyloxy)-2-hydroxypropanesulphonate is 150.293, the substance fulfils criteria for classification as Eye Dam. 1 according to CLP regulation.

10.3.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Based on the BCOP test, Sodium 3-(allyloxy)-2-hydroxypropanesulphonate fulfils criteria for Eye. Dam 1 – H318 according to CLP regulation.

10.4 Respiratory sensitisation

Not assessed in this report.

10.5 Skin sensitisation

Not assessed in this report.

10.6 Germ cell mutagenicity

Not assessed in this report.

10.7 Carcinogenicity

Not assessed in this report.

10.8 Reproductive toxicity

10.8.1 Adverse effects on sexual function and fertility

Table 7: 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
Reproduction/ Developmental Toxicity Screening Test OECD TG 421 GLP Male and female Wistar rats (12/sex/dose)	Aqueous solution with a concentration of 35.2% HAPS (see confidential annex for further information on composition) Dose levels: 0, 62.5, 250 and 1000 mg/kg bw/day by gavage. Dosing referred to the effective content of the active ingredient (HAPS). Due to several fatalities in the high dose group, satellite groups were included in the study (at 0 or 1000 mg/kg bw/day) Males were dosed daily for 42 to 57 days (two weeks of dosing prior to mating and continued throughout the mating period until approximately four weeks post-mating). Females were dosed at least 47 days to 55 days (two weeks prior to mating, covering at least two complete oestrous cycles, the variable time to conception, the duration of pregnancy and at least four days after delivery, up to and including the day before scheduled termination of the in-life phase)	LOAEL (P0 and F1) = 62.5 mg/kg bw/day (nominal) P0: - clinical signs (mild discomfort) in males and mortality at 1000 mg/kg bw/day - minimal to slight ovarian hypertrophy/ hyperplasia at 1000 mg/kg bw/day characterised by the presence of many, partly cystic corpora lutea, several tertiary follicles and increase in the number of interstitial cells[1] Reproductive performance: 11/12, 5/12, 0/12, 0/12, 0/12 animals achieved pregnancies (control, low, medium, high and satellite groups, respectively) F1 generation: Offspring was present only in the low dose group and in the control group.	Anonymous, 2013 Key study Klimisch score 2

Table 8: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
28-day study in accordance with the "28-day repeated-dose	Aqueous solution of HAPS (see confidential annex for composition)	male and female Crj:CD(SD) rats (5/sex/dose) 0, 25, 150 or 1000 mg/kg bw/day for	Uterine cyst in the muscle layer in one animal of the 25 mg/kg bw/day group. Other effects mainly reported in the 1000 mg/kg bw/day group: clinical signs (loose faeces and salivation), decreased amount of ultromotivity and hyperplasia of the	Anonymous , 2007

[1] The ovaries were only examined at the highest tested dose.

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
toxicity study using mammals" (Japan) GLP		28 days. Gavage, daily	squamous epithelium at the edge of the anterior stomach. The NOAEL = 150 mg/kg bw/day.	
14-day range finding study GLP	Aqueous solution of HAPS (no further information on disseminated dossier)	male and female Wistar rats (5/sex/dose) 0, 100, 300 or 1000 mg/kg bw/day for 14 days. Gavage, daily	No treatment-related effect identified. Regarding reproductive organs: slight or moderate hydrometra was noted for one female animal of each group. No histopathology performed.	Anonymous, 2016a
90-day toxicity study OECD TG 408; GLP	Aqueous solution of HAPS (see confidential annex for composition)	male and female Wistar rats (10/sex/dose) 0, 100, 300 or 1000 mg/kg bw/day for 90 days daily by gavage	No adverse effect reported. Regarding reproductive organs: slight or moderate hydrometra in the uterus in some female animals in all groups, with highest incidence at 1000 mg/kg bw/day. In one male animal at 300 mg/kg bw/day, larger than normal testis (left side). It consisted in focal granulomatous inflammation. Dilatation of the uterine horns in control and high dose group. NOAEL = 1000 mg/kg bw/day.	Anonymous, 2016b

