Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Benzyl alcohol

EC Number: 202-859-9
CAS Number: 100-51-6

CLH-O-0000007024-83-01/F

Adopted

16 September 2021

P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

16 September 2021

CLH-O-0000007024-83-01/F

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 alcohol**

EC Number: **202-859-9**

CAS Number: **100-51-6**

The proposal was submitted by **Germany** and received by RAC on **29 September 2020.**

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 **19 October 2020**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **18 December 2020**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Lea Stine Tobiassen**

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 **16 September 2021** by **consensus**.

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

	Index No	Chemical name	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	603-057-00-5	Benzyl alcohol	202-859-9	100-51-6	Acute Tox. 4* Acute Tox. 4*	H302 H332	GHS07 Wng	H302 H332			
Dossier submitters proposal	603-057-00-5	Benzyl alcohol	202-859-9	100-51-6	**Add** Eye Irrit. 2 Skin Sens. 1B **Modify** Acute Tox. 4 **Remove** Acute Tox. 4	**Add** H319 H317 **Modify** H302 **Remove** H332	**Retain** GHS07 Wng	**Add** H319 H317 **Modify** H302 **Remove** H332		**Add** Oral: ATE = 1570 mg/kg bw	
RAC opinion	603-057-00-5	Benzyl alcohol	202-859-9	100-51-6	**Add** Eye Irrit. 2 Skin Sens. 1B **Modify** Acute Tox. 4 **Remove** Acute Tox. 4	**Add** H319 H317 **Modify** H302 **Remove** H332	**Retain** GHS07 Wng	**Add** H319 H317 **Modify** H302 **Remove** H332	**-**	**Add** Oral: ATE = 1200 mg/kg bw	
Resulting Annex VI entry if agreed by COM	603-057-00-5	Benzyl alcohol	202-859-9	100-51-6	Acute Tox. 4 Eye Irrit. 2 Skin Sens. 1B	H302 H319 H317	GHS07 Wng	H302 H319 H317		Oral: ATE = 1200 mg/kg bw	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Benzyl alcohol is used as a solvent for inks, paints and lacquers. It has biocidal use (preservative) in a wide range of products (e.g. cosmetics, detergents, food additives) and is used as an odorant in e.g. cosmetics. The substance is also used in pharmaceutical products including treatment of head lice. Benzyl alcohol is a high tonnage chemical (≥ 10 000 tons per annum) under REACH.

The substance was classified under Directive 67/548/EC, preceding the CLP regulation. However, the data and reasoning for the classification at that time are not available. A re-evaluation for the use as food additive (E1519) was published in 2019[1]. The substance is currently under scrutiny as a new biocidal active substance (PT6) under the BPR; however, no information is yet publicly available.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute oral toxicity

Eleven studies on the acute oral toxicity of benzyl alcohol in rats, mice, rabbits and guinea pigs are presented by the dossier submitter. The studies were conducted between 1918 and 1980. All reports lack study details in varying degree. The LD_{50}s reported across all studies range from 1040 mg/kg bw (in the mouse and rabbit from 1918 and 1945, respectively) to 3100 mg/kg bw in one rat study (from 1951). One study in Wistar rats (males only) from 1978, and one in Sprague-Dawley rats (both sexes) from 1980 have been conducted according to OECD TG 401 or similar protocols. The DS proposed to use the LD_{50} from these two studies, i.e. 1620 mg/kg bw and 1570 mg/kg bw as the basis for confirming the existing classification as Acute Oral Toxicity category 4, H302. An ATE for acute oral toxicity of 1570 mg/kg bw is proposed.

Acute dermal toxicity

Only a few, older reports from 1945, 1973 and 1974 with very limited information on study designs were available to the DS. The LD_{50} values are reported to be over 2000 mg/kg bw in rabbits, less than 5.0 ml/kg bw (≈ 5225 mg/kg bw) in guinea pigs and 2940 mg/kg bw in cats. Based on these data, the dossier submitter proposed not to classify for acute dermal toxicity.

