CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification: Hexyl salicylate

EC Number: **228-408-6**

CAS Number: **6259-76-3**

Index Number: **-**

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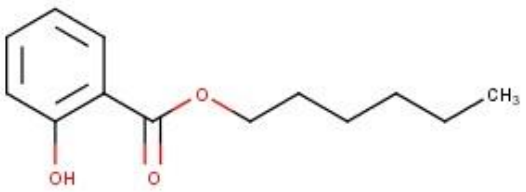
1 IDENTITY OF THE SUBSTANCE

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)	Hexyl 2-hydroxybenzoate
Other names (usual name, trade name, abbreviation)	Hexyl salicylate Benzoïc acid, 2-hydroxy-, 2-hexyl ester Salicylic acid, hexylester Hexyl *o*-hydroxybenzoate
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	228-408-6
EC name (if available and appropriate)	Hexyl salicylate
CAS number (if available)	6259-76-3
Other identity code (if available)	-
Molecular formula	$C_{13}H_{18}O_3$
Structural formula	
SMILES notation (if available)	CCCCCCOC(=O)C1=C(O)C=CC=C1
Molecular weight or molecular weight range	222.28 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	NA
Description of the manufacturing process and identity of the source (for UVCB substances only)	NA
Degree of purity (%) (if relevant for the entry in Annex VI)	≥98%, ≤100% (mono-constituent)

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)
Hexyl salicylate	≥98%	None	Skin Irrit. 2 – H315 Eye Irrit. 2 – H319 Skin Sens. 1 – H317 Skin Sens. 1B –H317 STOT SE 3 – H335 Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410 Aquatic Chronic 2 – H411

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 existing Annex VI entry										
Dossier submitters proposal	To be determined	Hexyl salicylate	228-408-6	6259-76-3	Skin Sens. 1 Repr. 2	H317 H361d	GHS07 GHS08 Warning	H317 H361d			
Resulting Annex VI entry if agreed by RAC and COM	To be determined	Hexyl salicylate	228-408-6	6259-76-3	Skin Sens. 1 Repr. 2	H317 H361d	GHS07 GHS08 Warning	H317 H361d			

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	Yes
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	data conclusive but not sufficient for classification	Yes
Flammable solids	hazard class not applicable	No
Self-reactive substances	data conclusive but not sufficient for classification	Yes
Pyrophoric liquids	data conclusive but not sufficient for classification	Yes
Pyrophoric solids	hazard class not applicable	No
Self-heating substances	hazard class not applicable	No
Substances which in contact with water emit flammable gases	data conclusive but not sufficient for classification	Yes
Oxidising liquids	data conclusive but not sufficient for classification	Yes
Oxidising solids	hazard class not applicable	No
Organic peroxides	data conclusive but not sufficient for classification	Yes
Corrosive to metals	data conclusive but not sufficient for classification	Yes
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	**harmonised classification proposed: Skin Sens 1 – H317**	Yes
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: Repro 2 – H361d**	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 current harmonised classification for hexyl salicylate (HS).

For information, hexyl salicylate was assessed by the Netherlands in the framework of the CoRAP (rolling plan 2012). Regarding the human health hazard assessment and related classification and labelling, the Netherlands concluded in its conclusion document dated on 2018 that information is sufficient for a proposal for harmonised classification and labelling for hexyl salicylate as Repr. 2; H361d (suspected of damaging the unborn child), which is based on a RAC (2016) opinion for salicylic acid, the main metabolite of hexyl salicylate.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level for classifying as reprotoxic. The harmonised classification and labelling of the main metabolite of hexyl salicylate, salicylic acid, is Repr. 2; H361d (suspected of damaging the unborn child). Based on a rapid and assumed complete hydrolysis of hexyl salicylate into salicylic acid, it justifies a harmonised classification and labelling according to article 36 of CLP for hexyl salicylate.

Concerning classification for skin sensitisation, justification that action is needed at Community level is required.

Differences in self-classification

Inconsistent self-classifications for skin sensitisation are reported in the ECHA inventory database. C&L Inventory (checked on 14th April 2020) reported that:

- 1829/1884 notifiers classify hexyl salicylate as Skin Sens. 1 – H317;

- 23/1884 notifiers classify hexyl salicylate as Skin Sens. 1B – H317 (lead dossier of the REACH registration joint submission).

- 32/1884 notifiers do not classify hexyl salicylate for its skin sensitisation properties

Finally, considering the identified uses of hexyl salicylate (especially in washing and cleaning products), an action at Community level is judged needed regarding classification as skin sensitiser.

5 IDENTIFIED USES

Hexyl salicylate is a fragrance ingredient used in many fragrance compounds. It may be found in fragrances used in decorative cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries as well as in non-cosmetic products such as household cleaners and detergents (Lapczynski *et al*. 2007).

According to ECHA website, the substance is manufactured and/or imported in the European Economic Area in 1 000 - 10 000 tonnes per year. This substance is used by consumers, by professional workers (widespread uses) and by industrial workers. It is used to formulate mixtures and as an intermediate to manufacture other products. This substance is used in the following products: air care products, washing & cleaning products, cosmetics and personal care products, biocides (e.g. disinfectants, pest control products), polishes and waxes, perfumes and fragrances (ECHA website, 2020).

6 DATA SOURCES

Information described in this CLH report are based on the REACH registration dossier, the Substance Evaluation Conclusion and Evaluation Report submitted by the Netherlands, the CLH reports of methyl salicylate and salicylic acid and bibliographic research (March – April 2020).

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	Colourless liquid	SEv Report, July 2018 (NL)	Visual inspection
Melting/freezing point	269 ± 0.5 K (-4 °C)	SEv Report, July 2018 (NL)	Measured
Boiling point	571 ± 0.5 K (298 °C) at 100.62 kPa	SEv Report, July 2018 (NL)	Measured
Relative density	1.038 g/mL at 20 °C	SEv Report, July 2018 (NL)	Measured
Vapour pressure	7.7 10^{-5} kPa at 23 °C	SEv Report, July 2018 (NL)	Measured
Surface tension	Not determined	SEv Report, July 2018 (NL)	Study scientifically unjustified
Water solubility	2 mg/L at 23 °C	SEv Report, July 2018 (NL)	Measured
Partition coefficient n-octanol/water	Log P_{ow} = 5.5	SEv Report, July 2018 (NL)	Measured
Flash point	151 °C	SEv Report, July 2018 (NL)	Measured
Flammability	Not flammable	SEv Report, July 2018 (NL)	Concluded from flash point value
Explosive properties	Not explosive	SEv Report, July 2018 (NL)	Statement
Self-ignition temperature	251 °C at 1013 hPa	SEv Report, July 2018 (NL)	Measured
Oxidising properties	Not classified	SEv Report, July 2018 (NL)	Statement
Granulometry	Not applicable	SEv Report, July 2018 (NL)	-
Stability in organic solvents and identity of relevant degradation products	Not critical	SEv Report, July 2018 (NL)	Statement
Dissociation constant	Not applicable	SEv Report, July 2018 (NL)	Statement
Viscosity	10 mPa.s at 25 °C (dynamic)	SEv Report, July 2018 (NL)	Measured

8 EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

Table 6: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
Statement	Not classified for explosive	-	SEv Report

Method	Results	Remarks	Reference
	properties		

8.1.1 Short summary and overall relevance of the information provided on explosive properties

Hexyl salicylate does not contain any groups associated with explosivity. Explosive properties are associated with the presence of certain chemical groups in a molecule which can react to produce very rapid increases in temperature or pressure. When there are no chemical groups associated with explosive properties present in the molecule then a substance or mixture shall not be classified as explosive.

8.1.2 Comparison with the CLP criteria

A statement based on the chemical structure of the substance is acceptable.

8.1.3 Conclusion on classification and labelling for explosive properties

Not classified for explosive properties.

8.2 Flammable gases (including chemically unstable gases)

8.2.1 Short summary and overall relevance of the provided information on flammable gases (including chemically unstable gases)

Not applicable as the substance is a liquid.

8.2.2 Comparison with the CLP criteria

Not applicable as the substance is a liquid.

8.2.3 Conclusion on classification and labelling for flammable gases

Not classified as flammable gas.