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

In a Reproduction/Developmental Toxicity Screening Test according to OECD TG 421, male and female Wistar rats were gavaged with aqueous solution of HAPS at 62.5, 250 and 1000 mg/kg body weight/day (Anonymous, 2013). The test item has been delivered as a 35.2% aqueous solution and a relative density of 1.17 g/cm^3. Dosing referred to the effective content of the active ingredient (HAPS). The doses were chosen based on a range-finding study where the test item was administered in escalating doses up to 1000 mg/kg bw/day over a time period of 22 days without acute toxic effects in the test animals. Males were dosed over a time period of 42 to 57 days (two weeks of dosing prior to mating and continued throughout the mating period until approximately four weeks post-mating) and females were dosed at least 47 days (14 days pre-mating, up to 14 days until mating, an average of 21 days of gestation, and between 8 and 14 days of lactation). Due to several fatalities in the high dose group, a satellite group was added with 24 animals (12 males/ 12 females) treated identically to the high dose group (1000 mg/kg body weight) and supplementary included into the study on day 32. These animals were dosed for either 42 (males) or 47 (females) days. Further 24 animals (12 male/ 12 female) served as vehicle control.

Mild discomfort throughout the whole application period was observed for the male animals treated with the high dose of the test item (wiping of nose and mouth through the cage bedding, salivation after application, bleeding of mucous membranes at nose and mouth, respiratory sounds). Mortality (3 males and 5 females) occurred within the animals treated with the high dose. Death could be a result of reflux after gavage dosing leading to an accidental aspiration of dose formulation. Due to the high incidence and the exclusive occurrence within the animals treated with the high dose, a test item related effect could not be excluded. However, only one female died in the satellite group also exposed to 1000 mg/kg bw/day, suggesting that the observed deaths were not treatment-related. There were no treatment-related effects on body weight and food consumption during pre-mating phase. During post-mating, the body weight of the female animals treated with the high and the medium doses slightly increased between days 0 and 7 and decreased between days 7 and 20 of gestation, indicating that pregnancies of these animals were aborted between days 7 and 14. An increased water intake of all animals (male and female) treated at 1000 mg/kg bw/day could be observed throughout the whole in-life phase. There was no treatment-related changes in absolute and relative weights for testes and epididymis. A statistically significant increase of the mean weight of ovaries and uterus was detected for all test item dose groups compared to the vehicle control group. These differences result with high probability from the physiological changes the organs passed during pregnancy. No test item related prevalent findings were observed during gross necropsy, neither for male nor for female animals. The ovaries, testes, and epididymis from a total of 51 adult rats (high dose: 10 males / 6 females; satellite group: 11 females; vehicle control: 12 males / 12 females) and all other organs showing macroscopic lesions were submitted to histopathological examination. A minimal to slight ovarian hypertrophy/hyperplasia characterised by the presence of many, partly cystic, corpora lutea, several tertiary follicles and an increase in the number of interstitial cells was noted in the treated females.

The tested substance prevented or significantly reduced the achievement of pregnancy in all tested dose levels. Offspring was only present in the control group (11/12 females achieved pregnancy) and in the low dose group (5/12 females achieved pregnancy). At a dosage of 62.5 mg/kg bw/day, 5 of 12 females were able to achieve pregnancy but only 2 of these animals had a normal litter size and development. One animal gave birth to 5 pups. One animal gave birth to 1 pup (runt) that could not be found on day 4 post-partum. One animal gave birth to at least 2 pups, but one was found dead the next day. There was no pregnancy at 250 and 1000 mg/kg bw/day (including satellite group). Nonetheless, based on the results of the study, these effects cannot be associated with general toxicity. According to the study report, the presence of corpora lutea about 24 days after first pairing in the satellite group indicated that an implantation of the zygote took place, but embryonic development did not occur or was aborted during the first days of gestation. It was suggested that the absence of corpora lutea about 24 days after second pairing (females showing no evidence of copulation were re-mated for a second mating phase, during which dosing was continued) in the medium and high dose groups then indicated that, with prolonged dosing the implantation of the zygote or the ovarian

maturation were impaired by the test item. Based on the results of the study, a specific physiological cause of the toxic effect could not be identified. Potential effects on the spermatogenesis may not have had a sufficient time to be observed (such as reduced sperm counts affecting the fertility), as chemical exposure did not cover a complete cycle of spermatogenesis in male test animals (about 53 days). Therefore, and due to the lack of pregnancies in the test item treated female animals, an effect of the test item on the spermatogenesis could not be excluded.