[1] EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Younes M, Aquilina G, Castle L, Engel K-H, Fowler P, Fürst P, Gürtler R, Gundert-Remy U, Husøy T, Mennes W, Moldeus P, Oskarsson A, Shah R, Waalkens-Berendsen I, Wölfle D, Boon P, Crebelli R, Di Domenico A, Filipic M, Mortensen A, Van Loveren H, Woutersen R, Gergelova P, Giarola A, Lodi F and Frutos Fernandez MJ, 2019. Scientific Opinion on the re-evaluation of benzyl alcohol (E 1519) as food additive. EFSA Journal 2019;17(10):5876, 25 pp. https://doi.org/10.2903/j.efsa.2019.5876

Acute inhalation toxicity

Two OECD TG 403 compliant unpublished studies[1] in rats from 1990 and 1993, conducted with aerosols were available using nose-only application. The maximum achievable concentrations 4.18 mg/L and 5.4 mg/L did not cause any mortalities in the studies. Only transient clinical signs (unkempt fur and slower breathing) were reported in the first study, and no effects were reported in the second study. The LC_{50} values in both studies is concluded to be above 5 mg/L.

Two older studies using rats exposed to vapour were also quoted in the dossier. However, details on study conduct are scarce. The study from 1949 (Carpenter et al. 1949), reported an LC_{50} for 4h exposure to be 8.8 mg/L (2000 ppm). The DS notes that the concentrations given are nominal only, and that no analytical measurements were performed. In the other of the older studies (Smyth et al. 1951), 3 out of 6 rats died following 8 hours exposure to 1000 ppm (4.4 mg/L) benzyl alcohol. An LC_{50} of 5.5 mg/L for a 4 hour exposure was extrapolated. A handbook citation (Clayton 1982) referring to the latter study reports that testing of a saturated vapour concentration of 200 ppm (>0.9 mg/L) did not lead to any mortalities after 2 hrs exposure, while one third of the animals died (LC_{33}) following 4 hour exposure, and 8 hours led to the death of all animals. However, the relation to the original report quoted above is very unclear.

The DS notes that the MAK-Kommission[2] (Hartwig 2017) calculated a saturated vapour concentration of 567 mg/m^3 indicating that there is an equilibrium between vapour and aerosol at 0.5-0.6 mg/L.

Having regard to the uncertainties related to the vapour data, the DS considers that the classification for acute toxicity by inhalation should be based on the two OECD TG 403 compliant studies from 1990 and 1993, conducted with aerosols, leading to a conclusion not to classify benzyl alcohol for acute inhalation toxicity.

Comments received during consultation

Acute oral toxicity

Comments were received from 2 MSCAs, both agreeing to the proposed classification for Acute Oral Toxicity in category 4. One of the commenting MSCAs stressed the uncertainty related to the scarce reporting of the studies used to derive the classification, including lack of information on the purity of the tested substance. The other MSCA commenter added that, due to the low level of details in the reports, using the generic ATE of 500 mg/kg bw may be considered in preference to the proposed ATE of 1570 mg/kg bw.

The DS responded that the ATE of 1570 mg/kg was proposed due to the similarity of the results in the two most reliable studies.

Acute dermal toxicity:

One MSCA expressed support for the proposal not to classify for this endpoint.

Another MSCA commented on the low quality of studies on acute dermal toxicity, and the lack of studies in rats or mouse. The MSCA noted that the guinea pig data do not exclude an LD_{50}

[1] Robust study summary available in REACH registration dossier. However, a full study report unavailable

[2] MAK: Maximale Arbeitsplatzkonzentrationen – German national occupational limit values.

below 2000 mg/kg bw. Finally, the MSCA proposed to stress the insufficiency of the database in the reasoning for no classification.

