baua:
Bundesanstalt für Arbeitsschutz
und Arbeitsmedizin
Federal Institute for Occupational
Safety and Health

Justification Document for the Selection of a CoRAP Substance

Substance Name (public name):	Benzyl salicylate
EC Number:	204-262-9
CAS Number:	118-58-1
Authority:	German CA
Date:	20/03/2018

Cover Note

This document has been prepared by the evaluating Member State given in the CoRAP update.

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1 IDENTITY OF THE SUBSTANCE

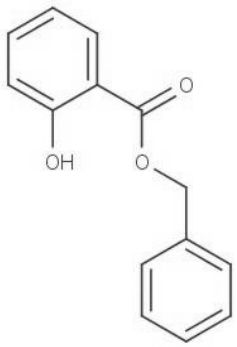
1.1 Other identifiers of the substance

Table: Other Substance identifiers

EC name (public):	Benzyl salicylate
IUPAC name (public):	Benzyl salicylate
Index number in Annex VI of the CLP Regulation:	N/A
Molecular formula:	$C_{14}H_{12}O_3$
Molecular weight or molecular weight range:	228.24 g/mol
Synonyms:	*2-hydroxybenzoic acid phenylmethyl ester* *Benzoic acid, 2-hydroxy-, phenylmethyl ester* *Benzyl 2-hydroxybenzoate* *Benzyl-2 hydroxibensoate* *Benzylsalicylat* *Phenylmethyl 2-hydroxybenzoate* *Salicylic acid, benzylester* *Benzyl o-hydroxybenzoate* *Phenylmethyl 2-hydroxybenzoate* *Salicylic acid, benzyl ester*

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



1.2 Similar substances/grouping possibilities

The group of salicylates (i.e. esters of 2-hydroxysalicylate as indicated below) can be considered as similar.

Structural formula:

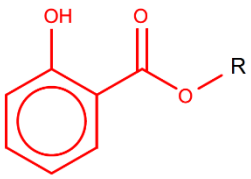
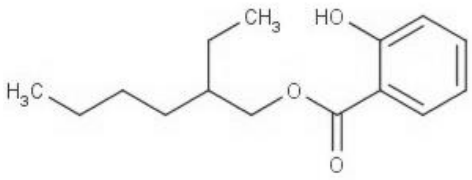


Table 2: Similar substance

EC number:	204-263-4
EC name (public):	2-ethylhexyl salicylate
CAS number:	118-60-5
IUPAC name (public):	2-ethylhexyl salicylate
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	$C_{15}H_{22}O_3$
Molecular weight or molecular weight range:	250.33 g/mol
Synonyms:	*2-ethylhexyl 2-hydroxybenzoate* *2-Ethylhexylsalicylate* *Ethylhexyl Salicylate* *p-menth-1-en-8-ol* *SOCT* *Sunobel® OS*

Structural formula:

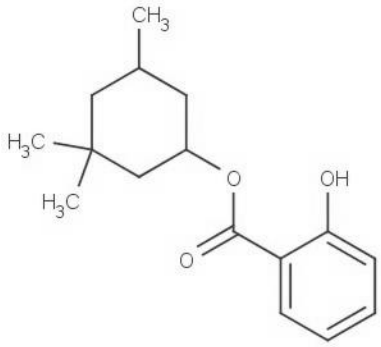


2-Ethylhexyl sailcylate is proposed for substance evaluation in parallel to benzyl salicylate due to their structural similarity.

Table 3: Similar substance

EC number:	204-260-8
EC name (public):	Homosalate
CAS number:	118-56-9
IUPAC name (public):	3,3,5-trimethylcyclohexyl salicylate
Index number in Annex VI of the CLP Regulation:	n.a.
Molecular formula:	$C_{16}H_{22}O_3$
Molecular weight or molecular weight range:	262,34 g/mol
Synonyms:	*(3,3,5-trimethylcyclohexyl) 2-hydroxybenzoate* *Homomenthylsalicylate* *Sunobel®HMS*

Structural formula:



