Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at EU level of

Benzyl salicylate

EC Number: 204-262-9
CAS Number: 118-58-1

CLH-O-0000001412-86-267/F

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

Adopted

15 March 2019

CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

Benzyl salicylate

EC Number: **204-262-9**

CAS Number: **118-58-1**

Index Number: **-**

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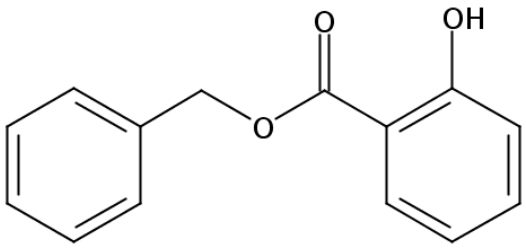
CONTENTS

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)	Benzyl salicylate
Other names (usual name, trade name, abbreviation)	Benzoic acid, 2-hydroxy-, phenylmethyl ester Benzyl 2-hydroxybenzoate 2-Hydroxybenzoic acid phenylmethyl ester
EC number (if available and appropriate)	204-262-9
EC name (if available and appropriate)	Benzyl salicylate
CAS number (if available)	118-58-1
Molecular formula	$C_{14}H_{12}O_3$
Structural formula	
SMILES notation (if available)	Oc1ccccc1C(=O)OCc2ccccc2
Molecular weight or molecular weight range	228.2 g mol^{-1}
Degree of purity (%) (if relevant for the entry in Annex VI)	100 %

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)**
Benzyl salicylate EC number 204-262-9 CAS number 118-58-1	-	n.a.	See section 4

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
None				

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 4: Current and proposed classification and labelling of benzyl salicylate

	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	-	-	-	-	-	-	-	-	-	-	-
Dossier submitters proposal	tbd	Benzyl salicylate	204-262-9	118-58-1	Skin Sens. 1B	H317	GHS07 Wng	H317	-	-	-
Resulting Annex VI entry if agreed by RAC and COM	tbd	Benzyl salicylate	204-262-9	118-58-1	Skin Sens. 1B	H317	GHS07 Wng	H317	-	-	-

Table 5: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier	No
Oxidising gases	Hazard class not assessed in this dossier	No
Gases under pressure	Hazard class not assessed in this dossier	No
Flammable liquids	Hazard class not assessed in this dossier	No
Flammable solids	Hazard class not assessed in this dossier	No
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not assessed in this dossier	No
Pyrophoric solids	Hazard class not assessed in this dossier	No
Self-heating substances	Hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not assessed in this dossier	No
Oxidising solids	Hazard class not assessed in this dossier	No
Organic peroxides	Hazard class not assessed in this dossier	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	Hazard class not assessed in this dossier	No
Acute toxicity via dermal route	Hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	Hazard class not assessed in this dossier	No
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	-	Yes
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity	Hazard class not assessed in this dossier	No
Reproductive toxicity	Hazard class not assessed in this dossier	No
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 currently no harmonised classification and labelling for benzyl salicylate.

RAC general comment
Benzyl salicylate is a widely used fragrance ingredient. It is found in many cosmetic products as well as in non-cosmetic products such as household cleaners and detergents. Benzyl salicylate has no existing entry in Annex VI of the CLP regulation. Benzyl salicylate is a well-recognized contact allergen in consumer products (SCCS, 2012) and is one of the 26 EU fragrance ingredients whose presence in cosmetic products has to be indicated on the label if present above 0.001% in leave-on products and 0.01% in rinse-off products according to the Cosmetics Products Regulation (CPR) (Regulation (EC) No 1223/2009, Annex III). These 26 allergens were added to Annex III of the Cosmetics Directive by the 7th amendment (2003/15/EC). It should be noted that the group of 26 fragrance allergens in Annex III is comprised of weak and strong sensitisers and therefore the generic labelling requirement indicated in the CPR (0.001% to 0.01%) is set to a level low enough to protect consumers from exposure to the most potent substances in that list. These 26 allergens are also subject to labelling if present at concentrations exceeding 0.01% in detergents according to Regulation (EC) No 648/2004.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

For benzyl salicylate, as of 21 November 2017, in total 1294 notifications to the C&L Inventory are reported on the ECHA website:

- 851 notifiers have self-classified benzyl salicylate as Skin Sens. 1B,
- 352 further notifiers have assigned a classification as Skin Sens. 1,
- while another 91 notifiers did not classify for skin sensitisation at all, and
- no notifier classified benzyl salicylate as Skin Sens. 1A.

Whereas the majority of C&L notifiers classified this substance as Skin Sens. 1B, self-classification by many other C&L notifiers is inconsistent, which therefore justifies a proposal for harmonised classification.

5 IDENTIFIED USES

5.1 Workers

Benzyl salicylate is used in the following products: air care products, biocides (e.g. disinfectants, pest control products), perfumes and fragrances, polishes and waxes, washing & cleaning products, welding & soldering products and cosmetics and personal care products.

Its main technical function is operating as an odour agent.

Inhalation and dermal exposure of workers to benzyl salicylate are anticipated under circumstances of industrial and professional use. Occupational exposure may arise during (i) the manufacturing, (ii) the use at industrial and institutional sites and (iii) widespread uses by professional workers (ECHA dissemination site;

accessed 15th Jan 2018).In a professional setting, the workers are likely to use one or a combination of products similar to those used by consumers on a daily basis (ECHA dissemination site).

Workers may be in direct contact with formulated products containing the substance during dosing and mixing the products with water. They may use them in liquid form with rollers, brushes, wipes or sprays or they may treat articles by dipping, pouring or immersion. The likely routes of exposure are dermal and inhalation.

The end-uses of fragranced end-products in an industrial and a professional work environment include for example:

- Dishwashing and rinsing products
- Laundry products (detergent, softener, aids (gassing, non-gassing)
- General purpose cleaner, sanitary cleaner, glass cleaner
- Kitchen cleaners
- Drain cleaners
- Surface disinfectant
- Floor strippers, carpet cleaners, floor cleaners, floor care products
- Vehicle cleaner (airplane, boat, car, train) and dewaxing products
- Facade/surface cleaners
- Wet wipes
- Oven/grill cleaner
- Descaling agent
- Maintenance products
- Medical devices

(ECHA dissemination site)

5.2 Consumers

Benzyl salicylate is mentioned in the EU Cosmetic Regulation EC No. 1223/2009, Annex III:

'This chemical may be used in cosmetics and personal care products, but 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.'

Benzyl salicylate is largely available to consumers for day-by-day use (e.g. Table 6). It is used as a component in fragrances, cosmetics, and personal care products, but it is also used as a UVB absorber and therefore prevalent in skin products, children's products, as well as lip products (Lapczynski et al., 2007; Wahie et al., 2007) while it is also used as a fragrance fixative in herbal marketed toiletries and cosmetic products (Alagappan et al., 2013). Thus, benzyl salicylate might be percutaneously absorbed over the entire body and/or on smaller localised skin sites due to the use of higher concentrated products, e.g. fine fragrances, cf. the Research Institute for Fragrance Materials (RIFM) Expert Panel's review (Belsito et al., 2007). In fragrances, benzyl salicylate has been detected up to levels of ca. 2 % (Sanchez-Prado et al., 2011) while the maximum skin exposure concentration to benzyl salicylate was ca. 7 % (e.g. due to the use of fine fragrances), as shown by Lapczynski et al., 2007. Overall, the calculated maximum daily exposure on the skin was 0.40 mg/kg body weight for high level users, as shown in the study of Lapczynski et al., 2007 (see Table 8).

Table 6: Calculation of the total human skin exposure from the use of multiple cosmetic products containing benzyl salicylate; taken from (Lapczynski et al., 2007)

Type of cosmetic product	Grams applied	Applications per day	Retention factor	Mixture/ product	Ingredient/ mixture[a]	Ingredient mg/kg/day[b]
Body lotion	8.00	0.71	1.000	0.004	15.79	0.0598
Face cream	0.80	2.00	1.000	0.003	15.79	0.0126
Eau de toilette	0.75	1.00	1.000	0.080	15.79	0.1579
Fragrance cream	5.00	0.29	1.000	0.040	15.79	0.1526
Antiperspirant	0.50	1.00	1.000	0.010	15.79	0.0132
Shampoo	8.00	1.00	0.010	0.005	15.79	0.0011
Bath products	17.00	0.29	0.001	0.020	15.79	0.0003
Shower gel	5.00	1.07	0.010	0.012	15.79	0.0017
Toilet soap	0.80	6.00	0.010	0.015	15.79	0.0019
Hair spray	5.00	2.00	0.010	0.005	15.79	0.0013
Total						**0.4023**

[a] Upper 97.5 percentile levels of the fragrance ingredient in the fragrance mixture used in these products.
[b] Based on a 60-kg adult.

Benzyl salicylate is included in the Council of Europe's list of substances granted ''B status'' (COE No. 436, i.e. substances requiring information, such as hydrolysis data). Nevertheless, benzyl salicylate is also naturally present in foods (Stofberg and Grundschober, 1987) and has been approved for use as a flavouring agent ("Generally Recognized as Safe" (GRAS) status by the Flavor and Extract Manufacturers' Association in the United States; Food and Drug Administration (FDA) in accordance with (21 CFR 172.515), for review see (Belsito et al., 2007)).

6 DATA SOURCES

Data for benzyl salicylate were taken from the publically disseminated REACH Registration Dossier (as of 21 November 2017), from summaries of reports on skin sensitisation made available by the Registrants in the REACH lead registration dossier, and from the results of a systematic literature screening.

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
Physical state at 20 °C and 101,3 kPa	Colourless to pale yellow liquid	REACH lead registration dossier 2016	Experimental
Melting/freezing point	24 °C (293 K)	Römpp online encyclopaedia	No further information
Boiling point	322 °C (595 K) at 1013 hPa	REACH lead registration dossier 2016	Measured according to EU A.2; EPA OPPTS 830.7220 and OECD 103 using the Siwoloboff method
Relative density	1.181 ± 0.001 at 20 °C	REACH lead registration dossier 2016	Measured according to EU A.3, EPA OPPTS 830.7300 and OECD 109 using the oscillating densimeter method
Vapour pressure	10.4 10^{-3} Pa at 25 °C	REACH lead registration dossier 2016	Measured by the gas saturated method similar, but not equivalent to OECD 104
Surface tension	69.0 mN m^{-1} at 20 °C	REACH lead registration dossier 2016	Measured by the ring method similar, but not equivalent to OECD 115 and EU A.5
Water solubility	8.8 mg L^{-1} at 20 °C	REACH lead registration dossier 2016	Measured according to OECD 105 using the column elution method
Partition coefficient n-octanol/water	Log P_{OW} = 4.0	REACH lead registration dossier 2016	Measured according to EU A.8 and OECD 117 using liquid chromatography
Flash point			

Property	Value	Reference	Comment (e.g. measured or estimated)
Flammability			
Explosive properties			
Self-ignition temperature			
Oxidising properties			
Granulometry	N.a. (substance is a liquid)		
Stability in organic solvents and identity of relevant degradation products	N.a. (stability in organic solvents is not considered to be critical)	REACH lead registration dossier 2016	
Dissociation constant	pK_a = 9.82 at 25 °C	REACH lead registration dossier 2016	pK_a was estimated using the SPARC software v.4.5
Viscosity	(17.0 ± 0.5) mm^2 s^{-1} at (20 ± 0.5) °C; (7.1 ± 0.5) mm^2 s^{-1} at (40 ± 0.5) °C	REACH lead registration dossier 2016	Measured according to OECD 114 and EPA OPPTS 830.7100 using the capillary viscometer

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this dossier

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not evaluated in this dossier which addresses skin sensitisation only. Induction of skin sensitisation takes place locally in the skin at the site of contact; therefore systemic availability of the hapten is not relevant. Proof of sensitisation after dermal contact also proves that a sufficient amount of hapten has been taken up.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

Not evaluated in this dossier

10.2 Acute toxicity - dermal route

Not evaluated in this dossier

10.3 Acute toxicity - inhalation route

Not evaluated in this dossier

10.4 Skin corrosion/irritation

Not evaluated in this dossier

10.5 Serious eye damage/eye irritation

Not evaluated in this dossier

10.6 Respiratory sensitisation

During the literature research, the Dossier Submitter (DS) did not identify studies positively demonstrating a potential of benzyl salicylate to cause respiratory sensitisation. Validated and accepted methods for the detection of respiratory sensitisation in animals are still lacking. Nevertheless there are non-validated tests

that have been used for that purpose, such as the "respiratory LLNA" test which gave a negative result for benzyl salicylate in a study performed by RIVM in 2014 (ter Burg et al., 2014).