The DS responded that all the currently available data were included in the present proposal of no classification.

Acute inhalation toxicity

One MSCA refers to the CLP guidance for differentiation between aerosols/mists and vapours, offering a calculation of the LC_{50} level of 3 mg/L above which the values for aerosols should be used to decide on classification of benzyl alcohol. However, the low data quality could raise a doubt when deleting an existing classification.

Another MSCA notes that the results reported from the aerosols would not lead to classification. However, due the poor database, and having regard to the current classification in category 4, the MSCA proposed to point to the inconclusiveness of the data in the justification for no classification.

Assessment and comparison with the classification criteria

Acute oral toxicity

All available results on acute oral toxicity show LD_{50} values between 1040 and 3100 mg/kg bw, across the species tested. RAC agrees to disregard LD_{50} values from studies where no details at all are available.

The DS based the proposal on two acute oral toxicity studies from 1978 and 1980 similar to OECD TG (no information on the purity of the test substance available), reporting LD_{50} values of 1620 mg/kg bw and 1570 mg/kg bw, respectively. RAC considers that the information on the study in rats by Jenner et al. (1964) included in the CLH report should also be considered. Although performed prior to OECD and GLP, using a lower number of animals and without information on the purity of the substance, the study is considered to be reported in sufficient details in the article for it to be suitable for classification purposes. The study reported acute oral toxicity testing of a number of chemicals in rats, guinea pigs and/or mice. With respect to benzyl alcohol, the study used 10 Osborne-Mendel rats fasted for 18 hours prior to treatment. The animals were treated by intubation with the undiluted substance. The LD_{50} value confidence limits are given as 1130 to 1330 mg/kg bw. The animals were observed for 14 days reporting clinical signs as depression and coma within 10-15 min, excitability for 3-4 days, and mortalities occurring from 4 hours up to 3 days. The reported LD_{50} from the rat study is 1230 mg/kg bw, calculated by the method of Litchfield and Wilcoxon (1949).

The guidance on classification recommends to use the most sensitive result from a relevant study. Although the age and reporting of acute oral studies brings some uncertainties to their evaluation, and the use of the generic ATE of 500 mg/kg bw could be considered, RAC considers that there are data available that point to an LD_{50} between 1000 and 2000 mg/kg bw.

The DS proposes to classify on the basis of LD_{50} values of 1620 mg/kg bw and 1570 mg/kg bw. RAC notes that the study by Jenner et al.(1964) appears to be reliable, and would include this study in the evaluation of acute oral toxicity. The LD_{50} value of 1230 mg/kg bw from this study, although slightly lower than from the two studies proposed by the DS, also indicates classification as Acute Tox. cat 4.

RAC agrees with the DS to base the classification on the most reliable experimental data and recommends **classification as Acute Tox. 4; H302** for benzyl alcohol.

RAC further proposes to use the LC_{50} value from the rat study by Jenner et Al. (1964) and set a rounded **ATE of 1200 mg/kg bw** for acute oral toxicity of benzyl alcohol.

Acute dermal toxicity

The DS evaluated that the dermal LD_{50} values were over 2000 mg/kg bw, and that the criteria for acute dermal toxicity classification were therefore not met. No classification is proposed for this endpoint.

RAC considers that the available data, although from elder studies and scarcely reported are sufficient to conclude on **no classification for acute dermal toxicity**.

Acute inhalation toxicity

The reported LC_{50} values from studies conducted with vapours appear to be within the criteria for classification of vapours in category 3; H331 (LC_{50} between 2.0 and 10.0 mg/L).

However, there are uncertainties on the conduct and results from these studies. Also, because benzyl alcohol is of low volatility (vp is 0.12hPa at 25ºC), the aerosols would be predominant in concentrations above the saturated concentration (calculated as 0.57 mg/L at 25ºC by the MAK-commission). The DS therefore proposes to disregard these studies in the classification of benzyl alcohol for acute inhalation toxicity.