8.3 Oxidising gases

8.3.1 Short summary and overall relevance of the provided information on oxidising gases

Not applicable as the substance is a liquid.

8.3.2 Comparison with the CLP criteria

Not applicable as the substance is a liquid.

8.3.3 Conclusion on classification and labelling for oxidising gases

Not classified as oxidising gas.

8.4 Gases under pressure

8.4.1 Short summary and overall relevance of the provided information on gases under pressure

Not applicable as the substance is a liquid.

8.4.2 Comparison with the CLP criteria

Not applicable as the substance is a liquid.

8.4.3 Conclusion on classification and labelling for gases under pressure

Not classified as gas under pressure.

8.5 Flammable liquids

Table 7: Summary table of studies on flammable liquids

Method	Results	Remarks	Reference
Flash point measurement	151 °C at 1013 hPa Not classified as flammable liquid	Purity of the test item was not reported	SEv Report

8.5.1 Short summary and overall relevance of the provided information on flammable liquids

A flash point of 151 ºC was recorded for hexyl salicylate. As hexyl salicylate is not a gas oil, diesel, light heating oil with flash point up to 75°C or a halogenated substance, mixture containing halogenated, volatile or non volatile flammable substance, it should not be subject to hazard class ‘flammable liquid’.

8.5.2 Comparison with the CLP criteria

Not classified as flammable liquid considering its flash point.

8.5.3 Conclusion on classification and labelling for flammable liquids

Not classified as flammable liquid.

8.6 Flammable solids

8.6.1 Short summary and overall relevance of the provided information on flammable solids

Not applicable as the substance is a liquid.

8.6.2 Comparison with the CLP criteria

Not applicable as the substance is a liquid.

8.6.3 Conclusion on classification and labelling for flammable solids

Not classified as flammable solid.

8.7 Self-reactive substances

Table 8: Summary table of studies on self-reactivity

Method	Results	Remarks	Reference
Statement	Not classified as self-reactive substance	-	SEv Report

8.7.1 Short summary and overall relevance of the provided information on self-reactive substances

Hexyl salicylate does not contain any groups associated with self-reactivity. Self-reactive properties are associated with the presence of certain chemical groups in a molecule which can react to produce very rapid increases in temperature or pressure. When there are no chemical groups associated with self-reactive properties present in the molecule then a substance or mixture shall not be classified as self-reactive.

8.7.2 Comparison with the CLP criteria

A statement based on the chemical structure of the substance is acceptable.

8.7.3 Conclusion on classification and labelling for self-reactive substances

Not classified as self-reactive substance.

8.8 Pyrophoric liquids

Table 9: Summary table of studies on pyrophoric liquids

Method	Results	Remarks	Reference
Statement	Not classified as pyrophoric liquid	-	SEv Report

8.8.1 Short summary and overall relevance of the provided information on pyrophoric liquids

Experience of handling and manufacturing shows that hexyl salicylate does not spontaneously ignite at ambient temperature when exposed to air.

8.8.2 Comparison with the CLP criteria

8.8.3 No experimental test is necessary when there is a sufficient knowledge and experience of the substance to consider that it is not pyrophoric.Conclusion on classification and labelling for pyrophoric liquids

Not classified as pyrophoric liquid.

8.9 Pyrophoric solids

8.9.1 Short summary and overall relevance of the provided information on pyrophoric solids

Not applicable as the substance is a liquid.

8.9.2 Comparison with the CLP criteria

Not applicable as the substance is a liquid.

8.9.3 Conclusion on classification and labelling for pyrophoric solids

Not classified as pyrophoric solid.

8.10 Self-heating substances

8.10.1 Short summary and overall relevance of the provided information on self-heating substances

Not applicable as the substance is a liquid.

8.10.2 Comparison with the CLP criteria

Not applicable as the substance is a liquid.

8.10.3 Conclusion on classification and labelling for self-heating substances

Not classified as self-heating substance.

8.11 Substances which in contact with water emit flammable gases

Table 10: Summary table of studies on substances which in contact with water emit flammable gases

Method	Results	Remarks	Reference
Solubility in water	2 mg/L at 23 °C	No emission of gas was reported when the substance was dissolved in water	SEv Report

8.11.1 Short summary and overall relevance of the provided information on substances which in contact with water emit flammable gases

No reaction is observed when the substance is diluted in water.

8.11.2 Comparison with the CLP criteria

Not necessary if experience in handling shows that the substance does not react with water.

8.11.3 Conclusion on classification and labelling for substances which in contact with water emit flammable gases

Not classified as substance which in contact with water emits flammable gases.

8.12 Oxidising liquids

Table 11: Summary table of studies on oxidising liquids

Method	Results	Remarks	Reference
Statement	Not classified as oxidising liquid	-	SEv Report

8.12.1 Short summary and overall relevance of the provided information on oxidising liquids

Considering the structural environment of oxygen in the molecule and the oxygen balance of hexyl salicylate (CAS: 6259-76-3), it can be concluded, beyond reasonable doubt, that hexyl salicylate (CAS: 6259-76-3) is unlikely to be an oxidizer and will be incapable of reacting exothermically with combustible materials. It needs not be tested experimentally for oxidizing properties.

8.12.2 Comparison with the CLP criteria

Test is not necessary as oxygen atoms are chemically bonded only to carbons and hydrogens.

8.12.3 Conclusion on classification and labelling for oxidising liquids

Not classified as oxidising liquid.

8.13 Oxidising solids

8.13.1 Short summary and overall relevance of the provided information on oxidising solids

Not applicable as the substance is a liquid.

8.13.2 Comparison with the CLP criteria

Not applicable as the substance is a liquid.

8.13.3 Conclusion on classification and labelling for oxidising solids

Not classified as oxidising solid.

8.14 Organic peroxides

8.14.1 Short summary and overall relevance of the provided information on organic peroxides

Hexyl salicylate is not classified as an organic peroxide as defined by its molecular structure.

8.14.2 Comparison with the CLP criteria

The substance does not contain any organic peroxide in its molecular structure.

8.14.3 Conclusion on classification and labelling for organic peroxides

Not classified as organic peroxide.

8.15 Corrosive to metals

Table 12: Summary table of studies on the hazard class corrosive to metals

Method	Results	Remarks	Reference
Statement	Not classified as corrosive to metals	Although no waiver is explicitly mentioned in CLP regulation, the statement is considered acceptable considering the chemical structure of the substance	SEv Report

8.15.1 Short summary and overall relevance of the provided information on the hazard class corrosive to metals

The substance does not contain any halogen atom, has neither acidic nor alkaline functional groups, and is not known to form complexes with metals.

8.15.2 Comparison with the CLP criteria

Although no waiver is explicitly mentioned in CLP regulation, the rationale above is sufficiently convincing considering the experience of handling of the substance.

8.15.3 Conclusion on classification and labelling for corrosive to metals

Not classified as corrosive to metals.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 13: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Dermal absorption *in vitro* in human abdominal or breast skin membranes (n=8) from 4 female donors Hexyl salicylate undiluted or as 0.1 and 20% in dipropylene glycol Diffusion cell: 9 mm automated flow-through cells Receptor fluid: physiological saline with 6% PEG 20 Exposure was terminated by washing at 8h with a 3% soap solution and the skin membranes were tape-stripped at termination of the study 24h after exposure Separate metabolism phase: 0.1% 14C-radiolabelled hexyl salicylate in dipropylene glycol applied to breast or abdomen skin membranes (n=3) from 2 female donors According to OECD Guideline 428; GLP compliant	Amount in receptor fluid: 0.15%, 0.64% and 1.00% hexyl salicylate at concentrations of 100, 20 and 0.1% resp. Separate metabolism phase: absence of hexyl salicylate in the receptor fluid but salicylic acid as major component; hexyl salicylate and salicylic acid identified in the skin extracts. => Calculation of dermal absorption taking into account the potential for metabolism to salicylic acid in viable skin: dermal absorption values of 0.8%, 7.8% and 2.7%, for hexyl salicylate concentrations of 100%, 20% and 0.1% resp.	1 (reliable without restriction) key study experimental result Test material (EC name): hexyl salicylate	Study report (2016) Cited in Lapczynski *et al.* (2007) and Belsito *et al.* (2007)

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

Data specifically related to the toxicokinetics of hexyl salicylate are limited. Information was only identified for dermal absorption of this substance. Distribution, metabolism and elimination were not investigated.

