Committee for Risk Assessment

RAC

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

Adopted

15 March 2019

15 March 2019

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **Benzyl salicylate**

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

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

The proposal was submitted by **Germany** and received by RAC on **28 June 2018.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **18 July 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **18 September 2018**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Michal Martínek**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **15 March 2019** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	Benzyl salicylate	204-262-9	118-58-1	Skin Sens. 1B	H317	GHS07 Wng	H317	–	–	–
RAC opinion	TBD	Benzyl salicylate	204-262-9	118-58-1	Skin Sens. 1B	H317	GHS07 Wng	H317	–	–	–
Resulting Annex VI entry if agreed by COM	TBD	Benzyl salicylate	204-262-9	118-58-1	Skin Sens. 1B	H317	GHS07 Wng	H317			

GROUNDS FOR ADOPTION OF THE OPINION

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.

HUMAN HEALTH HAZARD EVALUATION

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 sub-categorization 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 DEP:ethanol	101	0 (0%)
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[#]

Diagnostic patch tests				
Reference	**Area;** **Period**	**Concentration, vehicle**	**% testing positive**	**Frequency**
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 (1986)*	Japan 1984	2% in petrolatum	3.2% (5/157)	High
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

Diagnostic patch tests				
Reference	**Area;** **Period**	**Concentration, vehicle**	**% testing positive**	**Frequency**
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.* (2007)	Europe 2003-2004	1%	0.1% (2/2041)	Low
Heisterberg *et al.* (2011)	Europe 2008-2010	1% in petrolatum	0.2% (3/1503)	Low
	Europe	30% in petrolatum	2.6% (3/114)	N.A.

Diagnostic patch tests				
Reference	**Area; Period**	**Concentration, vehicle**	**% testing positive**	**Frequency**
Bruze *et al.* (2012)		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, SCCS (2012) reports preferably 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.

Additional references

IFRA (International Fragrance Association) (2007) Benzyl salicylate. 42th amendment to the IFRA Code of Practice

SCCS (Scientific Committee on Consumer Safety) (2012) Opinion on fragrance allergens in cosmetic products

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).