The two studies available using aerosols in nose-only application are considered to have LC_{50} over 5 mg/L. As the criteria for classifying in category 4 (dusts and mist: 1.0 mg/L < ATE ≤ 5.0mg/L) are not met, the DS proposes not to classify benzyl alcohol for acute inhalation toxicity.

RAC notes that the CLP guidance recommends classification based on the mists (aerosols) for substances for which LC_{50} values are above the Saturated Vapour Concentration (SVC): *"An LC_{50} well below the SVC will be considered for classification according to the criteria for vapours; whereas an LC_{50} close to or above the SVC will be considered for classification according to the criteria for mists."* At 20ºC, the SVC would be slightly lower than 0.57 mg/L at 25ºC as calculated by the MAK commission (i.e. ≈ 0.31 mg/L, when applying the equation proposed in the CLP guidance SVC= 0.0412 x MW x vp).

RAC agrees that the classification should be based on the data for aerosols, as both available studies conducted according to OECD test guidelines are regarded as valid and reliable based on the summaries available in the REACH registration dossier.

RAC considers that a new evaluation of the classification of benzyl alcohol for acute inhalation toxicity is justified, as the substance would occur as an aerosol at the concentrations of concern, and as the data on aerosols may not have been available when the substance was first classified under DSD.

As the LC_{50} values from the studies on aerosols are higher than 5 mg/L, RAC concurs with the DS that no classification for acute inhalation toxicity is warranted. In conclusion, RAC recommends **to remove the existing classification for acute inhalation toxicity on benzyl alcohol**.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The DS presented two unpublished OECD TG 405 compliant studies in rabbits from 1990 and 1998 (only summaries available). Both studies used 3 animals that were treated with 100µl benzyl alcohol of 99.99% purity. Observation periods were 21 and 18 days, respectively. Another unpublished eye irritation study conducted in 1979 with only 2 rabbits and an observation period of only 7 days was also available. This study also used 100µl benzyl alcohol (no information on the purity of the substance).

The scores from both studies led to an overall categorisation as an eye irritant. All effects were reversible, at the latest by day 21. The study from 1979 also led to an overall conclusion of moderate eye irritancy from benzyl alcohol. The results from three older studies were also included in the proposal, one reporting benzyl alcohol to be highly irritating to the rabbit eye, whilst 2 other testing very low concentrations showed no irritancy. However, these results were considered of low relevance due to poor reporting.

Based on the result from the OECD 405 compliant studies, the DS considered that benzyl alcohol should be classified as Eye Irritant, category 2; H319.

Comments received during consultation

Two MSCAs supported DS proposal for classification as Eye Irritant, category 2; H319.

The scores from the two OECD TG compliant studies are tabled below. For comparison, the results from the 2 animals in the 1979 study are also included. However, as this study is terminated at 7 days, the irreversibility of the effect on the cornea by the end of the study is not considered relevant for the evaluation. Also, it is noted that the scores are similar or less severe than in the two OECD TG studies.

Year of study report	**Mean scores (no animals/scores of individual animal)**			
	Corneal opacity	Iritis	Conjunctival redness	Conjunctival oedema (chemosis)
1990- study	1 (**3/score 2**)	0.1 (1/mean score 0.3; 2/ score 0)	2 (**3/ score 2**)	0.8 (1/ score 3; 2/mean score 0.7)
	Time to full reversibity 21 days	Time to full reversibity 48 hrs	Time to full reversibity 21 days	Time to full reversibity 7 days
1998-study	2 (**3/ score 2**)	1 (**3/ score 1**)	2.4 (**1/ score 3; 1/mean score 2.3; 1/ score 2**)	2.2 (**1/score 3; 1/score 2**; 1/mean score 1.7)
	Time to full reversibity 18 days	Time to full reversibity 11 days	Time to full reversibity 11 days	Time to full reversibity 7 days
1979-study	**2/score 1** Time to full reversibility: > 7 days	**2/score 1-2** Time to full reversibility: 7 hrs	2/score 0-2 Time to full reversibility: 7 days	1/score 0-1; 1/score 0-2 Time to full reversibility: 7 days

Assessment and comparison with the classification criteria

For classification in category 2, one or more of the following scores should be fulfilled in at least 2 of 3 tested animals: corneal opacity ≥1; iritis ≥1; conjunctival redness ≥2 and/or conjunctival oedema ≥ 2.