Oral route

No information on toxicokinetics after oral administration is available. According to REACH guidance document 7c, although the low water solubility (2 mg/L) and Log P of 5.5 indicates that hexyl salicylate would be poorly absorbed but could be taken up by micellular solubilisation, the molecular weight of 222.2 g/mol is favourable for oral absorption of hexyl salicylate.

An oral absorption from gastrointestinal tract for 1 mg dose is estimated at 100% and for 1000 mg dose at 95% by the DK QSAR database.

Dermal route

An *in vitro* dermal absorption test with freshly isolated human excised skin was performed by the registrant according to OECD Test Guideline 428 (Table 24). Three different conditions of dermal absorption (hexyl salicylate undiluted or as 0.1 and 20% in dipropylene glycol) were tested. After 24h-exposure, small amounts of hexyl salicylate were detected in the receptor fluid (0.15%, 0.64% and 1.00% at concentrations of 100, 20 and 0.1% respectively). In a separate metabolism phase, 0.1% of 14C-radiolabelled hexyl salicylate in dipropylene glycol was applied to breast or abdomen skin membranes (n=3) from two female donors using static diffusion cells and tissue culture medium as receptor fluid. Analysis of the receptor fluid showed an absence of hexyl salicylate, but identified salicylic acid as the major component, indicating extensive metabolism of hexyl salicylate by dermal esterases. Hexyl salicylate and salicylic acid were identified in the skin extracts. The authors indicated that calculation of dermal absorption for hexyl salicylate should take into account the potential for metabolism to salicylic acid in the skin. As non-viable skin membranes were used in the first phase of the study (diffusion cells), little or no metabolism would have occurred. Thus, the dermal absorption values in this first phase might underestimate the total level of absorption. The authors concluded that that all the hexyl salicylate present in the skin was potentially metabolised and absorbed as salicylic acid. Therefore, the calculated dermal absorption values were 0.8%, 7.8% and 2.7% for hexyl salicylate concentrations of 100, 20 and 0.1% respectively. It could not be explained why the dermal absorption values were not linear with dilution.

Dermal absorption of various salicylates including hexyl salicylate was investigated by Watkinson *et al.* (1992) using a mathematic method to estimate total body absorption (assumed applied dose of 40 µg/cm^2 and assumed body surface area of 1.4 m^2). Rate constants were calculated from the relevant physico-chemical properties. The estimated total body absorption of hexyl salicylate was 27 µg over 1.4 m^2 at 12h, which is equivalent to a dermal absorption rate of 0.005%. This study was summarized in several reviews (CIR, 2018, Lapczynski *et al*., 2007, Belsito *et al*., 2007). However, it is considered unreliable as the origin of default parameters in the prediction model is unknown.

Additionally, with a water solubility of 2 mg/L for hexyl salicylate, dermal absorption is anticipated to be low to moderate according to the REACH guidance document 7c, which is in line with the *in vitro* study. The Log P of 5.5 indicates that the rate of penetration may be limited by the rate of transfer between the stratum corneum and the epidermis, but uptake into the stratum corneum will be high. The DK QSAR database estimates the dermal absorption of hexyl salicylate at 0.00358 mg/cm^2/event.

Inhalation route

No information on toxicokinetics after inhalation is available. According to REACH guidance document 7c, the low vapour pressure (7.7x10^{-5} kPa), the Log P of 5.5 and the low water solubility indicate that hexyl salicylate would be poorly absorbed by inhalation route but could be taken up by micellular solubilisation.

Conclusion

No data is available regarding oral and inhalation absorption of hexyl salicylate. Based on Log P and water solubility, hexyl salicylate is expected to be poorly absorbed by inhalation route. Regarding oral absorption, available data (log P, water solubility, DK QSAR) are contradictory. Without experimental data, no conclusion can be drawn for oral route. For dermal route, the reported absorption varied from 0.8% to 7.8% for concentrations between 100 and 0.1% hexyl salicylate, taking into account the potential for metabolism to salicylic acid in viable skin.

Data from structurally-related salicylates indicate wide distribution *via* blood and no bioaccumulation is expected after oral and dermal exposure. Rapid metabolism by hydrolysis to liberate free salicylic acid is observed. In the case of hexyl salicylate, extensive metabolism to salicylic acid by human skin esterases was

observed in an *in vitro* dermal absorption test. Metabolism would also produce the corresponding alcohol (hexanol) as initial metabolite. The QSAR Toolbox confirmed these two initial metabolites and predicted that hexyl salicylate would also be biotransformed into hexanal and hexanoic acid. Salicylates are mainly and rapidly excreted in the urine.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

Not assessed in this report.

10.1 Skin corrosion/irritation

Not assessed in this report.

10.2 Serious eye damage/eye irritation

Not assessed in this report.

10.3 Respiratory sensitisation

Not assessed in this report.

10.4 Skin sensitisation

Table 14: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
Local lymph node assay equivalent or similar to OECD Guideline 429 GLP compliant	Mouse (CBA), female, 4/group	Hexyl salicylate Purity = 98.5%	1, 2.5, 5, 10, 25% w/v (experiment 1) 0.05, 0.25, 0.5, 1, 2.5% w/v (experiment 2) Vehicle used: 1:3 ethanol:diethylphtalate Daily for 3 consecutive days	**Positive** Stimulation index (relative to vehicle control): First experiment: > 3 at all concentrations Second experiment: 0.05%: 1.87 0.25%: 3.56 0.5%: 5.60 1%: 10.83 2.5%: 10.80 EC3 = 0.18%	Unnamed (2006) Cited in SCCS Opinion on Fragrance allergens in cosmetic products (2011) Klimisch score = 1
Modified Draize test Induction: 4 intradermal injections (0.1 mL at 0.25%) First challenge: intradermal injection 14 days later (0.1 mL at 0.1%) and topical application (0.1 mL at 5%) Second challenge conducted 7 days later Secondary literature	Inbred Hartley albino guinea pigs 4 or 6 of each sex, 10 total	Hexyl salicylate	0.25% for intradermal induction 0.1% and 5% for challenge (vehicle not reported)	**Positive** Sensitisation reactions observed after the second challenge at 5%	Sharp (1978) Cited in Lapczynski *et al*. (2007) Klimisch score = 4

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
Limitations: vehicle not specified					
Maximisation assay Intradermal induction: 6 injections (2 x 0.1 mL injections of 1% HS in 0.01% DOBS/saline, 2 x 0.1 mL injections of 1% HS in 50% Complete Freund's Adjuvant and 2 x 0.1 mL injections of 50% Complete Freund's Adjuvant Topical induction 7 days later: 40% HS in acetone (48h occluded patch) Topical challenge 13-14 days later: 10% HS in acetone (24h occluded patch) Secondary literature Similar to OECD 406 Limitation: few number of animals, tested concentrations not justified	Dunkin/ Hartley albino guinea pigs, 10 total	Hexyl salicylate	1% in 0.01% DOBS/saline and 1% in 50% Complete Freund's Adjuvant for intradermal induction 40% in acetone for topical induction 10% in acetone for challenge	Negative	Lapczynski *et al*. (2007) Klimisch score = 3
Sensitisation evaluated as part of a photoallergy study Intradermal induction: injection of 0.1 mL of a formulation of sterile water and Freund's complete adjuvant (1:1 v/v) Topical induction: 0.3 mL of 100% HS in 3:1 DEP:ethanol applied to 25 mm Hilltop Chambers® and then to the dorsal skin of animals (occluded patch for 2h) Followed by UVR exposure using a 6.5 kW long-arc xenon water-cooled lamp with a filter used to attenuate mid-range UVB. Delivered dose: 2.25 Minimal Erythema Doses (MED) (~2.25h). Procedure repeated once daily on days 3, 5, 8, 10 and 12 of the induction phase Topical challenge on day 22: 50% HS in 3:1 DEP:EtOH and 100% HS Observations 1, 4h later and 1,	Male albino hairless guinea pigs (5/group)	Hexyl salicylate	100% for topical induction 50 and 100% HS in 3:1 DEP:ethanol for topical challenge	Negative	Lapczynski *et al*. (2007) Klimisch score = 3