10.7 Skin sensitisation

Benzyl salicylate is regarded as a "common cosmetic sensitiser and primary sensitiser" ((Nakayama, 1998), cited in (Belsito et al., 2007)). Prior to the 1970s, benzyl salicylate was one of the common causes of Pigmented Contact Dermatitis (PCD) in Japan. Major cosmetic companies reduced the use of benzyl salicylate in their products (i.e. in the late 1970s) and thus, the incidence of PCD decreased (de Groot and Frosch, 1997). Until today, benzyl salicylate has been reported to cause skin sensitisation in several animal and *in vitro* studies as well as in human reports.

10.7.1 Animal data

Table 8: 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, findings**	**Results**	**Reference**
Key study					
LLNA (OECD TG 429) GLP claimed (no certificate) Reliability 2 (reliable with restrictions), since only a IUCLID summary of this test was available to the DS Deviations regarding reporting of justification for the choice of vehicle and pre-tests	Mouse, CBA, female N = 4/group	Benzyl salicylate Purity: 99.8 % <u>Vehicle:</u> Ethanol/ diethyl-phthalate (1:3)	0-2.5-5.10-25-50 % EC3 = 2.9 % Quantity applied = 725 µg/cm^2	Positive Skin Sens. 1B	(Central Toxicology Laboratory, 2005)
Supporting studies					
Cumulative contact enhancement test (CCET) Non-guideline study (method of (Tsuchiya et al., 1982)) No GLP Reliability 2 (reliable with restrictions)	Guinea pig, Tortoise shell N = 10/treated group N = 5/control	Benzyl salicylate Vehicle: Ethanol	3 x Closed patch topical induction with 100 % benzyl salicylate + 1 x FCA intradermally before 3rd induction Challenge with 50 % benzyl salicylate % Incidence of allergic reaction 24 h after the last application (grades -/±/+/++): 37/20/33/10) % Incidence of animals with pigmentation on day 25 after the last application (grades -/±/+/++): 90/10/0/0)	Positive Not suitable for sub-categorisation Skin Sens. 1	(Imokawa and Kawai, 1987)
GPMT, modified FCA method	Guinea pig, Pirbright	Benzyl salicylate	Findings (no. of +++/++/+/(+)/-	Positive	(Hausen and Wollenweber,

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels, duration of exposure, findings	Results	Reference
Similar to OECD 406 Deviations: 3 x intradermal induction (days 1, 5, and 9) instead of 1 intradermal and 1 topical induction; receiving in total 4.5 mg of the substance Study reliability 2 (reliable with restrictions)	White, female N=10/group	Vehicle for topical challenge: acetone	reactions) At 1 % induction concentration: 24 h: 0/5/2/3/0 48 h: 0/5/2/3/0 72 h: 1/3/2/2/2 At 0.1 % induction concentration: 24 h: 0/5/1/2/2 48 h: 0/2/2/4/2 72 h: 1/3/2/2/2	Not suitable for sub-categorisation Skin Sens. 1	1988)
Modified maximisation test in guinea-pigs Non-guideline study, induction protocol different from OECD 406 No GLP Reliability 2 (reliable with restrictions)	Guinea pigs, Pirbright White, males and females N = 5 per sex and group	Benzyl salicylate Vehicle: FCA (i. d. induction), petrolatum (topical challenge)	Induction: 30 % First and second challenge 10 % 40-50/100 % of the animals showed a positive response upon the first/second challenge	Positive Not suitable for sub-categorisation Skin Sens. 1	(Maurer and Hess, 1989)
GPMT Similar to OECD 406 No GLP Reliability 2 (reliable with restrictions)	Guinea pig, Hartley albino, female N = 10/group	Benzyl salicylate Vehicle: Liquid paraffin (for i.d. induction)/ Ethanol (for topical challenge)	Induction: 10 % for intradermal, 30 % topical Challenge: 0.003-0.01-0.03 % First/second challenge: Up to 30% sensitised already at 0.003 %	Positive Skin Sens. 1B	(Kashima et al., 1993b)
The enhancement effect of cyclophosphamide (CY) on delayed contact hypersensitivity ("CAP2 test") Non-guideline study No GLP Reliability 2 (reliable with restrictions)	Guinea pig, Hartley albino, sex not mentioned N=10/treated group N=5/untreated group	Benzyl salicylate	Induction concentration: 30% Sensitisation rates between 90 and 100 % (1^{st} challenge), 10-90 % (2^{nd} challenge), and 40-90 % (3^{rd} challenge) were achieved	Positive Not suitable for sub-categorisation	(Kashima et al., 1993a)

In an OECD TG 429-conform LLNA test, an EC3 of 2.9 % was found which is above, but close to, the border of 2 % between sub-categories 1A and 1B as specified in the CLP regulation (Table 3.4.3/3.4.4). A confidence interval for this value was not provided in the IUCLID summary available to the DS, therefore it is unknown whether the value of 2.9 % represents the mean or the lower bound estimate. Also keeping in mind the variability of LLNA results (Dumont et al., 2016), these test results suggest classification of benzyl salicylate as a moderate sensitiser of sub-category 1B, but borderline to sub-category 1A. This study is considered the key animal study for classification (Central Toxicology Laboratory, 2005).

In addition, five supporting maximisation tests in guinea pigs were available which all demonstrated the potential of benzyl salicylate to cause skin sensitisation. Four of the five tests (Hausen and Wollenweber, 1988; Imokawa and Kawai, 1987; Kashima et al., 1993a; Maurer and Hess, 1989), however, deviated from the typical GPMT induction design (as per OECD TG 406) to a degree that the boundaries set for sub-categorisation in the CLP regulation could not be applied. As a consequence, these studies are supporting classification as Skin Sens. 1 in general, but not sub-categorisation. In another study by Kashima and co-workers, however, an acceptable induction and challenge design resulted in a sensitisation rate of up to 30 % with challenge doses as low as 0.003 %, which supports classification as Skin Sens. 1B – but cannot rule out sub-category 1A – due to the absence of an experiment with an intradermal induction dose of ≤ 0.1 % (Kashima et al., 1993b).

Detailed summaries of all of these studies can be found in Annex I to this dossier. Part of the above as well as a number of other studies in animals have been summarised in reviews by (Belsito et al., 2007) and (Lapczynski et al., 2007), cf. Table 9.

Table 9: Summary of animal sensitisation studies performed with benzyl salicylate as reported by (Belsito et al., 2007) and (Lapczynski et al., 2007)

Study no.	Method	Concentration	Subjects	Results	References*
1	OET (Open Epicutan-eous Test)	Induction and challenge: 30 % (vehicle not specified)	Guinea pigs (≥ 6 animals)	No reactions	(Klecak, 1985)
2	OET	Induction and challenge: 10 % (vehicle not specified)	Guinea pigs (6–8 males and females)	No reactions	(Klecak, 1979)
3	OET	Induction and challenge: 0.03–100 % (vehicle not specified)	Himalayan white spotted guinea pigs (6–8 males and females)	Minimum con-centration (%): Induction: 30 % Elicitation: 0.03 %:	(Klecak et al., 1977)
4	Cumulative contact enhancement test (CCET)	Induction: 30 % in ethanol topically Challenge: 1 %, 3 %, or 10 % topically	Hartley albino guinea pigs (10 females/ group)	Sensitisation observed	(Kashima et al., 1993), cf. Table 8)
5	CCET	Induction: 3 %, 10 %, 30 % and 100 % topically Challenge: concentration not specified, topically under occlusive patch; also intradermal injection with FCA	Pirbright and Hartley guinea pigs (6–10 of each strain/ group)	Reactions: 10 %: - 30 %: 3/6 Pirbright 100 %: 1/10 Hartley	(Tsuchiya et al., 1982)
6	CCET	Induction: 100 % topically under occlusive patch; also intradermal injection with FCA Challenge: 50 % topically under occlusive patch	Tortoise shell guinea pigs (10, sex not specified)	Sensitisation observed	(Imokawa and Kawai, 1987) cf. Table 8
7	CET	Induction: 30 % (vehicle not specified) Challenge: 1 % (vehicle not specified)	Guinea pigs (20, sex not specified)	Sensitisation observed in 3/20	(Ishihara et al., 1986)
8	Modified Draize test	Induction and challenge: 0.1 % by intradermal	Himalayan whitespotted	No reactions	(Klecak et al. 1977)

Study no.	Method	Concentration	Subjects	Results	References*
		injection in isotonic saline	guinea pigs (6–8 males and females)		
9	Modified Draize test	Intradermal induction: 1.25 % (vehicle not specified) Intradermal challenge: 0.5 % Topical Challenge: 2 % (vehicle not specified)	Hartley albino guinea pigs (4 or 6 of each sex, 10 total)	No reactions	(Sharp, 1978)
10	Guinea pig maximization test	Intradermal induction: 10 % in FCA Topical induction: 10 % in acetone Topical Challenge: 5 %, 10 %, or 20 % in acetone	Albino Dunkin–Hartley guinea pigs (8 females)	Sensitisation observed	(RIFM, 1997c)
11	Guinea pig maximization test	Intradermal induction: 10 % in FCA; Topical induction: 50 % (vehicle not reported) Topical Challenge: 5 %, 10 %, or 20 % (vehicle not reported)	Hartley guinea pigs (20 females/group)	Sensitisation in 2/20 at 20 % questionable reactions observed in 3/20 at 5 %, 5/20 at 10 %, and 4/20 at 20 %	(Kozuka et al., 1996)
12	Guinea pig maximization test	Intradermal induction: 10% in liquid paraffin Topical induction: 30 % in ethanol Topical Challenge: 0.003 %, 0.01 %, or 0.03 % in ethanol	Hartley guinea pigs (10 females/group)	Sensitisation observed	(Kashima et al., 1993), cf. Table 8)
13	Guinea pig maximization test	Intradermal induction: 5 % in FCA Topical induction: 25 % in petrolatum Topical Challenge: sub-irritant concentration (< 0.1 %) in petrolatum	Male and female Himalayan guinea pigs (numbers not specified)	No reactions	(Klecak et al., 1977)
14	Guinea pig maximization test	Intradermal induction: 1 % (vehicle not specified) Topical induction: 100 % Topical Challenge: 100 %	Hartley guinea pigs (10/group)	No reactions	(Tsuchiya et al., 1982)
15	Guinea pig maximization test	Induction and challenge: 10 % (no further details provided)	Guinea pigs (sex and number not specified)	Sensitisation observed	(Ishihara et al., 1986)
16	Sensitisation evaluated as part of a photoallergy study	Induction: 10 % in ethanol Challenge: 10 % in ethanol	Dunkin–Hartley guinea pigs (25/group)	No reactions	(RIFM, 1983b)
17	FCAT	Induction: 50 % in FCA by intradermal injection Topical challenge: < 0.1 % (vehicle not specified)	Himalayan whitespotted guinea pigs (6–8 males and females)	No reactions	(Klecak et al., 1977)