Both studies following the OECD TG protocol fulfil the criteria for category 2 (see scores in bold in the table above). RAC agrees with the DS that benzyl alcohol should be **classified as Eye Irritant in category 2; H319.**

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Benzyl alcohol has a broad pattern of use in consumer and professional applications, and a large number of animal studies and human data investigating the skin sensitisation potential of benzyl alcohol as well as some *in vitro* data are presented in the classification proposal.

Benzyl alcohol is regulated in annex III (substances subject to restrictions due to its sensitising potential) of the Cosmetics Regulation and should be declared on the label of leave-on cosmetic products from 0.001%, and in rinse-off products from 0.001%. The DS further notes that the substances biocidal use as a preservative in ready-for-use is regulated at 1%.

Human data

There is a large data base on benzyl alcohol including results from experimental data in human volunteers (Human Result Insult Patch Tests, HRIPT, Human maximisation tests, HMT) and from patch tests in consecutive dermatitis patients from hospitals medical clinics, and case studies.

Table 1*: Experimental data in humans:*

Study description	Test substance, concentration	Number of volunteers	Results	Reference *
Human repeat insult patch test (HRIPT) 9 inductions under occlusion for 24 hrs over 3 weeks with 0.3 ml Benzyl alcohol 10-14 day rest period, then challenge patch for 24hrs (unexposed site) Reactions scored at 24, 48, 72 and/or 96hrs after application	20 % Benzyl alcohol in diethyl phthalate:EtOH (3:1) Hill Top chamber: 23622µg/cm²	56	Induction: oedematous skin reactions in 5 subjects *Challenge:* Oedema: **2/56 (3.6%) score 2+** **3/56 (5.4%) score 1+** Remaining subjects +/- (transient reaction) *Re-challenge:* Oedema: **1/56 (1.8%) score 2** **1/56 (1.8%) score 1+** 2/56 (3.6%) score +/-	(RIFM, 2002) Only short summary available
	15 % Benzyl alcohol in diethyl phthalate:EtOH (3:1) Hill Top chamber: 17717 µg/cm²	46	Induction: oedema in 5/46 subjects *Challenge:* Oedema: **4/46 (8.7%) score 2+** **1/46 (2.2%) score 1+** 1/46 (2.2 %) score +/- (transient reaction)	(RIFM, 2003) Only short summary available

	7.5 % Benzyl alcohol in diethyl phthalate:EtOH (3:1) Hill Top chamber: 8858µg/cm^2	110	Induction: Severe irritation in 1 subject *Challenge:* Oedema: **1/110 (0.9%) score 2+** (same subject as above - persistent at 96 h after challenge) **2/110 (1.8%) score not reported** *Re-challenge*: **1/3 positive at challenge sensitised** (after occlusive and semi-occlusive patches)	(RIFM, 2004b) Only short summary available
	5 % Benzyl alcohol in diethyl phthalate:EtOH (3:1) Hill Top chamber: 5906µg/cm^2	101	Induction: Oedema: 2 subjects - also at new sites. Transient reaction in 1 subject. *Challenge:* Oedema: **1/101 (1%)** score 3+ **1/101 (1%)** score 1+ Same subjects affected as at induction. Effects indicative of pre-sensitisation	(RIFM, 2005b)
	3 % Benzyl alcohol in diethyl phthalate:EtOH (3:1) Hill Top chamber: 3 543 µg/cm^2	107	Negative, no skin reactions	(RIFM, 2004a)
Human maximisation test (HMT) according to (Kligman, 1966) Patches on volar forearms under occlusion 5 alternate-day 48h periods 24 h pretreatment with 5% aqueous sodium lauryl sulphate (SLS) under occlusion. 10-14 day rest period 48h challenge Reading at 0, 48 and 72hrs upon removal	10 % Benzyl alcohol in petrolatum Hill Top chamber: 6 900 µg/cm^2	25	Negative	(RIFM, 1970)