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
2, 3 days later. Secondary literature					

Table 15: Summary table of human data on skin sensitisation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Induction studies				
Human repeated insult patch test (HRIPT) with 103 volunteers (29 male and 74 female)	30% hexyl salicylate in 3:1DEP:EtOH	Nine induction applications, 3 per week over a 3-week period After 2 weeks rest period, single application challenge test. Reactions were scored at 24h after challenge.	0/103 positive reactions Induction phase: 3 subjects with equivocal transient reactions After challenge: 2 subjects with equivocal transient responses	RIFM (2004a) Cited in Lapczynski *et al*. (2007)
Human maximisation with 22 selected volunteers	3% hexyl salicylate probably formulated in petrolatum	Applications of 3% hexyl salicylate in petrolatum under occlusion for 5 alternate-day 48h periods after pretreatment of patch site for 24h with 5% aqueous SLS under occlusion. After 10-14 days rest period, 2% SLS was applied under occlusion for 30 min on the left side of the back prior to challenge patch of hexyl salicylate under occlusion for 48h on the right side.	Initial positive "equivocal" reactions after challenge Subjects are re-tested later. No positive evidence of sensitisation was observed.	RIFM (1975b) Cited in Lapczynski *et al*. (2007)
Diagnostic studies				
Patch test in 218 fragrance sensitive patients with contact dermatitis (selected patients)	5% hexyl salicylate in petrolatum	Various fragrance materials including hexyl salicylate	0% positive reactions	Larsen *et al.* (2002) Cited in Lapczynski *et al*. (2007) and in SCCS Opinion on Fragrance allergens in cosmetic products (2011)
Patch test in ~100 patients with dermatitis (unselected patients)	5%, 7.5%, 11.3%, 16.9%, 25.3% hexyl salicylate	Test material suspended in pet. was applied to the upper back in Finn Chambers under occlusion for 2 days. Patch test readings performed on day (D) 2, D3, D4, D5 and D7	0% positive reactions in all test concentrations 5%: 2/100 "doubtful" reactions 16.9%: 1/100 "doubtful" reactions 25.3%: 1/87 "doubtful" reactions	Bennike *et al*. (2019)

10.4.1 Short summary and overall relevance of the provided information on skin sensitisation

Animal data

Some studies were available to assess skin sensitisation property of hexyl salicylate, including two standard test methods, LLNA and maximisation test. Hexyl salicylate was tested diluted in various solvents (1:3 ethanol:diethylphtalate, acetone or petrolatum) and tested concentrations ranged from 0.05 to 100%.

The key study is the LLNA which is in compliance with OECD Guideline 429 (Unnamed (2006)). Hexyl salicylate is positive in this test. Dose-response could be observed and the stimulation index was higher than 3, in both experiments performed, from 0.25% to 25% (the maximum concentration tested) hexyl salicylate in 1:3 ethanol:diethylphtalate, leading to an EC_3 of 0.18%.

Hexyl salicylate was not sensitising in a maximisation test and a photoallergy study evaluating sensitisation. These two studies summarized in the above table were cited in the review from Lapczynski *et al*. (2007). However, they were both considered unreliable because few animals were tested. In the maximisation test, at least 20 test animals are indeed recommended if it is not possible to conclude that the substance is a sensitiser with fewer than 20 test animals. This may be an explanation of the negative results. In addition, in the maximisation assay, there is no justification for the tested concentrations.

In a modified Draize test, 5% hexyl salicylate induced sensitising reactions in Hartley albino guinea pigs after a second challenge. A limitation of this test was that the vehicle used was not specified.

In a genomic allergen rapid detection assay utilising an *in vitro* model of dendritic cells, hexyl salicylate was predicted to be a skin sensitiser (Forreryda *et al.* (2018), cited in the Cosmetic Ingredient Review on salicylic acid and salicylates (2019)).

Overall, **hexyl salicylate was positive at concentrations above 0.25% in the LLNA, the only animal study of good quality available, with an EC_3 = 0.18%, indicating a strong potency of sensitisation. This result is supported by a genomic allergen rapid detection assay predicting hexyl salicylate as skin sensitiser.**

Human data

Some human data are available including 2 human volunteer induction studies and 2 diagnostic studies.

No sign of sensitisation to hexyl salicylate (30% in 3:1DEP:EtOH) was reported in one HRIPT (human repeated insult patch test) performed on 103 volunteers (RIFM (2004a), cited in Lapczynski *et al*. (2007)). During the induction phase, 3 subjects showed equivocal transient reactions, which could be linked to irritation, as hexyl salicylate was repeatedly applied on the same site. Equivocal transient responses were also observed in 2 subjects after challenge but it was not mentioned if these subjects were the same as during the induction phase. These equivocal reactions after challenge should have raised concern and led to further investigation with a second reading after 48h, followed by a re-challenge 3 weeks later. Besides, when a test shows several questionable results during the induction phase, the substance application site should be changed (ANSM 2008). Additionally, benzyl salicylate was used as negative control in this study whereas this substance will be soon classified Skin Sens. 1B under the CLP regulation. This information may question the negative result of this study. Finally, the number of tested volunteers remains low (103) in comparison with the recommendations of the Scientific Committee on Consumer Safety (SCCS) (150-200 volunteers). Although the equivocal reactions after challenge may be linked to irritation, due to the tested concentration of hexyl salicylate (30%), the reported data do not allow to rule out an allergic reaction. Considering these limitations, this HRIPT is not considered reliable.

A maximisation assay performed on 22 selected volunteers also concluded that hexyl salicylate was not sensitising (RIFM (1975b) cited in Lapczynski *et al*. (2007)). The study report indicated that positive equivocal reactions were observed after the challenge phase. Biopsies of these reactions were performed and it was followed by re-challenge, which produced no positive evidence of sensitisation. Although the test was performed on 22 volunteers instead of 25, it was overall in compliance with the method. The number of

volunteers was low to be able to get statistical values. Nevertheless, the use of sodium lauryl sulphate as adjuvant in order to maximise the reaction increases the risk of sensitising reactions.

Finally, two diagnostic studies were considered negative (Larsen (2002) and Bennike (2009)).

Bennike *et al*. studied three fragrance substances, including hexyl salicylate, on unselected patients with dermatitis, as discrepancies on their sensitising properties were observed in animal and human data. These 3 substances were classified as contact allergens on the basis of animal data but not in humans (SCCS 2011). Moreover, as these substances are widely used in consumer products, exposure is commonly occurring. Thus, the study aimed at studying increasing concentrations of these substances in order to determine their optimal patch test concentrations. Five concentrations of hexyl salicylate, from 5 to 25%, were tested on approximately 100 patients with dermatitis per concentration group. Some patients showed doubtful reactions at first reading but these reactions were not confirmed at second reading. The authors concluded that no positive patch test reactions occurred with hexyl salicylate up to a concentration of 25% and that the maximum tolerated concentration for most of the patients was 12.5% hexyl salicylate. This concentration was then recommended for patch testing. Additionally, they concluded that although the possibility of contact allergy to hexyl salicylate cannot be ruled out from this study, it seems unlikely that this substance is an extreme sensitizer in humans, contrary to in animals.

The study from Larsen *et al*. was performed according to internationally accepted criteria. It included 218 selected fragrance sensitive patients with contact dermatitis. It aimed at identifying new sensitising substances to screen on patients with suspect fragrance allergy. The 218 patients were exposed to a fragrance mixture (FM) and 17 individual fragrance materials including hexyl salicylate. The FM did not contain hexyl salicylate. This mixture induced positive reactions in 76% of the subjects. The patch test following the exposure to 5% hexyl salicylate appeared negative.

Finally, no case reports were reported in the literature for patients with dermatitis after the use of a product containing hexyl salicylate.

Differentiation between sensitising and irritating reactions

Contradictory results were found in both animal and human studies. In animals, positive effects were reported in one LLNA. The results of the LLNA suggested that hexyl salicylate would be a strong sensitiser as the EC_3 is clearly below 2%. As supporting data, hexyl salicylate was predicted to be as a skin sensitiser in a genomic allergen rapid detection assay. Data from other studies (maximisation assay and photoallergy study) showed negative results. In humans, studies were all considered negative, despite some methodological deficiencies (in particular in HRIPT). Special caution has to be paid to differentiate if the positive results are linked to irritating or real sensitising effects of hexyl salicylate.