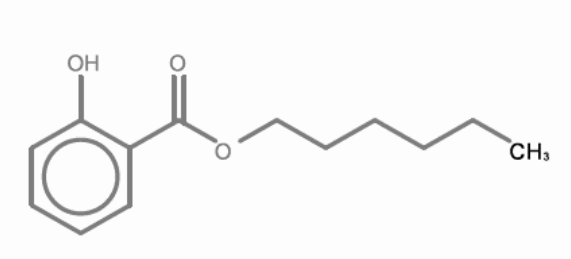
The substance has been included in the Public Activity Coordination Tool (PACT) due to an RMOA process initiated by France.[1]

[1] PACT section on homosalate: https://echa.europa.eu/de/addressing-chemicals-of-concern/substances-of-potential-concern/pact/-/substance-rev/12933/term?_viewsubstances_WAR_echarevsubstanceportlet_SEARCH_CRITERIA_EC_NUMBER=204-260-8

Table 4: Similar substance

EC number:	228-408-6
EC name (public):	hexyl salicylate
CAS number:	6259-76-3
IUPAC name (public):	hexyl salicylate
Index number in Annex VI of the CLP Regulation:	n.a.
Molecular formula:	$C_{13}H_{18}O_3$
Molecular weight or molecular weight range:	222.282 g/mol
Synonyms:	*Benzoic acid, 2-hydroxy-, hexyl ester* *Hexyl Salicylate* *Hexyl o-hydroxybenzoaten-Hexyl Salicylate*

Structural formula:



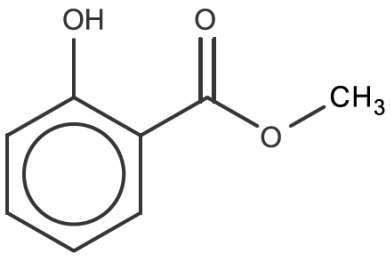
The substance has been subjected to REACH substance evaluation by the Netherlands in 2012.[2]

[2] CoRAP section on hexyl salicylate: https://echa.europa.eu/de/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1807e3d24

Table 5: Similar substance

EC number:	204-317-7
EC name (public):	methyl salicylate
CAS number:	119-36-8
IUPAC name (public):	methyl salicylate
Index number in Annex VI of the CLP Regulation:	n.a.
Molecular formula:	$C_8H_8O_3$
Molecular weight or molecular weight range:	152.1482 g/mol
Synonyms:	*methyl 2-hydroxybenzoate* *Methyl 2-hydroxybenzoate* *METHYL SALICYLATE* *methyl-2-hydroxybenzoate* *METHYL-SALICYLATE* *Metil szalicilát* *salicylic acid, methyl ester*

Structural formula:



The substance has been subjected to REACH substance evaluation by France in 2015.[3]

[3] CoRAP section on methyl salicylate: https://echa.europa.eu/de/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1807e9072

2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table: Completed or ongoing processes

RMOA	☐ Risk Management Option Analysis (RMOA)	
REACH Processes	Evaluation	☐ Compliance check, Final decision
		☒ Testing proposal
		☐ CoRAP and Substance Evaluation
	Authorisation	☐ Candidate List
		☐ Annex XIV
	Restric -tion	☐ Annex XVII[4]
Harmonised C&L	☐ Annex VI (CLP) (see section 3.1)	
Processes under other EU legislation	☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009	
	☐ Biocidal Product Regulation Regulation (EU) 528/2012 and amendments	
Previous legislation	☐ Dangerous substances Directive Directive 67/548/EEC (NONS)	
	☐ Existing Substances Regulation Regulation 793/93/EEC (RAR/RRS)	
(UNEP) Stockholm convention (POPs Protocol)	☐ Assessment	
	☐ In relevant Annex	
Other processes / EU legislation	☐ Other (provide further details below)	

[4] Please specify the relevant entry.

Further details	Substance listed in Annex III of substances which cosmetic products must not contain except subject to the restrictions laid down: The presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)(g) when its concentration exceeds 0.001 % in leave-on products and 0.01 % in rinse-off products. A compliance check is in progress for the substance. A decision on a testing proposal for short-term toxicity testing to terrestrial invertebrates has been finalised (Decision no. TPE-D-2114290448-39-01/F).[5]

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

There is no harmonised Classification for the substance in Annex VI.