Five unpublished reports (summaries available) from HRIPTs with doses ranging from 3543 µg/cm^2 to 23622 µg/cm^2 using 3 to 20% Benzyl alcohol for induction and challenge were reported. Scoring of skin reactions was performed, scores >1 being regarded as a positive sensitisation reaction. Three of the studies including 47-110 subjects resulted in sensitisation

in 2.7%-11% of subjects occurring from doses above 8858 µg/cm^2 or 7.5% benzyl alcohol. In a fourth HRPIT using 5% benzyl alcohol, pre-sensitisation was suspected in 2 subjects reacting already in the induction phase, and the results are ambiguous. The individual studies are reliable with restrictions, with scarce information given in the available summaries. Also, some studies use a relatively low number of subjects.

One HMT in 25 volunteers from 1970 for 10% Benzyl alcohol available as a summary was negative. The low number of subjects and low concentration of benzyl alcohol reduces the robustness of the result.

***Table 2**: Human patch tests studies*

Study description	**Test substance concentration**	**Number of patients**	**Results**	**Reference**
Human patch test Retrospective analysis of data on patch testing of preservatives contained in the standard series and special series collected by the IVDK 1996–2009.	**1%** Benzyl alcohol in petrolatum Purity not specified	79770	258/79770 subjects with positive reactions **(0.28%)** 64 **men (0.18 %),** 194 **women (0.34 %)**	(Schnuch et al., 2011a)
Human patch test Data on all patients patch tested in the departments of the Information Network of Departments of Dermatology between 2005 and 2008. Diagnostic procedure follows international guidelines.	**1%** Benzyl alcohol Purity and vehicle not specified	23257	51/23257 subjects with positive reactions **(0.22 %)**	(Uter et al., 2010)
Human patch test Frequency of sensitisation to preservatives analysed on the basis of data from the IVDK (2006–2009).	Benzyl alcohol Purity, vehicle and test concentrations not specified	17740	31 subjects with positive reactions **(0.17 %)**	(Schnuch et al., 2011b)
Human patch test Analysis of data on the frequency of sensitisation to selected antimicrobials in all patients with current or previous atopic eczema compared with patients without past or current atopic eczema, patch test data collected by Departments of Dermatology participating in the IVDK (1995-1999). (patient groups standardised for age and sex, patients with current leg ulcer/stasis dermatitis were excluded)	**1%** Benzyl alcohol in petrolatum Purity not specified	14722 (non-atopic) 5183 (atopic)	**44/14722 non-**atopic patients with positive reactions **(0.3 %)** 15/5183 atopic patients with positive reactions (0.28 %)	(Jappe et al., 2003)
Human patch test Retrospective study on patients with suspected allergic contact dermatitis tested with a preservative series, data collected between 1990 and	**1 %** Benzyl alcohol in petrolatum Purity not specified	11373	46/11373 subjects with positive reactions **(0.4 %)**	(Schnuch et al., 1998)