Some studies from the literature indicated that the positive result of the LLNA was considered a false-positive since hexyl salicylate up to 30% has not been sensitising in humans in one HRIPT (Roberts *et al*. 2015a & b). This argument should be discounted as the reliability of this HRIPT is questionable and negative human data cannot normally be used to negate positive results from animal studies according to the CLP regulation.

Another study explained the positive result of the LLNA by mentioning that the very low EC_3 (0.18%) might be due to irritating properties of hexyl salicylate or potential sensitising impurities (Urbisch *et al.* 2015).

From the literature, contradictory results were found regarding irritating properties of hexyl salicylate (Lapczynski *et al*. 2007, Belsito *et al*. 2007). However, it can be noted that irritation was only observed for high concentrations of hexyl salicylate: at least 25% but rather with concentrations above 50%. These concentrations are clearly above the concentrations for which skin sensitisation was observed in the LLNA.

Table 16: Summary table of animal data on skin irritation (extracted from Belsito *et al*. 2007)

Material	Method	Concentration	Species	Results	References
Hexyl salicylate	Irritation evaluated during an associated LD_{50} study	100%	10 Rabbits	Irritation observed	RIFM (1975a)
Hexyl salicylate	Primary skin irritation study (4-h occlusive patch)	10%, 15%, 25%, 50%, and 100% in DEP	4 Female New Zealand White Rabbits	10%, 15%, and 25%: no irritation 50% and 100%: irritation observed	RIFM (1986b)
Hexyl salicylate	Pre-test for Draize assay (dermal application)	5% (vehicle not specified)	4 Hartley albino guinea pigs	No irritation	Sharp (1978)
Hexyl salicylate	Irritation studied as part of a phototoxicity test	100%	6 Mice (hairless)	No irritation	RIFM (1975f)
Hexyl salicylate	Irritation studied as part of a phototoxicity test	100%	Miniature swine	No irritation	RIFM (1975f)
Hexyl salicylate	Irritation studies as part of a photoallergy test (2-h exposure with Hilltop chambers)	1%, 5%, 10%, 50%, 100% in 3:1 DEP:ethanol	Male albino hairless guinea pigs (5/group)	No irritation	RIFM (2003)
Hexyl salicylate	Preliminary irritation study	10%, 25% and 50% in acetone	4 Albino guinea pigs	10%; no irritation 25 and 50%: irritation observed	RIFM (1981e)
Hexyl salicylate	Primary skin irritation study (4-h semi-occlusive patch)	100%	3 New Zealand White Rabbits	Irritation observed	RIFM (1984) and RIFM (1985)
Hexyl salicylate	Primary skin irritation study (4-h occlusive patch)	10%, 15%, 50%, and 100% in DEP	4 Female New Zealand White Rabbits	10%, 15%, 25%, and 50%: no irritation 100%: irritation observed	RIFM (1986a)

Additionally, moderate skin irritation was reported in an OECD Guideline 404 study available in the registration dossier (Haynes, 1986). In this study, female rabbits were exposed to 50% and 100% hexyl salicylate in DEP for 4 hours under semi-occlusive conditions. At 50% hexyl salicylate, the mean erythema and oedema scores were respectively 2.0 and 1.4. The observed effects were fully reversible within 7 days. For the undiluted substance, the mean scores for erythema and oedema over the 24-72 hour period were respectively 2.0 and 2.16. In this case, it was reported that one rabbit showed remaining erythema and oedema after 7 days. Nevertheless, these effects concerned only one animal and no information was available until 14 days, which is the normal observation period recommended by OECD Guideline 404. Overall, the results of the study could not trigger a classification for skin irritation according to the CLP criteria.

Table 17: Summary table of human data on skin irritation (extracted from Belsito *et al*. 2007)

Material	Method	Concentration	Subjects	Results	References
Hexyl salicylate	Maximization pre-test (48-h occluded patch)	3% (vehicle not specified)	22 volunteers	No irritation (0/22)	RIFM (1975d)
Hexyl salicylate	Induction phrase HRIPT (24-h occluded patch, nine applications)	30% in 3:1 DEP:ethanol	103 volunteers	Slight irritation observed in 3/103	RIFM (2004a)
Hexyl salicylate	A 24-h occluded patch	0.3%, 3%, and 30% in 3:1 DEP:ethanol	56 volunteers	No irritation (0/56)	RIFM (2004b)
Hexyl salicylate	4-h occluded patch	100%	30 volunteers	No irritation (0/30)	Basketter et al. (2004)

In humans, hexyl salicylate does not seem to induce skin irritation based on the data available.

Therefore, the arguments from Urbisch *et al.* 2015, considering the result of the LLNA as false-positive due to the potential irritating properties of hexyl salicylate, cannot be considered as valid.

Regarding the other argument from these authors involving potential sensitising impurities, the purity of hexyl salicylate is > 98% and there are no impurities in amount exceeding 1% based on registration data. Besides, no impurities that would impact the classification of hexyl salicylate were identified.

Overall, there is no sufficient information to discount the effects reported in the LLNA. Thus the reported positive reactions should be considered as sensitising effects.

10.4.2 Comparison with the CLP criteria

The decision logic for classification of substance described in the CLP guidance version 5.0 (July 2017) has been followed:

"Are there data and/or information to evaluate skin sensitisation?"

Yes, there are both experimental animal studies and human data assessing skin sensitisation properties of hexyl salicylate.

a) "*Is there evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or*

No, there is no evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons. However, the HRIPT was considered unreliable due to methodological deficiencies.

a) Are there positive results from an appropriate animal test or in vitro/in chemico test?"

Positive results were obtained in a LLNA performed with hexyl salicylate at concentrations from 0.25%. Hexyl salicylate was predicted to be a skin sensitiser in a genomic allergen rapid detection assay.

"Are data sufficient for sub-categorisation?"

According to CLP, "*Substances shall be classified as skin sensitisers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria: (a) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons; or (b) if there are positive results from an appropriate animal test.*

***Sub-category 1A**: Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered.*

***Sub-category 1B**: Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitisation in humans. Severity of reaction may also be considered."*

Non-human and human data have been analysed to determine if they are sufficient for sub-categorisation.

Non-human data

Three types of animal tests can be used directly for classification purpose: LLNA, guinea pig maximisation test and Buehler assay.

Classification criteria according to CLP are the following:

Classification	Assay	Criteria
Subcategory 1A	LLNA	EC3 value ≤ 2%
Subcategory 1B	LLNA	EC3 value > 2%

With EC_3 values ≤ 2% in the LLNA, hexyl salicylate fulfils criteria for classification Skin Sens. 1A according to the CLP guidance.

Human data

Due to its low reliability, the HRIPT cannot be used for the purpose of classification. Nevertheless, the maximisation assay and the 2 diagnostic studies were negative and were considered reliable. The absence of sensitising reactions in these studies could be due to several reasons:

- The patch test for hexyl salicylate is not commercialized. Indeed, 46 fragrance substances are commercialized for patch testing by the firm Chemotechnique but hexyl salicylate is not part of the

list. Thus, hexyl salicylate was only tested for prospecting. This could explain why only 2 diagnostic studies with variable concentrations of this substance were published.

- Hexyl salicylate is not included in the list of the 26 sensitising fragrance substances in humans that require labelling. Thus, it would be difficult to determine if hexyl salicylate is responsible for a contact dermatitis following exposure to a fragrance.
- Although this substance is widely used in fragrances, the concentrations used are low. In face and body leave-on products, concentrations respectively range from 0.02 to 0.03% and from 0.08 to 0.12%. Maximal concentrations are related to rinse-off products and reach 0.52% in soaps and detergents (Cosmetic Ingredient Review on salicylic acid and salicylates (2018)). These concentrations are lower than concentration limits recommended by the International Fragrance Association (IFRA). **Therefore, the absence of sensitising reactions observed in humans could be due to primary prevention related to these concentration limits, more than the absence of sensitising properties.**

Overall conclusion :

Based on animal data, hexyl salicylate fulfills criteria for classification Skin Sens. 1A.