Study no.	Method	Concentration	Subjects	Results	References*
18	Modified FCAT	Induction: 10 % in FCA by intradermal injection Challenge: 10 % in acetone	Pirbright guinea pigs (10)	Sensitisation observed	(Hausen and Wollenweber, 1988), cf. Table 8)
19	Optimisation test	Intradermal induction: 1 % in saline Intradermal challenge: 0.1 % in saline Topical challenge: 10 % in petrolatum	Pirbright guinea pigs (10/sex)	Sensitisation observed in 1/20 after intradermal challenge and in 7/20 after topical challenge	(Maurer et al., 1980), cf. Table 8)
20	Delayed contact hypersensi-tivity assay using the AP2 test method	Induction: 30 % in ethanol Challenge: 1 %, 3 %, or 10 % in ethanol	10 Female Hartley guinea pigs	Sensitisation observed at all dose levels	(Kashima et al., 1993) , cf. Table 8)
21	LLNA	10 % in 4:1 acetone:olive oil	4 Female CBA/JN mice/group	EC3 %: 1.5 **Erroneous reporting****	(Yoshida et al., 2000)
22	LLNA	2.5 %, 5.0 %, 10 %, 25 %, and 50 % in 3:1 DEP:ethanol	4 Female CBA/Ca mice/group	EC3%: 2.9	(RIFM, 2005)

* Full references can be accessed from the original publication; ** In the original reference (SOT conference abstract), neither benzyl salicylate, nor the numbers reported by (Belsito et al., 2007) and (Lapczynski et al., 2007) are mentioned.

These reviews are reported in more detail in Annex I as well. In general, the results of the reported tests are in line with those in Table 8 in that they confirm the potential of benzyl salicylate to cause skin sensitisation. However, due to the fact that in none of them intradermal induction concentrations ≤ 0.1 % were used, they are principally unsuited to distinguish between sub-categories 1A and 1B.

10.7.2 Human data

A comprehensive human data base is available for benzyl salicylate (cf. Table 10), mostly reporting patch test results in individual dermatitis patients or retrospective analyses of hospital statistics regarding the number of dermatitis patients sensitised to benzyl salicylate vs. all tested patients over a certain time-window. Also a number of case reports were found. While the frequency is often "high" in terms of section 3.4.2.2.3.1 of the Guidance on the Application of the CLP Criteria (ECHA, 2017) (i.e., ≥ 1.0 % for unselected/consecutive dermatitis patients or ≥ 2.0 % for selected dermatitis patients) these data as a rule do not allow for a reliable estimate of the level of exposure which for most patients must be assumed as "relatively high" (again referring to (ECHA, 2017), section 3.4.2.2.3.1), given the ubiquitous presence of benzyl salicylate in a broad range of cosmetic products.

More specifically, and with respect to Table 3.3 of (ECHA, 2017), frequency of exposure can be assumed to be ≥ once/daily (score 2) and the total number of exposures can be estimated to exceed 100 (score 2), whereas the range of concentrations in those products is unknown (which would merit an intermediate score between 0 and 2, i.e. 1), resulting in an overall score of 5. As a result, Table 3.4 in (ECHA, 2017) recommends to assign classification as "Skin Sens. 1", i.e. without sub-categorisation.

In summary, the available data mostly confirm the potential of benzyl salicylate to cause skin sensitisation in humans, whereas they do not allow for sub-categorisation with respect to potency. However, it is noted that several of the authors cited in Table 10 rate benzyl salicylate as a sensitiser of comparatively moderate or lower potency, while no assessment to the opposite (i.e. claiming that the substance was a sensitiser of high potency) was found.

Table 10: Summary table of human data on skin sensitisation. Only studies have been considered for which at least an abstract in German or English was available.

Type of data/report	**Relevant information about the study (as applicable)**	**Observations**	**Resulting classification***	**Reference**
Allergy to perfumes from toilet soaps and detergents in patients with dermatitis Study reliability 4 (not assignable)	Patients (1,943, consecutive) with dermatitis have been examined with regard to sensitivity to perfumes from toilet soaps and detergents. Out of 78 patients, exactly 4% of each sex, showed positive reactions to perfumes and in three fourths of these cases, the reaction was found to be associated with sensitivity to benzyl salicylate. Of the perfume-positive patients, 64% had dermatitis of the extremities which are habitually most exposed to soap and water. Only abstract available	75 % of patients sensitive to perfumes from toilet soaps and detergents: sensitivity could be associated to benzyl salicylate	Positive High frequency, unclear exposure Skin Sens. 1	(Rothenborg and Hjorth, 1968)
Intensified contact sensitisation to benzyl salicylate. Study Reliability 4 (not assignable)	15 patients who applied a trioxsalen lotion: benzyl salicylate caused severe pruritus in six of patients; delayed hypersensitivity to benzyl salicylate was enhanced by the phototoxic effects of methoxsalen. In 14 control patients one reacted to benzyl salicylate. Only abstract available	6/15 patients with severe pruritus after benzyl salicylate In control: 1/14 reacted to benzyl salicylate.	Unclear influence of methoxsalen Not suitable for classification	(Kahn, 1971)
Contact allergy to an optical whitener, "CPY", in washing powders. Study Reliability 2 (reliable with restrictions)	In 16 months contact dermatitis from an optical whitener, Tinopal CH 3566, was diagnosed in 167 patients at the Finsen Institute. The dermatitis presented as textile dermatitis.	Positive reaction to 5% benzyl salicylate in soft paraffin in 16 /88 patients (18.18 %)	Positive High frequency, unclear exposure Skin Sens. 1	(Osmundsen and Alani, 1971)

Type of data/report	Relevant information about the study (as applicable)	Observations	Resulting classification*	Reference
Monographs on fragrance raw materials: Benzyl salicylate Observation Experimental conditions are not clearly described Low number of volunteers used for testing Reliability 3 (not reliable)	Several studies are described that resulted in: 1. No sensitisation reactions (in MAX test with 25 volunteers) 2. Causative agent in patients with dermatitis produced by Peru balsam 3. Cause severe pruritus	1. A maximisation test was carried out on 25 volunteers, tested at a concentration of 30 % in petrolatum and produced positive reactions in (0/25) 2. Hypersensitivity or excessive use may cause skin to blister, leading to an increase in pigmentation 3. Reactivity to benzyl salicylate was enhanced by the phototoxic effects of methoxsalen (positive effects in 6/15; 1 /14 of control patients reacted to the benzyl salicylate	Not reliable, not suitable for classification	(Opdyke, 1973)
Cases of contact dermatitis related to cosmetics Conference paper Reliability 4 (not assignable)	Nine dermatologists of the North American Contact Dermatitis Group submitted all of their cases of contact dermatitis related to cosmetics to the F.D.A. From November 15, 1976, to November 15, 1977, 111 cases were submitted of which 87 were confirmed through testing procedures; 24 were not confirmed. The total number of contact dermatitis cases seen by that group in the period was 2,171 while 4 % of all contact dermatitis cases seen were proven to be of cosmetic origin.	Frequency of contact dermatitis cases by confirmed related ingredient (1976-1977) benzyl salicylate = **2/87 (2.35 %)**	Positive High frequency, unclear exposure Skin Sens. 1	(Suskind, 1979)
Studies on the incidence of positive reactions in patch tests. Study reliability 4 (not assignable)	Results of patch tests performed from September 1973 to December 1980 were recorded over 500 patients with contact dermatitis were selected. Only abstract available, manuscript in Japanese	Benzyl salicylate (5 %; 2 %) was found positive in 62/987 (6.3 %) contact dermatitis patients	Positive High frequency, unclear exposure Skin Sens. 1	(Yamamoto et al., 1981)
Seven cases with melanosis faciei feminae December 1981 to November 1982. Study reliability 4 (not assignable)	5 cases with melanosis faciei feminae out of the 7 cases were patch tested with the cosmetics which they had used and 137 allergens which were thought to be contained in these cosmetics. Positive reactions to benzyl salicylate were recorded. Only abstract available, manuscript in Japanese	Patch test positive perfumes in melanosis faciei feminae benzyl salicylate (5 %) in Petrolatum= total of 25 cases 10/1977; 0/1978; 6/1979; 4/1980; 3/1981; 2/1982	Positive High frequency, unclear exposure Skin Sens. 1	(Hayakawa et al., 1983)

Type of data/report	Relevant information about the study (as applicable)	Observations	Resulting classification*	Reference
Human study survey of consumer patch-test sensitisation Study reliability 3 (not reliable with respect to tests using benzyl salicylate alone)	Results obtained from fragrance and formulator companies for a total of 10,538 patch tests with benzyl salicylate alone (35 tests only), with a variety of household and personal care consumer products and with fragrance blends containing benzyl salicylate were analysed as part of this survey. The highest concentration of benzyl salicylate tested in the consumer product tests was 0.02 %, and benzyl salicylate alone was tested at 10 % in ethanol (claimed in the abstract, no details in the report).	No induced or elicited responses directly attributable to benzyl salicylate were observed in - the 35 patch tests with benzyl salicylate alone or in - the 10,503 patch tests with consumer products or fragrance blends containing benzyl salicylate. The authors conclude that benzyl salicylate has a very low potential to induce hypersensitivity ('induced' reactions) or to elicit reactions presumably attributable to pre-existing sensitisation ('elicited' reactions)	Negative, but unreliable, as details are only reported for products/blends, not for the 35 tests with benzyl salicylate claimed to have been negative at a test concentration of 10 %	(Kohrman et al., 1983)
Results of patch tests with cosmetic ingredients conducted between 1979 and 1982 Study reliability 4 (not assignable)	The results of patch test raw fragrance materials are shown in eczema and dermatitis patients. Patch test results using fragrance materials were compared with related human and guinea pig sensitisation tests. It is suspected that not only sensitisation potency but also other factors, in particular the frequency of use of the chemicals, exert a great influence on the patch test results. Positive Frequency of allergic reactions (1978-1982) benzyl salicylate (5 %) was 4.6 % representing 24 positive reactions out of 522 patients' eczema and dermatitis. Only abstract available, manuscript in Japanese.	Positive frequency of allergic reactions (1978-1982) for 5 % benzyl salicylate: Cosmetic dermatitis 3.8 % (8/212); facial melanosis 20 % (7/35); 3.3% (9/275); 4.6 % (24/522); control 1 % (1/101). Cross-reaction between benzyl salicylate, benzyl acetate & benzyl alcohol: - 5 % benzyl salicylate vs. 5 % benzyl acetate: Positive 5/ positive 5; Positive 42/negative 26; negative 7/positive 2; - 5 % benzyl salicylate vs. 5 % benzyl alcohol: Positive 4/ positive 1; Positive 29/negative 18; negative 8/positive 2.	High frequency, unclear exposure Skin Sens. 1	(Ishihara et al., 1984)
Patch test in patients with various facial dermatoses Study reliability 2 (reliable with restrictions)	Fragrance materials were patch-tested in patients with various facial dermatoses. Study from 1976 to 1981 on suitable concentrations of various fragrance materials. 48 h closed-patch tests were performed using Al-tests or Torii-ban (a domestic product) in 1976, Al-tests, Torii-ban or Finn-chamber in 1977 and only Finn-chamber thereafter. Reactions were read approx. 1 h after the removal of the test material/48 h. after application) and 72 h after application. The ICDRG scoring standard was used: any reactions stronger than + by ICDRG reading were counted. Reactions at 72 h which were rated equal to or stronger than those at 48 h were assumed to be allergic reactions, while the reverse were deemed irritant reactions.	394 subjects were patch-tested with benzyl salicylate after 2 % benzyl salicylate was determined as the optimal concentration for testing Reactions: - 1 % in petrolatum: allergic 0 %/irritant 0.8 % - 5 % in petrolatum: allergic 5.8 %/ irritant 4.8 % - 2 % in petrolatum: allergic **2.3 %**/irritant 3.3 %	Positive High frequency, unclear exposure Skin Sens. 1	(Mid-Japan Contact Dermatitis Research Group, 1984)