Study description	Test substance concentration	Number of patients	Results	Reference
1994 from 24 departments participating in the German Information Network of Departments of Dermatology (IVDK).				
Human patch test Retrospective multicentre survey of patch test reactions to standard, cosmetic and hairdressing series collected by 7 Finnish dermatological clinics representing the Finnish Contact Dermatitis Group (comparing results from 1995-1996 and 2000-2002).	Benzyl alcohol Purity, vehicle and test concentrations not specified	6125 (2000-2002) 4922 (1995-1996)	2000-2002: **No** allergic reactions 1995-1996: 1/4922 subject with positive reaction **(0.02 %)**	(Hasan et al., 2005)
Human patch test Study on patients tested with Belgian Contact Patch-test series.	Benzyl alcohol Purity, vehicle and test concentrations not specified	5202 (with known contact dermatitis)	48 subjects with positive reactions **(0.9 %)**	(Broeckx et al., 1987)
Human patch test Retrospective study of patch testing results, aggregated from four patch test clinics in three centres in Melbourne and Sydney (1993–2006). Data were collected for a minimum of five years from each centre.	**1%** Benzyl alcohol Purity not specified	4552	18/4552 subjects with positive reactions **(0.4 %**)	(Chow et al., 2013)
Human patch test Study on the frequency of sensitisation to fragrances to be labelled according to current European regulation. 25 fragrances were successively patch-tested additionally to the standard series in a total of 21 325 unselected patients; the number of patients tested with each of the fragrances ranged from 1658 to 4238 in 2003-2004.	**1%** Benzyl alcohol Purity and vehicle not specified	2 166	7/2166 subjects with positive reactions **(0.3 %):** 3 subjects 1+, 3 subjects 2+, 1 subject 3+) 12 irritant or doubtful reactions Sensitisation to Benzyl alcohol associated with leg dermatitis (29 %).	(Schnuch et al., 2007)
Human patch test Retrospective study on data from all eczema patients routinely tested 2011-2012 with the fragrance series and the European baseline series at St John's Institute of Dermatology at St Thomas' Hospital, London. Co-reactions also reported.	**10%** Benzyl alcohol in petrolatum Purity not specified	1 951	4 subjects with positive reactions **(0.21 %)** Co-reactions with any fragrance marker 3/4 (75%) of reactions to fragrance series substance Co-reactions with fragrance mix I (FM I) 1/4 (25%)	(Mann et al., 2014)

Study description	Test substance concentration	Number of patients	Results	Reference
			of reactions to ingredient. Co-reactions with fragrance mix II (FM II) 2/4 (50%) of positive reactions to ingredient.	
Human patch test Patients were tested for their reaction to three different fragrance mixes (FM I, FM II, and "further fragrances"). Patients tested positive to a mix were tested with the individual components. The frequency of sensitisation in the study population was extrapolated from the frequency of reactions to the single compound.	Fragrances mix and Benzyl alcohol Composition of fragrances mix, purity of test substance(s), vehicle and test concentrations not specified	1 870	**0.7 %** of the patients sensitised to the fragrances mix tested positive for Benzyl alcohol. This corresponded with a frequency of **0.16 %** when extrapolated to all 1 870 patients.	(Schnuch et al., 2015)
Human patch test Retrospective study based on data from the Department of Dermato-Allergology, Copenhagen University Hospital Gentofte. Eczema patients were patch tested (2008- 2010) with the 26 fragrance ingredients, including Benzyl alcohol. All eczema patients suspected of having contact allergy were tested consecutively according to international guidelines.	**1%** Benzyl alcohol Purity and vehicle not specified	1 508	2/1508 subjects with positive reaction (**0.1 %**) In addition: - 3 subjects with doubtful reaction - 1 subject with irritant reaction	(Heisterberg et al., 2011)
Human patch test Prospective study of cosmetic adverse reactions by eleven dermatologists (1977-1980) using standard screening, perfume or vehicle-preservative series of the North American Contact Dermatitis Group	Benzyl alcohol Purity, vehicle and test concentrations not specified	487	2 subjects with positive reactions **(0.4 %)**	(Eiermann et al., 1982)
Human patch test (short report) Patients with clinical suspicion of cosmetic contact dermatitis patch tested at Contact Dermatitis Clinic of Rabin Medical Center in Israel from 1997-2000. European standard series and cosmetic series used.	Benzyl alcohol Purity, vehicle and test concentrations not specified	244	5 subjects with positive reactions (**2.0 %**)	(Trattner et al., 2002)
Human patch test Frequency of cosmetics as causal factors of allergic contact dermatitis are reported and the cosmetic allergens identified during the	Benzyl alcohol Purity, vehicle and test concentrations not specified	147	1 subject with positive reaction (**0.68 %**)	(Goossens, 2016)