However, the discrepancies between animal data showing hexyl salicylate as an extreme sensitiser and negative human data raise question about a classification into sub-categories. Indeed, according to the Guidance on the Application of the CLP criteria, “classification into sub-categories is required when data are sufficient. When Category 1A cannot be excluded, Category 1 should be applied instead of Category 1B”.

Thus, **Category 1 should be applied for hexyl salicylate**.

10.4.3 Conclusion on classification and labelling for skin sensitisation

Based on animal data, hexyl salicylate fulfills criteria for classification Skin Sens. 1A.

Although all human data are considered negative by the authors, one of them cannot be used for the purpose of classification due to its low reliability (HRIPT). Moreover, due to the significant discrepancies between positive animal data and negative human studies, sub-categorisation does not seem appropriate according to the Guidance on the Application of the CLP criteria.

With the positive results of the LLNA of good quality, Category 1A cannot be excluded. As data are not sufficient for sub-categorisation, **hexyl salicylate should be classified Skin Sens. 1 – H317 according to CLP regulation**.

10.5 Germ cell mutagenicity

Not assessed in this report.

10.6 Carcinogenicity

Not assessed in this report.

10.7 Reproductive toxicity

10.7.1 Adverse effects on sexual function and fertility

No fertility studies are available on hexyl salicylate. Therefore, assessment of the potential of hexyl salicylate to impair fertility has been based on read-across data from animal studies on methyl salicylate

(MeS) (see Annex II for rationale). The read-across approach is considered adequate since both methyl salicylate and hexyl salicylate metabolize to form salicylic acid (SA). No fertility studies are available with salicylic acid. In the RAC opinion dated on 2016 for salicylic acid, a read-across to methyl salicylate was agreed.

Table 18: 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
Study of fertility and early embryonic development to implantation Crj:CD(SD)IGS rats male/female Subcutaneous administration GLP and ICH guidelines	Methyl salicylate (purity: 100.1%) 0, 30, 100, 300 mg/kg/day in corn oil From 2 weeks prior to mating until sacrifice (total of 52 days) for males and until gestation day 6 for females (total of 30 days). Sacrifice of females on GD13.	NOAEL for general toxicity: 100 mg/kg/day based on one mortality in males, decreased body weight gain and food consumption at 300 mg/kg bw/day. NOAEL for fertility: 300 mg/kg/day (no effect). Increased plasmatic salicylic acid concentration dependent on the dose ratio but scarcely affected by repeated dosing. No clear sexual difference.	FDA (2006a) Klimisch score : 1 Key study **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Two-generation study Mouse (CD-1) male/female 20/sex/dose for MeS groups and 40/sex for vehicle group. Oral: gavage in corn oil Task 2 (continuous breeding phase) & 4 (offspring assessment) of the NTP continuous breeding protocol Limited examination NTP protocol, GLP	Methyl salicylate (purity ≥ 99%) 0, 25, 50 and 100 mg/kg/day. (nominal conc.) Exposure: 7 days prior to mating, during 98 days of cohabitation (allowing the production of about 4 litters) and then during a separation period of 21 days during which final litters were delivered (task 2). A second generation was then produced only for the highest dose group (task 4): the mothers were dosed through weaning and F1 mice were dosed until mated at about 74 days of age.	NOAEL (reproductive effects): 100 mg/kg bw/day – no adverse effect	NTP (1984a) Chapin & Sloane (1997) Morrissey *et al.*, (1989) Lamb *et al.*, (1997) Klimisch score : 2 Supporting study **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
One generation study + crossover mating study Mouse (CD-1) male/female 20/sex/dose for MeS groups and 40/sex for vehicle group. Oral: gavage in corn oil	Methyl salicylate (purity ≥ 99%) 100, 250 and 500 mg/kg/day. (nominal conc.) Exposure: 7 days prior to mating, during 98 days of cohabitation (allowing the production of about 4 litters) and then during a separation period of 21 days during which final	500 mg/kg bw/day – no effect on fertility index Task 3: due to fertility problem in the control groups (26% in the first task 3 and 41% in the second task 3) and lack of significant results in the litter analysis, an affected sex cannot be determined.	NTP (1984b) Chapin & Sloane (1997) Morrissey *et al.*, (1989) Klimisch score : 2

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Task 2 (continuous breeding phase) & 3 (crossover mating) of the NTP continuous breeding protocol Limited examination NTP protocol, GLP	litters were delivered (task 2). Task 3: high-dose animals of each sex were mated to control mice of the opposite sex.		Supporting study **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Three-generation study Rat (Osborne-Mendel); male/female (20/sex/dose) Oral: feed (no vehicle) A supplementary study was performed with adding calcium carbonate to MeS diet with the same examination. Examination very limited Several deficiencies from OECD 416, not GLP	Methyl salicylate 0, 500, 1500, 3000 and 5000 ppm (equivalent to 25, 75, 150, 250 mg/kg bw as MeS) (nominal in diet) Exposure: 100 days before the first mating and then throughout the experiment (until weaning of the 3rd generation).	NOAEL (fertility): 250 mg/kg bw/day (male/female) based on no statistically significant effect reported. The addition of calcium carbonate did not markedly differ from those obtained after administration of MeS alone.	Collins TFX *et al.* (1971) Gross MA, Fitzhugh OG (1977) Klimisch score : 3 Supporting study **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Two-generation study Rat (Wistar) male/female 25/sex/dose (F0); 30/sex/dose (F1) Oral: feed (no vehicle) Examination very limited Several deficiencies from OECD 416, not GLP	Methyl salicylate 0.25% and 0.5% (2500 ppm and 5000 ppm equivalent to 125 and 250 mg/kg bw MeS/day) (nominal in diet) Exposure: 60 days before the first mating and then throughout the experiment (weaning of the F2b litters).	No adequate NOAEL can be set based on the low quality of the reported results. Decreased litter size at all doses. Higher number of unsuccessful matings for the first generation and decreased reproduction index for both generations at the highest dose. Higher number of death between birth and day 5 at 250 mg/kg bw/day.	Anonymous (1978a) Klimisch score : 3 Supporting study **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Two-generation study Mouse male/female (no data on strain); 25/sex/dose (F0);	Methyl salicylate 0.25% and 0.5% (2500 ppm and 5000 ppm, equivalent to 375 and 750	No adequate NOAEL can be set based on the low quality of the reported results.	Anonymous (1978b) Klimisch score :

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
30/sex/dose (F1) Oral: feed (no vehicle) Examination very limited Several deficiencies from OECD 416, not GLP	mg/kg bw MeS/day) (nominal in diet) Exposure: 30 days before the first mating and then throught the experiment (weaning of the pups).	Litter size slightly smaller in test groups only in the first generation.	3 Supporting study **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
One-generation study Rat (Sprague-Dawley); male/female; 24-27 animals/dose Oral: feed (no vehicle) Guideline and GLP not stated – secondary litterature	Methyl salicylate 4000 ppm and 6000 ppm equivalent to 200 and 300 mg/kg bw/day (nominal in diet) Exposure: 60 days before the first mating and then throughout the experiment (until weaning of offspring on day 20-21)	NOAEL (F1): 300 mg/kg bw/day (male/female) based on no effect No abnormalities. Neonate survival at weaning was greater in the test group than in control.	FDA (1966) CIR (2003) Klimisch score : 4 Disregarded study **(See Annex II for justification of read-across)**

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

Animal data

According to the CLH report on methyl salicylate and the RAC opinion dated on September 2019 for this substance, the seven studies above showed no statistically significant effect on fertility and mating in rats at doses up to 250 mg/kg bw/day by oral route and 300 mg/kg bw/day by subcutaneous application and in mice at doses up to 750 mg/kg bw/day (highest doses tested). **Even if most of the fertility studies on methyl salicylate showed a number of deficiencies compared to OECD guidelines in term of parameters studied, none reported any significant and/or consistent effect on fertility. Therefore, based on a read-across with methyl salicylate, it can be concluded that hexyl salicylate is not likely to have any significant adverse effect on fertility.**

Human data

No human data has been found with hexyl salicylate.