Type of data/report	Relevant information about the study (as applicable)	Observations	Resulting classification*	Reference
Age and sex distribution of the incidence of contact sensitivity to representative fragrance materials Study reliability 4 (not assignable)	Incidence of contact sensitivity to benzyl salicylate was investigated based on cumulative data of patch test results over 10 years. Only abstract available, manuscript in Japanese	The incidence of contact sensitivity to benzyl salicylate was significantly higher in women than in men ($p < 0.01$). Incidence of contact sensitivity to benzyl salicylate in each age stratum is found to be higher with the increase of decades in women.	Not suitable for classification	(Sugai et al., 1984).
The incidence of positive reactions to cosmetic ingredients in patch tests Study reliability 4 (not assignable)	The incidence of positive reactions to the "worst 20 ingredients of cosmetic and toiletry products" in patch tests from September, 1983 to August, 1984. Positive reactions to benzyl salicylate dropped markedly. Only abstract available, manuscript in Japanese.	Positive reactions to benzyl salicylate were 6/316; (1.9 %). Unclear whether the study was performed in selected or continuous patients.	Positive Frequency could be relatively high or low, depending on the nature of the examined patients, unclear exposure Skin Sens. 1	(Asoh and Sugai, 1985)
Cases with melanosis/pigmented contact dermatitis showing reaction to 2 % benzyl salicylate Study reliability 4 (not assignable)	18 cases with melanosis (pigmented contact dermatitis showing "incontinentia pigmenti") 14 cases were friction melanosis due to repeated mechanical stimulation, one case was occupational pigmented cutting oil dermatitis and 3 cases were pigmented cosmetic contact dermatitis. Only abstract available, manuscript in Japanese	Patch tests were carried out in 2 cases with pigmented cosmetic contact dermatitis which reacted to 2 % benzyl salicylate	Not suitable for classification	(Hosokawa et al., 1985)
Incidence of cases testing positive to 2 % benzyl salicylate among out-patients with Riehl's melanosis Study reliability 4 (not assignable)	Evaluation of the results of positive patch tests and incidence of positive cases to 2 % benzyl salicylate among out-patients with Riehl's melanosis Mid-Japan Contact Dermatitis Research Group Only abstract available, manuscript in Japanese	2 cases with Riehl's melanosis showed positive reactions to 2 % benzyl salicylate.	Positive Low frequency, unclear exposure, low number of cases Skin Sens. 1	(Mid-Japan Contact Dermatitis Research Group, 1985)

<table>
<tr><th>Type of data/report</th><th>Relevant information about the study (as applicable)</th><th>Observations</th><th>Resulting classification*</th><th>Reference</th></tr>
<tr><td>Human study (three patient cases)

Study reliability 2 (reliable with restrictions)</td><td>Three cases of patients where reaction to propolis or poplar buds was detected (case history/positive epicutaneous tests) were included in the standard series.</td><td><u>Patient testing (3 cases):</u> no reaction to benzyl salicylate 1 % pet. (0/3)<table><tr><td></td><td>24 h</td><td>48 h</td></tr><tr><td>Patient no. 1</td><td>nt</td><td>nt</td></tr><tr><td>Patient no. 2</td><td>0</td><td>0</td></tr><tr><td>Patient no. 3</td><td>0</td><td>0</td></tr></table></td><td>Negative, but low number of patients, previous exposure not established

Not suitable for classification</td><td>(Hausen and Wollenweber, 1988)</td></tr>
<tr><td>Case Report
Short communication

Study reliability 2 (reliable with restrictions)</td><td>A 28-year-old metal grinder developed an itchy, patchy rash of the finger webs and dorsa of the hands, which spread to the arms, face, thighs and feet upon introduction of a new cutting oil. Rash resolved after treatment with systemic steroids and avoiding work. 2 days after returning to work, the rash recurred. He again stopped work and the rash cleared. After stopping the use of the new cutting oil the rash has remained clear.</td><td>The patient was tested against a fragrance and flavours battery, benzoic acid, and the ingredients of the reodorant provided by the manufacturer. He reacted to a number of fragrances including benzyl salicylate 1 % in petrolatum as follows: 48 h ± (faint); 96h ± (faint).</td><td>Positive, but not suitable for classification</td><td>(Mitchell and Beck, 1988)</td></tr>
<tr><td>Annual changes of allergic reactions in patch tests with fragrance materials

Study reliability 4 (not assignable)</td><td>Results of patch testing with cosmetic ingredients as well as cosmetic and toiletry products which patients brought are described. Annual changes of allergic reactions in patch tests with fragrance materials are shown.

Only abstract available, paper in Japanese</td><td>Patch tests with benzyl salicylate, positive responses:

1974-1981
77/1255 (6.1 %)
1982-1987
42/1851 (2.3 %)
1988-1993
23(3)/1356 (1.7 %)
1994-1997
10/1000 (1.0 %)</td><td>Positive

High frequency, unclear exposure

Skin Sens. 1</td><td>(Sugai, 1998)</td></tr>
<tr><td>Retrospective European survey of allergic contact reactions to cosmetics

Study reliability 2 (reliable with restrictions)</td><td>Data on 475 patients with contact allergy to cosmetic ingredients, observed during a 4-month period (January–April 1996), were collected in 5 European dermatology centres (1 BE, 2 UK, 2 DE)</td><td>During the time window investigated, one case from Germany with a positive reaction to benzyl salicylate was reported</td><td>Positive

Low frequency, but very short time window

Not suitable for classification</td><td>(Goossens et al., 1999)</td></tr>
</table>

Type of data/report	Relevant information about the study (as applicable)	Observations	Resulting classification*	Reference
Allergic contact dermatitis from propolis Study reliability 4 (not assignable)	Only abstract available	Benzyl salicylate is less frequently a sensitiser than 3-methyl-2-butenyl caffeate and phenylethyl caffeate	Positive Not suitable for classification	(Walgrave et al., 2005)
Review Article on sensitisation to fragrances Study reliability 2 (reliable with restrictions)	To study the frequency of sensitisation to fragrances to be labelled according to current European regulation. During 4 periods of 6 months, from 1 January 2003 to 31 December 2004, fragrances were patch-tested additionally to the standard series in a total of 21,325 patients; the number of patients tested with each of the fragrances ranged from 1658 to 4238. Reaction pattern (irr: irritant; f: follicular; ?: doubtful)	Findings for 1 % benzyl salicylate: 2/2041 (0.1%) patients with a positive reaction	Positive Low frequency, unclear exposure Skin Sens. 1	(Schnuch et al., 2007)
Contact allergy to the 26 specific fragrance ingredients to be declared on cosmetic products in accordance with the EU Cosmetics Directive Clinical study Study reliability 2 (reliable with restrictions)	This was a retrospective study based on data from the Department of Dermato-Allergology, Copenhagen University Hospital Gentofte. Eczema patients (n = 1508) were patch tested (January 2008 to July 2010) with the 26 fragrance ingredients; all eczema patients suspected of having contact allergy were tested consecutively. Responses were categorized in terms of the following categories: Positive: +++/+++/+ Doubtful: +? Irritant reactions: IR	Results for benzyl salicylate (1% in petrolatum, N = 1503): Positive: 3 (all +) = 0.2% Doubtful: 5 = 0.3% Irritant: 2 = 0.1%	Positive Low frequency, unclear exposure Skin Sens. 1	(Heisterberg et al., 2011)
Patch test concentrations (doses in mg/cm^2) for the 12 non-mix fragrance substances regulated by European legislation. Study reliability 2 (reliable with restrictions)	To establish the optimal patch test doses in mg/cm^2 for the 12 fragrance substances that are not included in fragrance mix I or II in the European baseline patch test series; performed in a stepwise manner encompassing up to five rounds in at least 100 consecutive dermatitis patients for each round.	Results for 5/7.5/12/18/30% benzyl salicylate in petrolatum: Positive: 0/0/0/1/3 Doubtful: 1/0/1/0/5 N= 108/103/110/106/114	Positive High frequency, unclear exposure Skin Sens. 1	(Bruze et al., 2012)

Type of data/report	Relevant information about the study (as applicable)	Observations	Resulting classification*	Reference
Case report Short communication Study reliability 2 (reliable with restrictions)	A 74-year-old woman with no personal or family history of atopy presented with a 2-month history of worsening non-pruritic pigmented patches over the face. She had started using a new brand of commercial face wash (a priori: 2 months) to the usual toiletries and make-up. She displayed hyper-pigmented patches, distributed symmetric over her forehead and cheeks with relative sparing of the nose. Differential diagnoses considered included pigmented contact dermatitis and melasma. Patch tests were performed with department's standard series, cosmetic series and the patient's own products. Patches were removed from the back after day 2 and readings were performed on day 3, according to the International Contact Dermatitis Research Group guidelines.	**P**ositive reactions to benzyl salicylate (+) and own face wash (+) that contained benzyl salicylate.	Positive Not suitable for classification	(Alagappan et al., 2013)
Case report Patch testing and histopathology in Thai patients with hyperpigmentation due to Erythema dyschromicum perstans, lichen planus pigmentosus, and pigmented contact dermatitis Study reliability 2 (reliable with restrictions)	To determine differences in the natural history, clinical features, histopathology and relevant contact allergens in patients those were clinically diagnosed as AD, LPP and PCD (Erythema dyschromicum perstans (EDP)/Ashy dermatosis (AD), Lichen planus pigmentosus (LPP) and Pigmented contact dermatitis (PCD)). 43 patients were enrolled in the study. Patients' demographic details, histological findings, DIF staining, provisional and histology diagnosis were recorded. Closed patch tests with standard fragrance and cosmetic series allergens were performed in all patients. 36 of the patients were female and all of them had dark skin complexion (Fitzpatrick's skin type IV-V).	Allergens in the fragrance series with positive patch test results: Benzyl salicylate: 1/43 (2.32 %)	Positive High frequency, but low number of patients, unclear exposure Skin Sens. 1	(Tienthavorn et al., 2014)

Type of data/report	**Relevant information about the study (as applicable)**	**Observations**	**Resulting classification***	**Reference**
Clinical study on the fragrance series Study reliability 1 (reliable without restrictions)	The records of 1951 eczema patients, routinely tested with the labelled fragrance substances and with an extended European baseline series in 2011 and 2012, were retrospectively reviewed. Patch test reactions to the fragrance series. Includes concentrations of allergens in the fragrance series and fragrance mixes, and data on co-reactions between fragrance series allergens and fragrance markers, fragrance mix I (FM I), or fragrance mix II (FM II).	Positive reactions to 1 % benzyl salicylate in petrolatum: 5/1951 (0.26 %) Co-reactions with any fragrance marker (% of reactions to fragrance series substance) 3/5 (60) Co-reactions with FM I (% of reactions to ingredient): 3/5 (60) Co-reactions with FM II (% of positive reactions to ingredient): 1/5 (20)	Positive Low frequency, unclear exposure Skin Sens. 1	(Mann et al., 2014)
Data comparison: (LLNA vs. Human repeated insult patch test HRIPT and Human Maximisation Test (HMT). Study reliability 2 (HRIPT)/4 (HMT) (reliable with restrictions/not assignable)	Human HRIPT study was carried out according to the basic principles described in (McNamee et al., 2008) and (Politano and Api, 2008). Historical HMT were collected from the RIFM database	Results for benzyl salicylate ($n \geq 100$): NOEL HRIPT (induction): 17 717 mg/cm^2 (MT-NOEL = Maximum Tested No Effect Level. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL) NOEL HMT (induction) = 20 690 mg/cm^2 (MT-NOEL = Maximum Tested No Effect Level. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL) LOEL (induction): > 20690 mg/cm^2 WoE NESIL 17 700 mg/cm^2 (limited to three significant figures)	Negative Not suitable for classification, because of unclear correlation to classification criteria	(Api et al., 2015) For the LLNA section, the data from (Central Toxicology Laboratory, 2005) were reported (cf. section on animal data above and in Annex I to this dossier).