3.1.2 Self classification

- In the registration:

Skin Sens. 1B	H317
Eye Irrit. 2B	H320
Aquatic Chronic 3	H412

- The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory:

Skin Irrit. 2	H315	
STOT SE 3	H335	(respiratory tract)
STOT SE 2	H371	(Spleen, Oral)
Aquatic Acute 1	H400	
Aquatic Chronic 1	H410	
Aquatic Chronic 2	H411	

Not classified

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

No Proposal for Harmonised Classification and Labeling has been submitted to the Registry of Intentions.

[5] Section on dossier evaluation decisions for benzyl salicylate: https://echa.europa.eu/de/information-on-chemicals/dossier-evaluation-decisions/-/dislist/substance/100.003.876

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[6]

4.1 Tonnage and registration status

Table: Tonnage and registration status

From ECHA dissemination site *		
☒ Full registration(s) (Art. 10)	☐ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☐ 1 – 10 tpa	☐ 10 – 100 tpa	☐ 100 – 1000 tpa
☒ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential

*****the total tonnage band has been calculated by excluding the intermediate uses, for details see the Manual for Dissemination and Confidentiality under REACH Regulation (section 2.6.11):

https://echa.europa.eu/documents/10162/22308542/manual_dissemination_en.pdf/7e0b87c2-2681-4380-8389-cd655569d9f0

4.2 Overview of uses

Part 1:

☒ Manufacture	☒ Formulation	☒ Industrial use	☒ Professional use	☒ Consumer use	☐ Article service life	☒ Closed system

Part 2:

[6] *Dissemination site accessed on 20 July 2017*

	Use(s)
Uses as intermediate	
Formulation	Manufacturing of fragrances substances Compounding (mixing of fragrances) Formulation of fragranced end-products
Uses at industrial sites	Manufacturing of the substance Industrial end-use of fragranced end-products
Uses by professional workers	Professional end-use of fragranced end-products
Consumer Uses	laundry and dish washing products, liquid cleaners (all-purpose cleaners, sanitary products, floor cleaners, glass cleaners and so on), air fresheners, furniture, floor and leather care products, repellents and insecticides.
Article service life	

Part 3: There is high potential for exposure of

☐ Humans	☒ Environment

5. JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE

5.1. Legal basis for the proposal

☒ Article 44(2) (refined prioritisation criteria for substance evaluation)

☐ Article 45(5) (Member State priority)

5.2. Selection criteria met (why the substance qualifies for being in CoRAP)

☐ Fulfils criteria as CMR/ Suspected CMR

☐ Fulfils criteria as Sensitiser/ Suspected sensitiser

☒ Fulfils criteria as potential endocrine disrupter

☐ Fulfils criteria as PBT/vPvB / Suspected PBT/vPvB

☒ Fulfils criteria high (aggregated) tonnage (*tpa > 1000*)

☒ Fulfils exposure criteria

☐ Fulfils MS's (national) priorities

5.3. Initial grounds for concern to be clarified under Substance Evaluation

Hazard based concerns		
CMR ☐ C ☐ M ☐ R	Suspected CMR[1] ☐ C ☐ M ☐ R	☒ Potential endocrine disruptor
☐ Sensitiser	☐ Suspected Sensitiser[7]	
☐ PBT/vPvB	☐ Suspected PBT/vPvB[1]	☐ Other (please specify below)
Exposure/risk based concerns		
☐ Wide dispersive use	☐ Consumer use	☐ Exposure of sensitive populations
☐ Exposure of environment	☐ Exposure of workers	☐ Cumulative exposure
☐ High RCR	☐ High (aggregated) tonnage	☐ Other (please specify below)

[7] CMR/Sensitiser: known carcinogenic and/or mutagenic and/or reprotoxic properties/known sensitising properties (according to CLP harmonized or registrant self-classification or CLP Inventory)
Suspected CMR/Suspected sensitiser: suspected carcinogenic and/or mutagenic and/or reprotoxic properties/suspected sensitising properties (not classified according to CLP harmonized or registrant self-classification)
Suspected PBT: Potentially Persistent, Bioaccumulative and Toxic