Based on this study, the LOAEL for parental toxicity was set by the registrants at the lowest dose of 62.5 mg/kg (lack of achieving pregnancy; target organs: ovary, uterus; treatment-related). No NOAEL can be identified. According to the registrants, the reproductive LOAEL is set at 62.5 mg/kg bw/day (nominal) (reproductive effects in the absence of other toxic effects, treatment related). No NOAEL can be identified. For F1, the LOAEL is also 62.5 mg/kg bw/day (nominal) (male/female; viability). No NOAEL can be identified.

Other studies, that can bring additional information regarding reproductive toxicity potential of Sodium 3-(allyloxy)-2-hydroxypropanesulphonate, are available:

A short-term repeated dose toxicity study was performed according to the “28-day repeated-dose toxicity study using mammals” specified in the “Guideline for Toxicity Testings of New Chemical Substances (Japan) (Anonymous, 2007). In this study, male and female Crj:CD(SD) rats (5/sex/dose) were exposed daily by gavage to aqueous solution of HAPS at dose levels of 0, 25, 150 or 1000 mg/kg bw/day for 28 days. Recovery groups were provided in the 1000 mg/kg bw/day group and vehicle control group. Regarding reproductive organs: testes, epididymides and ovaries were weighted, and histopathology included examination of testes, epididymides, prostate, seminal vesicles, ovaries, uterus and vagina. Uterine cyst in the muscle layer in one animal of the 25 mg/kg bw/day group was the only reported effect in reproductive organs. The other effects were mainly reported in the 1000 mg/kg bw/day groups and included clinical signs in both sexes (loose faeces and salivation), decreased amount of ultromotivity at 30 to 40 minutes in males and hyperplasia of the squamous epithelium at the edge of the anterior stomach in both sexes. These effects were not found in the recovery group. The NOAEL was set by the registrants at 150 mg/kg bw/day.

A 14-day study was performed in male and female Wistar rats (5/sex/dose) to define the dose to be tested in a subsequent subchronic toxicity test (Anonymous, 2016a). Animals were exposed daily by gavage to aqueous solution of HAPS at dose levels of 0, 100, 300 or 1000 mg/kg bw/day. The substance was well tolerated by animals, with no treatment-related effect identified. Regarding reproductive organs: slight or moderate hydrometra was noted for some female animal in the control (1/5), at 100 mg/kg bw/day (1/5) and at 1000 mg/kg bw/day (1/5). No histopathology was performed.

A subchronic toxicity study was performed according to OECD TG 408 (Anonymous, 2016b). In this study, male and female Wistar rats (10/sex/dose) were exposed daily by gavage to aqueous solution of HAPS at dose levels of 0, 100, 300 or 1000 mg/kg bw/day for 90 days (doses determined on the basis of HAPS content in the product). No mortality occurred during the course of the treatment period. There was no adverse sign reported in the examined parameters (clinical observation, body weight, body weight gain, food consumption, ophthalmological, haematological and biochemistry examinations, gross pathology and histopathology). Regarding reproductive organs, testes, epididymides, uterus with fallopian tubes and ovaries were weighted. Full histological examinations were performed on preserved organs and tissues of the animals from both the control and high dose groups. Additionally, the testes and epididymides of one animal at 300 mg/kg bw/day were also processed histologically based on the necropsy observation in one side testis. The following effects were reported on reproductive organs. Slight or moderate hydrometra in the uterus was observed in some female animals in all groups, i.e. in the control (2/10), at 100 mg/kg bw/day (1/10), at 300 mg/kg bw/day (2/10) and at 1000 mg/kg bw/day (6/10) at the termination of the treatment period. Although the incidence of hydrometra was the highest in 1000 mg/kg bw/day, in the lack of pathological or inflammatory lesions, it was not considered to be toxicologically significant by the laboratory. In one male animal at 300 mg/kg bw/day, larger than normal testis was seen on the left side. It consisted in focal granulomatous inflammation. Dilatation of uterine horns was observed in 2/10 controls and 6/10 animals from the high dose group. Based on the study report, no effects were attributed to the treatment or judged as biologically significant. The NOAEL was set by the registrants at 1000 mg/kg bw/day.