Type of data/report	Relevant information about the study (as applicable)	Observations	Resulting classification*	Reference
Case report Study reliability 2 (reliable with restrictions)	27-year-old man was referred with a history of an itchy skin rash on the neck, arms, armpits, knee folds, and eyelids which appeared following the application of sunscreen products and exposure to sunlight; but no lesions on his legs or trunk. Repeated open application test on his forearm with the sunscreen products had produced a skin reaction, even without specific sun exposure. The patient remembered having had a skin eruption at the age of 9 years, but no association with any topical product applied could be established. Patch testing with European baseline series, cosmetic and sunscreen series, and the patient's own products (deodorants and sunscreens tested 'as is'). Readings were performed according to ICDRG guidelines after 2 and 4 days.	Patient showed eczematous reactions at the sites of all patch test chambers, which made interpretation of the original patch test results impossible Results of photo-patch testing with the photo-patch series and the patient's own products ('as is'): Positive reactions were observed to benzyl salicylate (D2, +?; D4, +) and the patient's own deodorant (D2, +; D4, ++; D7, +?) The reactions were positive on both the UV-exposed side and the non-exposed side, confirming allergic contact dermatitis (D=day; "-"=negative; "+?"= doubtful; "+" = weak positive; "++" = strong positive; "+++" = extreme positive; "IR" = irritant).	Positive Skin Sens. 1 Not suitable for sub-categorisation (only 1 patient)	(Werbrouck et al., 2015)
Risk of sensitisation to fragrances estimated on the basis of patch test data and exposure according to volume used and a sample of 5451 cosmetic products Study reliability 4 (not assignable)	Frequencies of sensitisation in 1870 tested patients and share of allergic reactions (%), accompanied by the 95% CI. Patients were tested for their reaction to three different fragrance mixes (FM I, FM II, and "further fragrances" not contained in the former two mixes, the latter including benzyl salicylate). In addition, for each mix a smaller number of patients positive to this mix was tested for their response to the individual components ("breakdown testing", only reported for FM I and FMII). Based on these results, the "share of allergic reactions" was calculated (i.e. the number of patients testing positive to that component divided by the number of patients testing positive to that particular fragrance mix). Assuming that patients sensitised to any of the components of a given fragrance mix would also respond to that mix and *vice versa*, the "share of allergic reactions" was then used to extrapolate the frequency of sensitisation to the whole study population. The share of volumes sold as provided by IFRA for the year 2008 ('market share') was then used to calculate the Sensitisation Exposure Quotient (SEQ), on the basis	0.9% (95% CI: 0.2-2.2) of the patients sensitised to the "further fragrances" mix tested positive for benzyl salicylate. This corresponded with a frequency of 0.21% when extrapolated to all 1870 patients. SEQ (CVUA): 0.18 (rank 20/26, together with benzyl alcohol), SEQ (IFRA): 0.12) (rank 20/26, together with hexyl cinnamal and citronellol); not relevant for classification and labelling	Positive Frequency is borderline i.e. value is below, but CI encompasses the border between high and low/moderate frequency; exposure unclear Reliability is limited by lack of reporting of the breakdown testing for the fragrance series including benzyl salicylate Skin Sens. 1	(Schnuch et al., 2015)

Type of data/report	Relevant information about the study (as applicable)	Observations	Resulting classification*	Reference
	of INCI labelling frequencies from the CVUA (Chemical Veterinary Examination Offices of the German Länder) data set for all products (n = 5451) and for leave-on products only (n = 3541). Comparison of sensitisation exposure quotient (SEQs) based on exposure according to volume data from IFRA vs. exposure data according to labelling from CVUA.			
Allergic contact dermatitis caused by benzyl salicylate Conference abstract Study reliability 4 (not assignable)	Review of patients at two Belgian university patch test clinics during the period 1994–2015.	In total, 15 patients sensitised to benzyl salicylate were identified, all patch-tested with the Belgian baseline series and with additional series depending on their individual history. Benzyl salicylate at a concentration of 10% in petrolatum was patch-tested in all of them. Sensitised patients included nine women and six men, with a median age of 46 years, mostly affected with dermatitis on the hands and/or face. Late patch-test reactions (i.e. only clearly positive at day 7) were observed in two of the 15 patients. Allergen sources were mainly leave-on cosmetics, including deodorants, accounting for axillary dermatitis; and sunscreens, related to dermatitis on sun-exposed skin areas. Rinse-off products – shampoos and conditioners in particular – also sometimes contributed to the patients' dermatitis. Concomitant reactions to other ultraviolet filters and to related salicylates (i.e. glycol salicylate in one patient, and octyl salicylate in another subject) were sometimes observed. Patients did not always react to other fragrance screeners in the baseline series (balsam of Peru, colophonium, Fragrance Mix I, Fragrance Mix II and Lyral). Thus a diagnosis of benzyl salicylate contact allergy would have been missed in nearly half of the patients (seven of 15) if it had not been specifically tested for.	Positive Not suitable for sub-categorisation, since frequency cannot be calculated and exposure can be presumed high. Skin Sens. 1	(Aerts et al., 2016)
Cosmetic contact allergens	Reports frequency of cosmetics as causal factors of allergic contact dermatitis during a 26-year period in 14,911 patients patch-tested between 1990 and 2014,	3/124 (2.42%) patients tested reacted positive to benzyl salicylate	Positive High frequency,	(Goossens, 2016)

Type of data/report	Relevant information about the study (as applicable)	Observations	Resulting classification*	Reference
Study reliability 2 (reliable with restrictions)	and discusses the cosmetic allergens identified during the previous six years (2010–2015) in 603 patients out of 3105 tested. The data were retrieved from, and evaluated with, a patient database developed in-house.		unclear exposure Skin Sens. 1	
Case report Contact allergy to benzyl salicylate. Short communication Study reliability 4 (not assignable)	A 60-year-old housewife presented with an 11-month history of chronic eyelid erythema and swelling with slight pruritus. On examination, weak oedema and erythema were observed in the upper and lower eyelids, with a bilateral and symmetrical distribution. The patient was patch-tested with an exposure time of two days, using two different allergen series (Spanish Standard Patch Test Series supplemented with further allergens (not benzyl salicylate) and another cosmetics and fragrance series (presumably containing benzyl salicylate, which, however, was not reported), and readings were performed on days (D) 2 and 4.	D4: weak positive reaction (+) to benzyl salicylate in 10% petrolatum in both series. There is insufficient information on whether benzyl salicylate was present in both series. Within a month, after avoidance of all products containing benzyl salicylate that the patient had contact with (shower gel, deodorant, fabric softener, nail-polish remover, and cologne) the lesions had completely cleared	Positive Not suitable for sub-categorisation Skin Sens. 1 However, due to lack of information it is unclear whether benzyl salicylate really was the unambiguous source of the allergic reaction	(Fernández-Canga et al., 2017)
Contact allergy to salicylates and cross-reactions Short communication Study reliability 4 (not assignable)	Evaluation of in-house data from a cosmetic dermatology centre regarding positive patch tests with benzyl salicylate, which were compiled between January 2014 and January 2016. Patients testing positive to benzyl salicylate were also tested with methyl, phenyl, and octyl salicylate and evaluated for cross-reactions.	Positive reactions in 2.2% of 600 patients tested with benzyl salicylate; weak evidence of cross-reactivity to methyl and phenyl salicylate (1 patient), and octyl salicylate (1 other patient).	Positive High frequency, unclear exposure Skin Sens. 1	(Scheman and Te, 2017)

* Subjective assessment by the DS for each individual study upon comparison with the criteria laid out in (ECHA, 2017), section 3.4.2.2.3.1. The resulting classification is given assuming that the respective information result was the only one available and was sufficient for direct classification (which would not be the case, e.g. for such studies with a single or a few patients).

A number of other studies in humans have been summarised in reviews by (Belsito et al., 2007) and (Lapczynski et al., 2007), cf. Table 11 and Table 12 below.

Table 11: Human volunteer studies on the potential of benzyl salicylate to induce sensitisation in humans in either a maximisation test or in a repeated insult patch test (HRIPT); data taken from (Belsito et al., 2007).

Method	Concentration	No. of volunteers	Results	References*
MAX	20 % in petrolatum	25	Sensitisation observed in 2/25 (**8** %)	(RIFM, 1980c)
MAX	20 % in petrolatum	25	Sensitisation observed in 1/25 (**4** %)	(RIFM, 1979)
MAX	30 % in petrolatum	25	No sensitisation reactions	(RIFM, 1970e)
MAX	30 % in petrolatum	25	No sensitisation reactions	(RIFM, 1975c)
MAX	30 % in petrolatum	22 (all male)	No sensitisation reactions	(RIFM, 1975d)
HRIPT	15 % in 3:1 DEP:ethanol	101	No sensitisation reactions	(RIFM, 2004c)
HRIPT	10 % in alcohol SD 39	35	No sensitisation reactions	(RIFM, 1975h)
HRIPT	5 % in dimethyl phthalate	52	No sensitisation reactions	(RIFM, 1968b)

* Full references can be accessed from the original publication

While some of the maximisation tests were positive and others negative, all three HRIPT results reportedly were negative. However, in the absence of more details regarding the experimental conditions, the reasons for the negative results cannot be further evaluated. In any case, in the view of the DS, they do not outweigh the comprehensive positive database as described in Table 10 above.

Table 12: Human patch tests for benzyl salicylate in ≥ 100 patients (data taken from Lapczynski et al., 2007).