10.7.3 Comparison with the CLP criteria

According to the CLH report on methyl salicylate and the RAC opinion dated on September 2019 for this substance, e**ven if most of the fertility studies on methyl salicylate showed a number of deficiencies compared to OECD guidelines in term of parameters studied, none reported any significant and/or consistent effect on fertility. The RAC agreed with the proposal by FR that no classification was justified for methyl salicylate for adverse effects on sexual function and fertility.**

Therefore, through a read-across with data on methyl salicylate, no classification is justified for hexyl salicylate for adverse effects on sexual function and fertility.

10.7.4 Adverse effects on development

No developmental studies are available on hexyl salicylate. Therefore, assessment of the potential of hexyl salicylate to impair development has been based on read-across data from animal studies on salicylic acid, sodium salicylate and methyl salicylate (see Annex II for rationale). The read-across approach is considered adequate since sodium salicylate, methyl salicylate and hexyl salicylate metabolize to form salicylic acid.

Table 19: 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
Data on salicylic acid			
Prenatal developmental assay (G8-14) Rat (Wistar) (female) oral: in the diet equivalent or similar to OECD Guideline 414	Salicylic acid 0.06, 0.1, 0.2, 0.4% (corresponding to 50.7 +/- 0.6, 77.4 +/- 1.0, 165 +/- 2.1, 205.9 +/- 18.9 mg/kg bw/d Exposure: day 8 to 14 (daily)	NOAEL (maternal toxicity): 165 mg/kg bw/day NOAEL (developmental toxicity): 77.4 mg/kg bw/day	Tanaka S *et al.* (1973a) Klimisch score = 2 **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Prenatal developmental assay (G8-14) Rat (Wistar) (female) oral: gavage equivalent or similar to OECD Guideline 414	Salicylic acid 75, 150, 300 mg/kg bw/d in CMC (carboxymethyl cellulose) Exposure: day 8 to 14 (daily)	NOAEL (maternal toxicity): 150 mg/kg bw/day NOAEL (developmental toxicity): 75 mg/kg bw/day	Tanaka S *et al.* (1973b) Klimisch score = 2 **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Rat (Sprague-Dawley) (17 female) subcutaneous no guideline followed Limitation: not GLP compliant	Salicylic acid 380 mg/kg (nominal conc.) Vehicle: water Exposure: 2 salicylic acid administrations at 2 hr interval, on day 9, followed by mineral isotopes administration on day 9 or 16 of pregnancy Urinary excretion and fetal uptake of the mineral isotopes were measured and the fetuses (on day 20 of gestation) were removed and inspected noting death, resorption, as well as external congenital malformations.	No NOAEL identified Marked maternal body weight loss, loss of appetite, complete relaxation, weakness, drowsiness, muscular limpness, inactivity, accelerated respiration rate, and occasionally elevated water intake and urinary excretion High incidence of fetal malformations and resorption, abnormally small fetuses	Koshakji and Schulert (1973) Klimisch score = 3 **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Data on sodium salicylate			

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Prenatal developmental assay (G6-15) Rat (Sprague-Dawley) (17-19 female/dose) oral: gavage equivalent or similar to OECD Guideline 414	Sodium salicylate 30, 90 or 180 mg/kg (nominal conc.) Vehicle: water Exposure: day 6 to 15 (daily)	NOAEL (embryotoxicity/ fetotoxicity): 90 mg/kg bw/day NOAEL (teratogenicity): 30 mg/kg bw/day	Fritz and Giese (1990) Klimisch score = 2 **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Rabbit (New Zealand White) (4 female) oral: gavage Limitation: few number of animals, only one concentration tested	Sodium salicylate 100 mg/kg (actual ingested) Vehicle: water Exposure: day 4 to 7 (daily)	No effect on the number of implantations or on foetal development	Fabro S *et al.* (1984) Klimisch score = 3 **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Data on methyl salicylate			
Prenatal developmental assay (GD6-18) Rabbit New Zealand White (18-20 females/group) Subcutaneous administration Study performed according to ICH guidelines and GLP	Methyl salicylate (purity: 100.1%) 0, 30, 100, 300 mg/kg bw/day in corn oil Exposure: day 6 to 18 (daily)	NOAEL (development): 300 mg/kg/day based on no effect. NOAEL (maternal): 100 mg/kg/day based on abortion in one dam and on decreased body weight gain at 300 mg/kg/day. Increase of the plasma salicylic acid concentration nearly dependent of increases in the dose ratio and scarcely affected by repeated dosing.	FDA (2006b) Klimisch score : 1 Key study **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Prenatal developmental assay (GD6-17) Rat Crj:CD(SD)IGS (20 females/group) Subcutaneous administration Study performed according to ICH guidelines and GLP	Methyl salicylate (purity: 100.1%) 0, 50, 100, 200 mg/kg bw/day in corn oil Exposure: day 6 to 17 (daily)	NOAEL (development): 100 mg/kg bw/day based on decreased body weight, external and skeletal anomalies at 200 mg/kg bw/day. NOAEL (maternal): 100 mg/kg bw/day based on depression of the body weight gain and decrease in food consumption at 200 mg/kg bw/day.	FDA (2006c) Klimisch score : 1 Key study **(See Annex I for more details on the results)** **(See Annex II for justification**

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
			of read-across)
Study for effects on pre and postnatal development including maternal function Crj:CD(SD)IGS pregnant female rats (20/group) Subcutaneous administration. Groups of offspring sacrificed on lactation day 22 for organ weight and skeletal examination. Remaining males and females were mated to assess reproductive performance. Females sacrificed on gestation day 13. GLP and ICH guidelines	Methyl salicylate (purity: 100.1%) 0, 20, 60, 200 mg/kg/day in corn oil Exposure: from gestation day 6 to lactation day 21	NOAEL maternal: 60 mg/kg/d based on decreased body weight, food consumption and mortality at 200 mg/kg bw/day. NOAEL development < 60 mg/kg/day based on skeletal variations at 60 mg/kg bw/day. Decreased birth index, delayed balanopreputial separation, delayed incisor eruption and skeletal anomalies and variations at 200 mg/kg/day.	FDA (2006d) Klimisch score : 1 Key study **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Two-generation study Mouse (CD-1) male/female 20/sex/dose for MeS groups and 40/sex for vehicle group. Oral: gavage in corn oil Task 2 (continuous breeding phase) & 4 (offspring assessment) of the NTP continuous breeding protocol NTP protocol, GLP	Methyl salicylate (purity ≥ 99%) 0, 25, 50 and 100 mg/kg/day. (nominal conc.) Exposure: 7 days prior to mating, during 98 days of cohabitation (allowing the production of about 4 litters) and then during a separation period of 21 days during which final litters were delivered (task 2). A second generation was then produced only for the highest dose group (task 4): the mothers were dosed through weaning and F1 mice were dosed until mated at about 74 days of age.	NOAEL (reproductive effects): 100 mg/kg bw/day – no adverse effect NOAEL (developmental effects): 100 mg/kg bw/day – no adverse effect	NTP (1984a) Chapin & Sloane (1997) Morrissey *et al*., (1989) Lamb *et al*., (1997) Klimisch score : 2 Supporting study **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
One generation study + crossover mating study Mouse (CD-1) male/female 20/sex/dose for MeS groups and 40/sex for	Methyl salicylate (purity ≥ 99%) 100, 250 and 500 mg/kg/day. (nominal conc.) Exposure: 7 days prior to mating, during 98 days of cohabitation (allowing the production of about 4 litters) and then during a separation	500 mg/kg bw/day – no effect on fertility index NOAEL (developmental effect): 100 mg/kg bw/day based on a reduction in pup weight from 250 mg/kg bw/day. At 500 mg/kg bw/day, a	NTP (1984b) Chapin & Sloane (1997) Morrissey *et al*., (1989) Klimisch score :