In conclusion, the repeated-dose toxicity studies (from 14 days to 90 days of exposure) do not identify reproductive organs as a target of HAPS toxicity. In contrast, the well-conducted OECD TG 421 study reports clear fertility effects since the tested substance prevented or significantly reduced the achievement of pregnancy in all tested dose levels, in the absence of general toxicity.

10.8.3 Comparison with the CLP criteria

According to CLP: *"Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans.*

*The classification of a substance in this **Category 1A** is largely based on evidence from humans."*

There is no human data with HAPS. Therefore, classification as Repr. 1A is not fulfilled.

*The classification of a substance in this **Category 1B** is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the*

absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects.

There is clear evidence of an adverse effect on fertility in the absence of other toxic effects in a reproduction/developmental toxicity screening test according to OECD TG 421. There was no offspring produced at the tested doses of 250 and 1000 mg/kg bw/day, and only 2/12 dams with normal litter at 62.5 mg/kg bw/day. The doses of 62.5 and 250 mg/kg bw/day were not associated with general toxicity that can be evidenced by clinical signs, mortality, body weight changes or histopathological examination. At the highest tested dose, clinical signs and minimal to slight ovarian hypertrophy/hyperplasia were reported as possibly treatment-related. In this context, the reduction / absence of litter – which is a severe adverse effect - cannot be considered secondary to the (no or) minimal general toxicity reported. It is not clear if the numerous mortalities reported in the high dose group are related to the treatment since only one female died in the satellite group also exposed to 1000 mg/kg bw/day.

In addition, it can be noted that the OECD 421 guideline study is a screening assay. According to the OECD guideline, this protocol is only "*designed to generate limited information concerning the effects of a test chemical on male and female reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition*". Therefore, the fact that reproductive effects are clearly observed in this type of study supports that they must be considered as a frequent and severe toxicity.

Therefore, HAPS fulfils criteria for classification as Repr. 1B – H360 for fertility based on clear evidence of toxicity on reproduction.

However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in ***Category 2*** *may be more appropriate.*

Clear evidence of adverse effect on fertility that cannot be considered as secondary to general toxicity is reported in a well-conducted OECD TG 421 study, and there is no mechanistic information raising doubt about the relevance of these effects for humans. Thus, classification as Repr. 2 is not appropriate.

10.8.4 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
OECD TG 414 GLP Pregnant female Wistar rats 24/dose	Aqueous solution with a concentration of 38.2% HAPS (see confidential annex for further information on composition) Dose levels: 0, 100, 300 and 1000 mg/kg bw/day by gavage. Dosing referred to the effective content of the	No treatment related effects on clinical signs, mortality, body weight and gross pathology in dams. No treatment related effects on pre- and post-implantation losses, number of viable foetuses, sex distribution, malformation and variations. NOAEL (maternal and foetuses) =	Anonymous, 2017a Key study Klimisch score 2

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
	active ingredient (HAPS). Duration: GD6 to GD19	1000 mg/kg bw/day	
Dose-range finding study for OECD TG 414 GLP Pregnant female Wistar rats 5-6/dose	Aqueous solution containing 38.2% concentration of HAPS Dose levels: 0, 10, 37.5, 125 and 500 mg/kg bw/day by gavage. Dosing referred to the effective content of the active ingredient (HAPS). Duration: GD5 to GD19	No treatment related effects in dams and foetuses NOAEL (maternal and foetuses) = 500 mg/kg bw/day	Anonymous, 2017b

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

HAPS, as aqueous solution at 38.2%, was administered by gavage to pregnant female Wistar rats (24/dose) at dose levels of 0, 100, 300 or 1000 mg/kg bw/day (dose levels refer to HAPS quantity in the dosing solutions calculated with 38.2 wt% in mixture) from gestation day 6 to 19 (Anonymous, 2017a). The doses were selected based on a dose-range finding study showing no treatment-related effects in dams and foetuses up to the highest tested dose of 500 mg/kg bw/day.