Method	Concentration	Incidence (%)	References*
1. Closed patch test	0.05–0.5 % in a base cream or 99 % ethanol	5/313 **(1.6)**	(Takenaka et al., 1986)
2. Patch test	1 %, 2 %, 5 % in petrolatum	1/394 **(0.25)**	(Ueda, 1979; Ueda, 1994)
3. Patch test	2 % in an unspecified vehicle	4/183 **(2.1)**	(Rudner, 1977; Rudner, 1978
4. Patch test	2 % in paraffin	6/241 **(2.5)**	(Ferguson and Sharma, 1984)
5. Patch test	2 % in paraffin	1/457 **(0.22)**	(Addo et al., 1982)
6. Patch test	2 % in petrolatum	10/1825 **(0.5)**	(deGroot et al., 2000)
7. Patch test	2 % in petrolatum	1/89 **(1.12)**	(Nethercott et al., 1989)
8. Patch test	2 % in an unspecified vehicle	13/200 **(6.5)**	(Asoh et al., 1985a)
9. Patch test	2 % in petrolatum	5/157 **(3.18)**	(Hayakawa, 1986)
10. Patch test	2 % in petrolatum	38/788 **(4.8)**	(Sugai, 1986)
11. Patch test	5 % in an unspecified vehicle	30/756 **(4)**	(Itoh et al., 1988)
12. Patch test	5 % in an unspecified vehicle	12/155 **(7.74)**	(Itoh, 1982)
13. Patch test	0.2 %, 1 %, or 10 % in ethanol	0/10538 **(0)**	(Kohrman et al., 1983)
14. Patch test	1 % in petrolatum	5/180 **(2.78)**	(Ishihara et al., 1979)
	2 % in petrolatum	9/180 **(5.0)**	
	5 % in petrolatum	16/254 **(6.29)**	
15. Patch test	1 % in petrolatum	6/394 **(1.52)**	(Ueda, 1979)
	2 % in petrolatum	9/394 **(2.28)**	
	5 % in petrolatum	23/394 **(5.84)**	
16. Patch test	5 % in an unspecified vehicle	27/680 **(3.97)**	(Itoh et al., 1986)
17. Patch test	5 % in petrolatum	12/212 **(5.66)**	(Hada, 1983)
18. Patch test	2 % in an unspecified vehicle	2/103 **(1.94)**	(Fujimoto et al., 1997)
19. Patch test	5 % in petrolatum	0/315 **(0)**	(Heydorn et al., 2002)
20. Patch test	2 % in petrolatum	1/386 **(0.26)**	(Sugai, 1996)
21. Patch test	0.1 % in petrolatum	1/65 **(1.54)**	(Kozuka et al., 1996)
	1 % in petrolatum	3/201 **(1.49)**	
22. Patch test	5 % in petrolatum	14/176 **(7.95)**	(Shoji, 1982)
23. Patch test	2 % in petrolatum	3/102 **(2.94)**	(Hausen, 2001)
24. Patch test	1 % in petrolatum	3/747 **(0.4)**	(Wohrl et al., 2001)
25. Patch test	2 % in petrolatum	7/706 **(0.99)**	(Katoh et al., 1995)
26. Patch test	5 % in petrolatum	2/658 **(0.3)**	(Heydorn et al., 2003)
27. Patch test	2 % in petrolatum	77/1255 **(6.1)**	(Sugai, 1982)
28. Patch test	0.2 % in perfumed base cream	3/313 **(0.96)**	(RIFM, 1974)

Method	Concentration	Incidence (%)	References*
29. Patch test	5 % in an unspecified vehicle	24/522 **(4.6)**	(Nishimura et al., 1984)
30. Patch test	5 % in petrolatum	25/181 **(13.8)**	(Hayakawa et al., 1983)
31. Patch test	1 % in petrolatum	6/394 **(1.5)**	(MJDRG, 1984)
	2 % in petrolatum	9/394 **(2.3)**	
	5 % in petrolatum	23/394 **(5.8)**	
32. Patch test	5 % in petrolatum	1/64 **(1.6)**	(Haba et al., 1993)
33. Patch test	2 % in petrolatum	4/482 **(0.83)**	(Nagareda et al., 1996)
34. Patch test	2 % in petrolatum	8/436 **(1.83)**	(Nagareda et al., 1992)
35. Patch test	2 % in petrolatum	5/167 **(3)**	(Larsen et al., 1996)
	5 % in petrolatum	8/167 **(4.8)**	
36. Patch test	1 % in petrolatum	0/100 **(0)**	(Frosch et al., 1995b)
	5 % in petrolatum	1/100 **(1)**	
37. Patch test	5 % in petrolatum	20/362 **(5.52)**	(Ishihara et al., 1981)

* Full references can be accessed from the original publication

In the patch tests the percent incidence observed ranged from 0 to 13.8 %. These data confirm that sensitisation to benzyl salicylate is often observed with "relatively high frequency" (ECHA, 2017), however, again no information on the level of previous exposure of the patients is available, therefore sub-categorisation based on these data is not possible.

10.7.3 Other studies relevant for skin sensitisation

A number of other studies were identified in which the skin sensitisation potential of benzyl salicylate was addressed by means of in chemico, in vitro, or in silico tests. At this point in time (November 2017), the CLP regulation does not yet include criteria for how to use such data in the context of classification and labelling for skin sensitisation, let alone for sub-categorisation. Recently some in chemico and in vitro methods have been validated at OECD level and their use, albeit in concert and not as standalone methods, has been principally endorsed under REACH via a change in Annex VII of the legal text. Nevertheless, as of November 2017, none of these methods can be used for sub-categorisation. Also at the OECD level, a project has just started aiming at establishing a performance-based test guideline for their combined use for regulatory purposes in the form of so-called "Defined Approaches".

For benzyl salicylate, with human and animal data already sufficiently justifying classification as Skin Sens. 1 (or even pointing at sub-category 1B) and the new methods/approaches currently not being able to sub-categorise, the DS therefore has reviewed the publications available for benzyl salicylate (Dearden et al., 2015; Emter et al., 2010; Galbiati et al., 2017; Hirota et al., 2015; Natsch and Emter, 2008; Natsch et al., 2009; Saito et al., 2017; Urbisch et al., 2015), but did not consider them further in the overall assessment.

Detailed summaries of these studies can however be found in Annex I to this dossier.

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

From the animal (LLNA and non-LLNA) studies there is a clear outcome that benzyl salicylate acts as a skin sensitiser in vivo. In a GLP-conform LLNA test performed using OECD test guideline 429, benzyl salicylate acted as a moderate sensitiser, category 1B (EC3= 2.9 %), which, however, might be considered borderline to 1A, taking into consideration the inherent variability and uncertainty of the LLNA test method.

Additional animal studies using GPMT, CCET and modified versions of those tests, either support the classification of benzyl salicylate as Skin Sens. 1B (Kashima et al., 1993b) or - where the test design was chosen such that the CLP criteria for sub-categorisation cannot be applied – classification as Skin Sens. 1 in general (Hausen and Wollenweber, 1988; Imokawa and Kawai, 1987; Kashima et al., 1993a; Maurer and Hess, 1989); further reports, mostly to the same end, but also including a few tests with negative results - were cited in a review by the RIFM Expert Panel (Belsito et al., 2007).

In addition, a comprehensive human data base is available, which mainly consists of reports about clinical patch-testing in dermatitis patients, but also includes a number of case reports and a few tests in volunteers.

A large majority of the patch test results confirms the skin sensitisation potential of benzyl salicylate as well as a "relatively high frequency" (in the sense of Table 3.2 in (ECHA, 2017)) of occurrence of sensitisation to benzyl salicylate in dermatitis patients, which could justify classification into sub-category 1A. However, from the available data it was not possible to establish whether the patients tested had a history of "relatively high" or "relatively low" exposure. Given the ubiquitous use of benzyl salicylate in cosmetic and other consumer products, likely many people are exposed to this substance on a daily basis. Therefore the DS concluded that overall the available data are not sufficient to allocate benzyl salicylate into sub-category 1A.

In contrast to the studies in dermatitis patients, most of the HMT or HRIPT tests in (presumably) healthy volunteers were negative. In the view of the DS, however, this cannot disprove the proposed classification, as the number of volunteers was low and the extent of possible previous exposure of the volunteers to benzyl salicylate was unknown.

Finally, a number of publications on *in silico*, *in chemico*, and/or *in vitro* methods were reviewed by the DS, which were however excluded from further assessment due to the fact that the skin sensitisation potential of benzyl salicylate as such was sufficiently established by the more robust human and animal in vivo data, while these alternative data at this point in time are considered not robust enough to aid in sub-categorisation.

10.7.5 Comparison with the CLP criteria

The results from the relevant positive experiments in animals and humans are compared with the CLP criteria in Table 10. Only studies with at least reliability 2 are included in this overview, which excludes all studies for which only an abstract was available.

Table 13: Comparison of experimental results (from studies with at least reliability 2) confirming the skin sensitisation potential with benzyl salicylate in animal and humans with the respective criteria of the CLP regulation

Reference(s)	**Criteria acc. to CLP regulation, as laid out in detail in (ECHA, 2017)**	**Relevant result**	**Resulting Classification**
Animal data			
LLNA test (Central Toxicology Laboratory, 2005)	**Skin Sens. 1A:** EC3 ≤ 2 % **Skin Sens. 1B:** EC3 > 2 %	EC3 = 2.9	**Skin Sens. 1B***
GPMT test (Kashima et al., 1993b)	**Skin Sens. 1A:** ≥ 30% responding at ≤ 0.1% intradermal induction dose or ≥ 60% responding at > 0.1% to ≤ 1% intradermal induction dose **Skin Sens. 1B:** ≥ 30% to < 60% responding at > 0.1% to ≤ 1% intradermal induction dose or ≥ 30% responding at > 1% intradermal induction dose	Up to 30 % responding at 10 % intradermal induction dose	**Skin Sens. 1B** (but Skin Sens. 1A cannot be excluded as intradermal induction doses ≤ 0.1 % were not tested)

Reference(s)	Criteria acc. to CLP regulation, as laid out in detail in (ECHA, 2017)	Relevant result	Resulting Classification
Other maximisation tests (Hausen and Wollenweber, 1988; Imokawa and Kawai, 1987; Kashima et al., 1993a; Maurer and Hess, 1989)	No criteria for sub-categorisation based on modified GPMT methods	Up to 100% responding	**Skin Sens. 1** (no sub-categorisation possible)
Human data			
Consecutive dermatitis patients (Bruze et al., 2012; Goossens, 2016; Heisterberg et al., 2011; Lapczynski et al., 2007; Mann et al., 2014; Osmundsen and Alani, 1971; Schnuch et al., 2007; Schnuch et al., 2015)	**Skin Sens. 1** Frequency ≥ 1.0% and "relatively high exposure"** or Frequency < 1.0% and "relatively low exposure"** **Skin Sens. 1A:** Frequency ≥ 1.0 % and "relatively low high exposure"** **Skin Sens. 1B:** Frequency < 1.0 % and "relatively high exposure"**	Frequency from "relatively low" to "relatively high", exposure unclear, but can be presumed "relatively high"	**Skin Sens. 1** (no sub-categorisation possible)
Selected dermatitis patients (Goossens et al., 1999; Mid-Japan Contact Dermatitis Research Group, 1984)	**Skin Sens. 1** Frequency ≥ 2.0 % and "relatively high exposure"** or Frequency < 2.0 % and "relatively low exposure"** **Skin Sens. 1A:** Frequency ≥ 2.0 % and "relatively low high exposure"** **Skin Sens. 1B:** Frequency < 2.0 % and "relatively high exposure"**	Frequency from "relatively low" to "relatively high", exposure unclear, but can be presumed "relatively high"	**Skin Sens. 1** (no sub-categorisation possible)
Case reports (Tienthavorn et al., 2014; Werbrouck et al., 2015)	**Skin Sens. 1** Number of published cases ≥ 100 and "relatively high exposure"** or number of published cases < 100 and "relatively low exposure"** **Skin Sens. 1A:** Number of published cases ≥ 100 and "relatively low high exposure"** **Skin Sens. 1B:** Number of published cases < 100 and "relatively high exposure"**	< 100 cases and exposure presumed "relatively high"	**Skin Sens. 1B**

* Borderline case 1A/1B, given the inherent variability of the SI (Dumont et al., 2016) **Cf. (ECHA, 2017), Table 3.3

10.7.6 Conclusion on classification and labelling for skin sensitisation

Based on the results shown in Table 10 above, the DS proposes to classify benzyl salicylate as a **skin sensitiser, subcategory 1B (Skin Sens. Category 1B H317 - May cause an allergic skin reaction)**. The DS notes that this classification is supported by the majority of the notifiers to the C&L Inventory (with no notifier proposing a more severe classification), including the registrants from the joint registration submission under REACH. In line with (ECHA, 2017), Table 3.9, no Specific Concentration Limit (SCL) is proposed.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

A number of animal studies on skin sensitisation are available for benzyl salicylate but few of them employed a standard design according to OECD test guidelines. The key animal study, a local lymph node assay (LLNA) performed by Central Toxicological Laboratory (2005), was positive with an EC3 value of 2.9%. This EC3 value corresponds to subcategory 1B but the dossier submitter (DS) noted its closeness to the border of 2% (between subcategories 1A and 1B).