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
vehicle group. Oral: gavage in corn oil Task 2 (continuous breeding phase) & 3 (crossover mating) of the NTP continuous breeding protocol NTP protocol, GLP	period of 21 days during which final litters were delivered (task 2). Task 3: high-dose animals of each sex were mated to control mice of the opposite sex.	significant decrease in the mean number of litter and in the average of pups per litter, the proportion of pups born alive was observed. Task 3: due to fertility problem in the control groups (26% in the first task 3 and 41% in the second task 3) and lack of significant results in the litter analysis, an affected sex cannot be determined.	2 Supporting study **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Three-generation study Rat (Osborne-Mendel); male/female (20/sex/dose) Oral: feed (no vehicle) A supplementary study was performed with adding calcium carbonate to MeS diet with the same examination. Examination very limited Several deficiencies from OECD 416, not GLP	Methyl salicylate 0, 500, 1500, 3000 and 5000 ppm (equivalent to 25, 75, 150, 250 mg/kg bw as MeS) (nominal in diet) Exposure: 100 days before the first mating and then throughout the experiment (until weaning of the 3rd generation).	NOAEL (fertility): 250 mg/kg bw/day (male/female) based on no statistically significant effect reported. NOAEL (development): 75 mg/kg bw/day based on statistically significant decrease of litter size, viability (D0), survival (D4), weaning data in the second generation and decreased pup body weight at 150 mg/kg bw/day. The addition of calcium carbonate did not markedly differ from those obtained after administration of MeS alone.	Collins TFX *et al*. (1971) Gross MA, Fitzhugh OG (1977) Klimisch score : 3 Supporting study **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Two-generation study Rat (Wistar) male/female 25/sex/dose (F0); 30/sex/dose (F1) Oral: feed (no vehicle) Examination very limited Several deficiencies from OECD 416, not GLP	Methyl salicylate 0.25% and 0.5% (2500 ppm and 5000 ppm equivalent to 125 and 250 mg/kg bw MeS/day) (nominal in diet) Exposure: 60 days before the first mating and then throughout the experiment (weaning of the F2b litters).	No adequate NOAEL can be set based on the low quality of the reported results. Decreased litter size at all doses. Higher number of unsuccessful matings for the first generation and decreased reproduction index for both generations at the highest dose. Higher number of death between birth and day 5 day at 250 mg/kg bw/day.	Anonymous (1978a) Klimisch score : 3 Supporting study **(See Annex I for more details on the results)** **(See Annex II for justification of read-across)**
Two-generation study Mouse male/female (no data on strain); 25/sex/dose (F0); 30/sex/dose (F1) Oral: feed (no vehicle) Examination very	Methyl salicylate 0.25% and 0.5% (2500 ppm and 5000 ppm, equivalent to 375 and 750 mg/kg bw MeS/day) (nominal in diet) Exposure: 30 days before the first mating and then through the experiment (weaning of the pups).	No adequate NOAEL can be set based on the low quality of the reported results. Litter size slightly smaller in test groups only in the first generation.	Anonymous (1978b) Klimisch score : 3 Supporting study **(See Annex I for more details**

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
limited Several deficiencies from OECD 416, not GLP			**on the results)** **(See Annex II for justification of read-across)**
One-generation study Rat (Sprague-Dawley); male/female; 24-27 animals/dose Oral: feed (no vehicle) Guideline and GLP not stated – secondary literature	Methyl salicylate 4000 ppm and 6000 ppm equivalent to 200 and 300 mg/kg bw/day (nominal in diet) Exposure: 60 days before the first mating and then throughout the experiment (until weaning of offspring on day 20-21)	NOAEL (F1): 300 mg/kg bw/day (male/female) based on no effect. No abnormalities. Neonate survival at weaning was greater in the test group than in control.	FDA (1966) CIR (2003) Klimisch score : 4 Disregarded study **(See Annex II for justification of read-across)**

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

Animal data

According to the RAC Opinion dated on March 2016 for salicylic acid and the studies listed in the above table on this substance and sodium salicylate, there is robust evidence of developmental effects in rats following exposure to salicylic acid. Salicylic acid has embryo-/foetotoxic effect in rats with dose-dependent growth delays, foetal death and malformations. Early developmental effects were clearly seen in the absence of maternal effects.

According to the CLH report on methyl salicylate and the RAC opinion dated on September 2019 for this substance, there is clear evidence of developmental effects in two well-conducted studies in rats (FDA, 2006 c, d). Following subcutaneaous exposure to 200 mg/kg bw/day of methyl salicylate, several developmental effects were observed. FDA 2006d reported lethality, growth retardation, external malformation, delay in post-natal differentiation indices, skeletal anomalies, skeletal variations and delay of ossification at this concentration. FDA 2006c observed significant lower foetal body weight, external malformations, visceral anomalies and skeletal variations. Although maternal toxicity also occurred at 200 mg/kg bw/day in these two studies, the observed developmental effects were not considered to be secondary to this maternal toxicity. Additionally, developmental effects were reported in fertility studies in both mice and rats (Collins *et al*. 1971, Anonymous 1978a, 1978b, NTP 1984b).

Therefore, based on a read-across with salicylic acid and methyl salicylate, it can be concluded that hexyl salicylate is likely to induce similar developmental effects in animals.

Human data

No human data has been found with hexyl salicylate.

10.7.6 Comparison with the CLP criteria

Based on the developmental effects observed in animal studies with salicylic acid, sodium salicylate and methyl salicylate, hexyl salicylate is likely to induce adverse effects on development. Specifically based on the data about methyl salicylate, it is assumed that the developmental effects caused by hexyl salicylate would be considered not to be secondary to maternal toxicity if it may occur at similar concentrations. Thus, this information would justify classification in Category 1B.

Nevertheless, salicylic acid has been classified by RAC in Category 2 for developmental toxicity in March 2016. In a weight of evidence approach, the concluding choice of Category 2 (instead of 1B) was mainly based on the lack of robust evidence of birth defects in humans, in particular with another salicylate compound, aspirin (acetyl salicylic acid), despite clear teratogenicity in rats. Similar approach and conclusion were reached for the classification as Repr. 2 for methyl salicylate in the RAC (2019) opinion. The same concluding choice of Category 2 is considered relevant for hexyl salicylate.

"Neither ASA nor SA are proven human developmental toxicants. There is a lack of evidence to support an increased risk of birth defects following exposure to ASA. Also, the evidence for other developmental effects has uncertainties. Taking that into account, classification in Category 1A is not justified.

In the study of Wilson et al. (1977), when general embryotoxicity of rats and monkeys to ASA was compared at equivalent dosages, some differences were detected. According to the study author this difference in effects seen can be attributable to the differences in embryonic exposure; since the free (unbound) SA is responsible for the teratogenic potential and the binding capacity differs between species, the rat embryo is exposed to higher levels and for a longer duration than the monkey embryo.

In rats plasma concentrations of salicylate 20 minutes after oral administration of methyl-or acetylsalicylate at a dose of 500 mg/kg bw were 217 ± 16.1 mg/L (MeS) and 209 ± 18.6 (ASA) and 60 minutes after dosing salicylate concentrations of 278 ± 16.7 mg/L (MeS) and 274 ± 23.5(ASA) mg/L were measured (Davison et al., 1961) indicating a similar toxicokinetic behaviour of both esters in rats.

In humans, no malformations could be detected; based on the assumption of a similar teratogenic potency in all species, a hypothetical human threshold for malformations around of 200 mg/L of total salicylate in maternal serum was calculated.

RAC is of the view that, with MeS, the situation is similar to SA and it is a matter of consistency to classify the methylester of SA accordingly."

Therefore, based on the weight of the evidence, hexyl salicylate should be classified as Repr. 2; H361d (Suspected of damaging the unborn child).

10.7.7 Conclusion on classification and labelling for reproductive toxicity

Based on a read-across with salicylic acid and methyl salicylate, the same approach was undertaken for hexyl salicylate.

Therefore, considering the RAC opinions for these substances as Repr. 2 for development, hexyl salicylate should also be classified as Repr. 2 – H361d.

No classification is proposed for toxicity on fertility.

10.8 Specific target organ toxicity-single exposure

Not assessed in this report.

10.9 Specific target organ toxicity-repeated exposure

Not assessed in this report.

10.10 Aspiration hazard

Not assessed in this report.

11 EVALUATION O 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.

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15 ANNEXES

ANNEX I: confidential and non-confidential annex to the CLH report (separate document)

ANNEX II: non confidential annex: rationale for read-across (separate document)