In the main study, there was no maternal toxicity in any of the groups. The treatment did not increase the pre and post-implantation loss and had no effect on viability and sex distribution. There was no treatment related effect on foetal and placental weights.

The number of litters with malformed foetuses was 2 in the 100 and 3 in the 1000 mg/kg bw/day groups, none at 300 mg/kg bw/day.

There were 3 foetuses with external / skeletal malformations in the 100 mg/kg bw/day group and 3 in the 1000 mg/kg bw/day group. In the high dose group, one foetus was found with bent scapula (bilateral), bent ulna (unilateral) and slightly shorter femur (unilateral). Another foetus had bent scapula (bilateral). A third foetus had a bipartite thoracic vertebra with dumb-bell shaped cartilage. In the 100 mg/kg bw/day dose group, two foetuses were found with short tail and one of them with hypoplastic pollex (not proved at skeletal examination). Both of these foetuses had multiple malformed vertebrae and in addition one of them had fused ribs. In this group a third foetus had also fused ribs and multiple malformations of the thoracic vertebrae. These malformations occurred with a low incidence or without dose response. There was no malformation found at visceral examination.

There was no treatment-related variations at external and visceral examinations. There was a statistically significant increase of markedly incomplete ossification of one or more skull bones in the 300 and 1000 mg/kg bw/day dose group as well as wavy ribs in the low and high dose. These effects did not reach statistical significance (if litter incidence was evaluated) and/or were within historical control level.

The NOAEL for maternal and developmental toxicity is set by the registrants at 1000 mg/kg bw/day.

10.8.6 Comparison with the CLP criteria

According to CLP: *"Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans.*

*The classification of a substance in this **Category 1A** is largely based on evidence from humans."*

There is no human data with HAPS. Therefore, classification as Repr. 1A is not fulfilled.

*The classification of a substance in this **Category 1B** is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in **Category 2** may be more appropriate.*

One prenatal developmental toxicity study according to OECD TG 414 is available with HAPS. Malformations were reported in some foetuses without dose-response relationship. Thus, no classification is required for HAPS regarding developmental toxicity.

10.8.7 Adverse effects on or via lactation

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

There is no study with HAPS that provide information on effects on or via lactation.

10.8.9 Comparison with the CLP criteria

There is no study with HAPS that provide information on effects on or via lactation. Thus, no classification can be proposed for this endpoint.

10.8.10 Conclusion on classification and labelling for reproductive toxicity

Classification as Repr. 1B – H360 for fertility is required based on a clear effect on fertility characterized by reduction / absence of pregnancy in a reproduction/developmental toxicity screening test according to OECD TG 421, not associated with other general toxicity.

No classification is required for developmental toxicity based on a prenatal developmental toxicity study (OECD TG 414).

10.9 Specific target organ toxicity-single exposure

Not assessed in this report.

10.10 Specific target organ toxicity-repeated exposure

Not assessed in this report.

10.11 Aspiration hazard

Not assessed in this report.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not assessed in this report.

12 EVALUATION OF ADDITIONAL HAZARDS

Not assessed in this report.

13 ADDITIONAL LABELLING

Not assessed in this report.

14 REFERENCES

ECHA, European Chemicals Agency (2020)

Information on Chemicals - Registered Substances

Online: https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/13109

https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID6028028#exposure (June 2020)

https://pubchem.ncbi.nlm.nih.gov/compound/Sodium-3-_allyloxy_-2-hydroxypropanesulphonate#section=Industry-Uses (June 2020)

http://qsar.food.dtu.dk/ (June 2020)

See Confidential Annex

15 ANNEXES

ANNEX I to the CLH report

ANNEX CONFIDENTIAL to the CLH report