A guinea pig maximisation test (GPMT) by Kashima (1993b) gave a positive result, with 30% of the animals sensitised after an intradermal induction dose of 10%. This supports classification in subcategory 1B, but subcategory 1A cannot be excluded due to the absence of an experiment with an intradermal induction dose of ≤ 0.1%. Many other animal experiments were considered by the DS to support classification but not subcategorization, mostly because of not following a recognised guideline (OECD, etc.).

An extensive human database is available, mainly consisting of reports from clinical patch-testing in dermatitis patients. According to the DS, the large majority of the patch test results confirms the skin sensitisation potential of benzyl salicylate as well as a "relatively high frequency" in the sense of Table 3.2 in the "Guidance on the application of the CLP criteria" ("CLP guidance"). However, from the available data, it was not possible to establish whether the patients tested had a history of "relatively high" or "relatively low" exposure. The DS noted that due to the ubiquitous use of benzyl salicylate in cosmetics and other consumer products, many people are likely to be exposed to this substance on a daily basis. Therefore, the available human patch-test data were not considered suitable for subcategorization.

In contrast to the studies in dermatitis patients, most of the available human maximisation tests (HMT) or human repeat insult patch tests (HRIPT) in (presumably) healthy volunteers were negative.

The DS also noted that despite a "relatively high" exposure, the number of published case-reports is relatively low, i.e. less than 100.

Finally, the DS reviewed several publications on *in silico*, *in chemico* and *in vitro* methods. However, these were not considered further as the skin sensitisation potential as such was sufficiently established by the more robust human and animal *in vivo* data. In addition, these alternative methods, as yet, do not allow for subcategorisation.

The DS proposed to classify benzyl salicylate as a skin sensitiser in subcategory 1B and to base the subcategorization on the results of the LLNA study (Central Toxicology

Laboratory, 2005), the GPMT study by Kashima *et al.* (2003b) and the low number of published human cases despite the relatively high exposure.

Comments received during public consultation

Comments were received from 2 MSCAs. Both of them supported the proposed classification with Skin Sens. 1B.

These MSCAs mentioned two additional sources of information: (1) the Scientific Committee on Consumer Safety (SCCS) opinion on fragrance allergens (SCCS, 2012), and (2) the maximum recommended limits of benzyl salicylate in specific product categories by the International Fragrance Association (IFRA). One of the MSCAs pointed out that considering the wide use of benzyl salicylate in various consumer products, everyday exposure is very likely.

The DS appreciated especially the reference to the SCCS opinion and added the following citation to their assessment:

"Benzyl salicylate was found present in 9.6 – 38.9 % of the products covered. Benzyl salicylate was indicated as one of the most frequently reported and well-recognised consumer allergens. (SCCS, 2012)"

Assessment and comparison with the classification criteria

Animal data

LLNA study (Central Toxicology Laboratory, 2005)

This study, performed according to OECD TG 429, was available to the DS as a robust study summary from IUCLID. Benzyl salicylate was administered in ethanol:diethyl phthalate (1:3) at concentrations 0, 2.5, 5, 10, 25 and 50% w/v to 4 animals per group. Hexyl cinnamic aldehyde in acetone:olive oil (4:1) was used as a positive control. Stimulation indices (SI) are shown in the following table.

Concentration (%)	SI
2.5	2.6
5	5.5
10	6
25	19
50	26

An EC3 value of 2.9% was obtained by simple interpolation. This value is above the cut-off value of 2% for subcategorization, thus pointing towards classification in subcategory 1B. In the absence of statistical analysis, the confidence intervals are not known, so it cannot be decided whether the cut-off value is within the confidence interval. However, this uncertainty factor is not considered to prevent using the result for subcategorization.

Other animal studies

A number of additional animal studies are mentioned in the CLH report (Table 8; Table 9). Although most of them confirm the skin sensitisation potential of benzyl salicylate, they cannot be used for subcategorization, mostly due to a non-guideline design (e.g., an induction protocol different from that in OECD TG 406), insufficient reporting or both.

According to the DS, the GPMT by Kashima *et al.* (1993b) could be potentially used to support subcategorization. The study used 10 animals per group. The intradermal induction concentration was 10% in liquid paraffin, topical 30% in ethanol. Three challenge concentrations were employed (0.003%, 0.01% and 0.03% in ethanol). A positive reaction was observed in 20-30% of animals, which may indicate weak potency. However, the available description of the GPMT part of the study is very limited (the main focus of the publication was on the development of an alternative method to GPMT, not on the GPMT itself).

RAC further notes that the GPMT by Kozuka *et al.* (1996) is of a standard design and a relatively detailed description of the study is available in Annex I to the CLH report. The study used 20 animals per group. The intradermal induction concentration was 10% in liquid paraffin, topical 50% in petrolatum. As the topical induction concentration was not irritant, dermal irritation was induced by SLS (sodium laurilsulfate) pre-treatment. Three challenge concentrations (5%, 10% and 20% in white petrolatum) were employed. A positive reaction was observed in 2/20 animals at a challenge concentration of 20%; additionally, questionable reactions were seen in 3/20 animals at 5% topical challenge, 5/20 at 10% and 4/20 at 20%. If the questionable reactions are taken as positive, the overall result is borderline positive, which is consistent with subcategory 1B.

Although subcategory 1A cannot be formally excluded based on these two GPMTs as intradermal induction doses ≤ 0.1% were not tested, it is highly unlikely that with a response rate of only 20-30% after an intradermal induction concentration of 10%, the intradermal induction concentrations below 0.1% would give a response of ≥ 30%, or intradermal induction concentrations between 0.1 and 1% a response of ≥ 60%.

Human data

Induction studies (HRIPT, HMT)

Data from human volunteers are summarised in the following table (the list of the studies comes from Belsito *et al.*, 2007, and Lapcynski *et al.*, 2007; both publications provide the same list of studies; in addition, a test by Api *et al.*, 2015 is included).

Human repeat insult patch tests and human maximization tests			
Reference (as in Belsito *et al.*, 2007)	**Concentration**	**No. of volunteers**	**Incidence of positive reactions**
HRIPT			
RIFM (1968b)	5% in dimethyl phthalate	52	0 (0%)
RIFM (1975h)	10% in alcohol SD39	35	0 (0%)
RIFM (2004c)	15% in 3:1	101	0 (0%)

	DEP:ethanol		
Api *et al.* (2015)		≥ 100	0 (0%)
HMT			
RIFM (1970e)	30% in petrolatum	25	0 (0%)
RIFM (1975c)	30% in petrolatum	25	0 (0%)
RIFM (1975d)	30% in petrolatum	22	0 (0%)
RIFM (1979)	20% in petrolatum	25	1 (4%)
RIFM (1980c)	20% in petrolatum	25	2 (8%)

All four HRIPTs were negative. Two of the HMTs were positive (with a relatively low sensitisation rate) and the remaining three were negative. The dose in µg/cm^2 in the individual tests is not available in the CLH report but Lapcynski *et al.* (2007) reports a NOEL derived from HRIPTs of 17700 µg/cm^2 and a NOEL derived from HMTs of 20700 µg/cm^2. This indicates that the doses used were probably far in excess of 500 µg/cm^2 at least in some of the tests. Overall, the results of the available HRIPTs and HMTs point towards low potency.

Case reports

Several case reports are presented in the CLH report. While these confirm the skin sensitisation potential of benzyl salicylate, they do not aid in subcategorization. They are, however, taken into account in the calculation of the number of published cases.

Diagnostic patch tests

The available results of diagnostic patch tests involving at least 100 subjects are summarised in the table below (compiled from Table 10 and Table 12 of the CLH report; studies not included in this table are listed in the background document under 'supplemental information' together with the justification for not including them). According to the Guidance on the application of the CLP criteria (CLP guidance), the cut-off value between a low/moderate and high frequency is 1.0% for unselected (consecutive) patients and 2.0% for selected patients. RAC notes that the relative frequencies depend heavily on the selection of patients for patch testing and in many of the studies summarised below the criteria for the selection of patients are not known. Thus, the assignment of frequency in the last column of the table is rather uncertain.

The high number of older Japanese studies in the data set probably reflects the fact that in Japan in the 1960s and 1970s many women suffered from hyperpigmentation of the face. From 1969 on, systematic investigations of these patients revealed that many of them had contact allergy to cosmetics. The major sensitisers in such cosmetics were coal tar dyes and fragrances including benzyl salicylate. Major cosmetic companies in Japan began to phase-out various sensitisers in their products in 1977. Since then, the number of patients suffering from pigmented cosmetic dermatitis has decreased remarkably (de Groot and Frosch, 1997).