Kunz and Fent (2006) found weak estrogenic and strong anti-estrogenic and anti-androgenic effects using yeast assays expressing human estrogen receptor alpha or human androgen receptor, respectively. The antagonistic effects were stronger than that of the positive controls (flutamide and 4-hydroxytamoxifen). Miller et al. 2001 confirmed the weak estrogenic effects of benzyl salicylate using a recombinant yeast estrogen assay. Estrogenic responses in the breast cancer cell line MCF-7 were demonstrated by Charles and Darbre, 2009 (binding to the human estrogen receptor, induction of estrogen receptor mediated gene expression and stimulation of the proliferation of MCF-7 cells). In contrast, benzyl salicylate failed to stimulate the proliferation and to antagonize E2-induced proliferation in MCF-7 cells (Jiménez-Díaz et al. 2013). However, these results might be related to the low concentrations tested. Zhang et al. 2012 confirmed the *in vitro* estrogenic activity of benzyl salicylate which was higher than that of bisphenol A. Furthermore, they observed effects in rat and mouse uterotrophic assays almost in all concentrations tested.

Benzyl salicylate is structural related to other salicylates like homosalate or 2-ethylhexyl salicylate used in personal care products that also show *in vitro* endocrine properties.

5.4. Preliminary indication of information that may need to be requested to clarify the concern

☐ Information on toxicological properties	☐ Information on physico-chemical properties
☐ Information on fate and behaviour	☐ Information on exposure
☐ Information on ecotoxicological properties	☐ Information on uses
☒ Information ED potential	☐ Other (provide further details below)
Based on the preliminary evaluation of the data related to endocrine disrupting properties of benzyl salicylate, *in vitro* studies and chronic studies using aquatic vertebrate (e.g. fish sexual development test) could be requested to clarify the concern on the estrogenic effects in the environment. Additionally, a detailed evaluation of the available data may lead to further information requirements.	

5.5. Potential follow-up and link to risk management

☐ Harmonised C&L	☒ Restriction	☒ Authorisation	☒ Other (provide further details)
Depending on the outcome of the substance evaluation, an analysis of Risk Management Options shall be carried out to identify appropriate risk management measures. If the substance is to be considered an Endocrine Disruptor according to WHO/IPCS definition, SVHC identification and candidate listing might be the first steps that will be further analysed in a risk management option analysis.			

References

Charles AK & Darbre PD (2009): Oestrogenic activity of benzyl salicylate, benzyl benzoate and butylphenylmethylpropional (Lilial) in MCF7 human breast cancer cells in vitro. J Appl Toxicol 29 (5), 422-34.

Jimenez-Diaz I, Molina-Molina JM, Zafra-Gomez A, Ballesteros O, Navalon A, Real M, Saenz JM, Fernandez MF & Olea N (2013): Simultaneous determination of the UV-filters benzyl salicylate, phenyl salicylate, octyl salicylate, homosalate, 3-(4-methylbenzylidene) camphor and 3-benzylidene camphor in human placental tissue by LC-MS/MS. Assessment of their in vitro endocrine activity. J Chromatogr B Analyt Technol Biomed Life Sci 936, 80-7.

Kunz PY & Fent K (2006): Multiple hormonal activities of UV filters and comparison of in vivo and in vitro estrogenic activity of ethyl-4-aminobenzoate in fish. Aquatic Toxicology 79 (4), 305-24.

Miller D, Wheals BB, Beresford N & Sumpter JP (2001): Estrogenic activity of phenolic additives determined by an in vitro yeast bioassay. Environ Health Perspect 109 (2), 133-8.

Zhang Z, Jia C, Hu Y, Sun L, Jiao J, Zhao L, Zhu D, Li J, Tian Y, Bai H, Li R & Hu J (2012): The estrogenic potential of salicylate esters and their possible risks in foods and cosmetics. Toxicology Letters 209 (2), 146-53.