Diagnostic patch tests				
Reference	**Area; Period**	**Concentration, vehicle**	**% testing positive**	**Frequency**
RIFM (1974)*	Japan	0.2% in perfumed base cream	1.0% (3/313)	High[#]
Rudner (1977); Rudner (1978)*	North America 1975-1976	2%	2.1% (4/183)	High
Ishihara *et al.* (1979)*	Japan(?)	1% in petrolatum	2.8% (5/180)	High
		2% in petrolatum	5.0% (9/180)	
		5% in petrolatum	6.3% (16/254)	
Ueda (1979)*	Japan	1% in petrolatum	1.5% (6/394)	High
		2% in petrolatum	2.3% (9/394)	
		5% in petrolatum	5.8% (23/394)	
Ueda (1979); Ueda (1994)*	Japan(?)	1%, 2%, 5% in petrolatum	0.3% (1/394)	Low
Yamamoto *et al.* (1981)	Japan 1973-1980	2%; 5%	6.3% (62/987)	High
Ishihara *et al.* (1981)*	Japan(?) 1978-1980	5% in petrolatum	5.5% (20/362)	High
Addo *et al.* (1982)*	Europe(?)	2% in paraffin	0.2% (1/457)	Low
Itoh (1982)*	Japan(?)	5% in petrolatum	7.7% (12/155)	High
Shoji (1982)*	Japan	5% in petrolatum	8.0% (14/176)	High
Hada (1983)*	Japan	5% in petrolatum	5.7% (12/212)	High
Hayakawa *et al.* (1983)*	Japan(?)	5% in petrolatum	14% (25/181)	High
Nishimura *et al.* (1984)*	Japan 1978-1982	5%	4.6% (24/522)	High
Ferguson and Sharma (1984)*	Europe(?) 1981-1983	2% in paraffin	2.5% (6/241)	High
Asoh *et al.* (1985a)*	Japan(?) 1982	2% in petrolatum	6.5% (13/200)	High
Asoh and Sugai (1985)	Japan 1983-1984		1.9% (6/316)	N.A.
Takenaka *et al.* (1986)*	Japan(?)	0.05–0.5% in a base cream or ethanol	1.6% (5/313)	High[#]
Hayakawa	Japan	2% in petrolatum	3.2% (5/157)	High

(1986)*	1984			
Sugai (1986)*	Japan 1981-1983	2% in petrolatum	4.8% (38/788)	High
Itoh *et al.* (1986)*	Japan(?) 1978-1985	5%	4.0% (27/680)	High
Itoh *et al.* (1988)*	Japan(?) 1978-1986	5%	4.0% (30/756)	High
Nagareda *et al.* (1992)*	Japan(?) 1990-1991	2% in petrolatum	1.8% (8/436)	High
Katoh *et al.* (1995)*	Japan 1992-1993	2% in petrolatum	1.0% (7/706)	N.A.
Frosch *et al.* (1995b)*	Europe	1% in petrolatum	0% (0/100)	Low
		5% in petrolatum	1% (1/100)	
Sugai (1996)*	Japan(?) 1994	5% in petrolatum	0.3% (1/386)	Low
Kozuka *et al.* (1996)*	Japan	1% in petrolatum	1.5% (3/201)	High
Nagareda *et al.* (1996)*	Japan(?) 1992-1993	2% in petrolatum	0.8% (4/482)	Low
Larsen *et al.* (1996)*	Worldwide	2% in petrolatum	3% (5/167)	High
		5% in petrolatum	4.8% (8/167)	
Fujimoto *et al.* (1997)*	Japan(?) 1989-1992	2%	1.9% (2/103)	High
Sugai (1998)	Japan 1974-1997		1974-1981: 6.1% (77/1255) 1982-1987: 2.3% (42/1851) 1988-1993: 1.7% (23/1356) 1994-1997: 1.0% (10/1000)	High
deGroot *et al.* (2000)*	Europe 1998-1999	2% in petrolatum	0.5% (10/1825)	Low
Hausen (2001)*	North America(?)	2% in petrolatum	2.9% (3/102)	High
Wohrl *et al.* (2001)*	Europe(?)	1% in petrolatum	0.4% (3/747)	Low
Heydorn *et al.* (2002)*	Europe	5% in petrolatum	0% (0/315)	Low
Heydorn *et al.* (2003)*	Europe	5% in petrolatum	0.3% (2/658)	Low
Schnuch *et al.*	Europe	1%	0.1% (2/2041)	Low

(2007)	2003-2004			
Heisterberg *et al.* (2011)	Europe 2008-2010	1% in petrolatum	0.2% (3/1503)	Low
Bruze *et al.* (2012)	Europe	30% in petrolatum	2.6% (3/114)	N.A.
		12% in petrolatum	0% (0/110)	
Mann *et al.* (2014)	Europe 2011-2012	1% in petrolatum	0.3% (5/1951)	Low
Schnuch *et al.* (2015)	Europe 2007-2009		0.2%	Low
Goossens (2016)	Europe 2010-2015		2.4% (2/124)	High
Scheman and Te (2017)	2014-2016		2.2% (600 patients tested)	High

* reference from Lapcynski *et al.* (2007) (Table 12 of the CLH report)

N.A. = not assignable (borderline, or several results, out of which some indicating high and some low frequency, or a result between 1.0% and 2.0% and not clear whether selected or consecutive patients)

[#] borderline, but considering the low concentration used, pointing towards a high frequency

The older studies indicate a relatively high frequency and a decreasing trend, particularly in the Japanese populations. Most of the recent studies in European populations indicate low/moderate frequency.

Due to the potential bias in selection of the subjects for testing, the Scientific Committee on Consumer Safety prefers to use absolute numbers of cases of sensitisation. SCCS (2012) reports the absolute number of published cases of sensitisation to benzyl salicylate to be between 11 and 100. RAC notes that the data in the CLH report indicate a higher number of cases by 2012, with a significant contribution of the older Japanese studies. Sugai (1998) reported 152 cases in Japan between 1974 and 1997 (it can be assumed that this number already includes many if not most of the Japanese cases from this period published by other Japanese authors) and at least 30 cases were published by non-Japanese authors during this period. According to the information in the CLH report, about 70 cases were published worldwide between 1998 and 2017. Thus, the total number of published cases is considered to exceed 100, which is consistent with high frequency according to the CLP guidance. Similarly to the frequency data, the number of published cases shows a decreasing trend.

For the purpose of subcategorization the frequency data have to be evaluated together with information on previous exposure of the tested subjects. The CLP guidance recommends considering three factors when estimating the level of exposure in the studied populations:

- Concentration or dose (a concentration cut-off between relatively low and relatively high exposure is 1.0%)
- Frequency of exposure (less than once daily vs more than once daily)
- Number of exposures (less than 100 vs more than 100)

The actual concentrations to which the subjects participating in the patch testing had been exposed previously are not known and are difficult to estimate especially for the older studies. Relatively recent data on benzyl salicylate in cosmetic products (Lapczynski

et al., 2007, referring to a survey from 2002; Sanchez-Prado *et al.*, 2011) indicate concentrations below 1% in the majority of products but also concentrations above 1% in some fragrances and eau de toilettes (a maximum of 2.3% found by Sanchez-Prado *et al.*, 2011; a 97.5th percentile of ca. 7% estimated by Lapczynski *et al.*, 2007, for fine fragrances). The IFRA standard (IFRA, 2007) recommends a maximum concentration of 0.7% for deodorants, 2.7% and 8.0% for hydroalcoholics for shaved and unshaved skin respectively and 4.2% for hand creams.

Frequency of exposure and the number of exposures is likely to be high given the presence of benzyl salicylate in a wide range of cosmetic and other consumer products. Due to the EU labelling requirement for 26 fragrance substances, the frequency of exposure can be estimated from the proportion of products labelled to contain benzyl salicylate. SCCS (2012) summarises the results of several surveys, indicating a labelling frequency ca. 50% for deodorants (both in 1998 and 2007) and between 20% and 40% for mixes of consumer products. Schnuch *et al.* (2015) found benzyl salicylate on the label of 14% cosmetic products purchased between 2007 and 2009.

The CLP guidance proposes a scoring system assisting in the decision whether the overall level of exposure is low or high. The overall exposure index is calculated by summing up three scores. For benzyl salicylate, the exposure index is calculated as follows:

- Concentration: recently mainly below 1% but in some products such as perfumes and eau de toilettes possibly exceeding 1% → **score 0 or 2**; in the more distant past, concentrations may have been higher (especially in the Japanese populations)
- Repeated exposure: more than once daily (exposure from various cosmetic and household products, benzyl salicylate is widely used) → **score 2**
- Number of exposures: more than 100 (cosmetic products are used on a daily basis) → **score 2**

The resulting exposure index is **4 or 6** depending on the concentration. This corresponds to a low or high exposure respectively.

In summary, the recent European studies report a low frequency and the exposure is likely to range from low to high. The older Japanese studies reported a high frequency and the exposure was probably high. The decision scheme from the CLP guidance is copied below. The patch test data for benzyl salicylate correspond to the situations highlighted in bold.

	Relatively low frequency	Relatively high frequency
Relatively high exposure (score 5-6)	**Subcategory 1B**	**Category 1 or case by case evaluation**
Relatively low exposure (score 1-4)	**Category 1 or case by case evaluation**	Subcategory 1A

Although the diagnostic patch test database for benzyl salicylate does not clearly point towards classification in subcategory 1B, it does not indicate a high potency.

Conclusion on classification

The available data clearly demonstrates the skin sensitisation potential of benzyl salicylate in both humans and laboratory animals.

As to subcategorization, the LLNA by Central Toxicology Laboratory (2005) reports an EC3 of 2.9%, which indicates subcategory 1B. The GPMTs by Kashima *et al.* (1993b) and Kozuka *et al.* (1996) are also consistent with subcategory 1B.

Two HMTs indicate a weak sensitisation potential while the remaining seven HRIPTs and HMTs are negative. Overall, the results of the HRPITs and HMTs point towards low potency. The large database of diagnostic patch tests cannot be used for subcategorization but does not indicate high potency.

Considering all available information in a weight of evidence assessment, RAC agrees with the DS that classification of benzyl salicylate with **Skin Sens. 1B; H317** is appropriate.

Supplemental information - In depth analyses by RAC

Studies not mentioned in the opinion

Several studies presented in the CLH report have not been included in the table listing diagnostic patch tests because they did not provide a reliable estimate of frequency. These studies, however, have not been excluded from the assessment; their results have been taken into account in the total number of published cases. Other studies were not included in the opinion because the same data were already presented in another publication included in the main table. Studies not included in the main table for any reason are listed in the table below.

Reference	**Justification for not including the study in the table listing diagnostic patch tests**
Table 10 of the CLH report	
Rothenborg and Hjorth (1968)	Less than 100 subjects
Kahn (1971)	Less than 100 subjects; unclear influence of methoxsalen
Osmundsen and Alani (1971)	Less than 100 subjects
Opdyke (1973)	HMT probably included in the reviews by Lapczynski *et al.* (2007) and Belsito *et al.* (2007); the other study is Kahn (1971)
Suskind (1979)	Less than 100 subjects
Hayakawa *et al.* (1983)	= Hayakawa *et al.* (1983) in Table 12
Kohrmann *et al.* (1983)	Insufficient reporting
Ishihara *et al.* (1984)	= Nishimura *et al.* (1984) in Table 12
Mid-Japan Contact Dermatitis Research Group (1984)	= Ueda (1979) in Table 12
Sugai *et al.* (1984)	Incidence not available in the CLH report
Hosokawa *et al.* (1985)	Less than 100 subjects
Mid-Japan Contact Dermatitis Research Group (1985)	Incidence not available in the CLH report
Hausen and Wollenweber (1988)	Less than 100 subjects

Mitchell and Beck (1988)	Case report (1 subject)
Goossens *et al.* (1999)	Incidence not available in the publication (it is not clear whether all 475 patients were tested for benzyl salicylate)
Walgrave *et al.* (2005)	Incidence not available in the CLH report
Alagappan *et al.* (2013)	Case report (1 subject)
Tienthavorn *et al.* (2014)	Less than 100 subjects
Werbrouck *et al.* (2015)	Case report (1 subject)
Aerts *et al.* (2016)	Incidence not available (the total number of subjects tested not available in the publication)
Fernández-Canga *et al.* (2017)	Case report (1 subject)
Table 12 of the CLH report	
Nethercott *et al.* (1989)	Less than 100 subjects
Sugai (1982)	Same data as in Sugai (1998) in Table 10
MJDRG (1984)	Same data as in Ueda (1979) in Table 12
Haba *et al.* (1993)	Less than 100 subjects

10.8 Germ cell mutagenicity

Not evaluated in this dossier

10.9 Carcinogenicity

Not evaluated in this dossier

10.10 Reproductive toxicity

Not evaluated in this dossier

10.11 Specific target organ toxicity-single exposure

Not evaluated in this dossier

10.12 Specific target organ toxicity-repeated exposure

Not evaluated in this dossier.

10.13 Aspiration hazard

Not evaluated in this dossier

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this dossier

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this dossier

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