Study description	Test substance concentration	Number of patients	Results	Reference
previous six years are discussed (2010–2015). The data were retrieved from and evaluated with a patient database developed in-house.				
Human patch test Prospective study of 93 consecutive patients suspected of having allergic contact dermatitis tested 2005-2006 with the European standard series and cosmetic series at the Dermatology Department, Baskent University Faculty of Medicine, Ankara, Turkey.	**10%** Benzyl alcohol Purity and vehicle not specified	93	1 subject with positive reaction **(1.1 %)**	(Ada and Seckin, 2010)
Human patch test 4-year retrospective study of selected patients tested with a fragrance series (2004-2008). Patients selected were either positive to the Spanish baseline series (54 patients) or there was clinical suspicion (32 patients).	**1%** Benzyl alcohol in petrolatum Purity not specified	86	2/86 subjects with positive reactions (**2.3 %**)	(Cuesta et al., 2010)
Human patch test Study on 35 consecutive patients tested with chemical compounds recommended by North American Contact Dermatitis Group. In cases with positive reactions chemical compounds were re-applied at day 7 and read again at day 9.	Benzyl alcohol Purity, vehicle and test concentrations not specified	35	2 subjects with positive reactions on day 2 and at re-testing **(6 %)**	(Mitchell, 1977)

The largest study included 79 770 consecutive dermatitis patients from 1996 to 2009 analysed retrospectively (Schnuch et al. 2011a), in which a concentration of 1% benzyl alcohol was used for patch testing. The authors of that study conclude that benzyl alcohol is a rare contact allergen (combined incidence of 0.28%) and report a higher incidence in women (0.34 %) compared to men (0.18 %).

Two human patch testing studies of dermatitis patients (table 2) with 10% Benzyl alcohol resulted in sensitisation rates of 0.21 % and 1.1 %, respectively, whilst patch testing of benzyl alcohol at a concentration of 1% led to sensitisation rates ranging from 0.1 % to 2.3 %. There are also a number of studies not specifying the concentration of benzyl alcohol used, resulting in sensitisation rates in the same range (up to 2% positives).

The highest incidence of sensitisation reported stems from a study based on 35 patients (6 %) (Mitchell 1977). The lowest incidence reported was of no positive reactions amongst 6 125 patients between 2000 and 2002, and 0.02 % positive reactions amongst 4 922 between 1995 and 1996 (Hasan et al. 2005).

Overall, patch test studies including more than 100 patients show sensitisation rates between 0.1 and 1%.

Furthermore, 38 patch test studies as summarised by the DS from a review article (Scognamiglio et al. 2012) are included in the table below. Details of these studies are lacking.

***Table 3**: Human diagnostic patch test data*

Concentration of benzyl alcohol	Incidence	Original references
20% in petrolatum	**5%** from 1971-74; **4%** from 1975-77, **1%** from 1978-80 in cosmetic dermatitis patients Number of patients not reported	(Nakayama et al., 1984)
10% in petrolatum	0/501 (0%)	(De Groot et al., 1986)
10% in petrolatum	2/394 **(0.5%)**	(Mid-Japan Contact Dermatitis Research Group, 1984) (Ueda, 1994)
5% in petrolatum	1/394 **(0.3%)**	
1% in petrolatum	0/394 (**0%)**	
10% (vehicle not reported)	3/182 **(1.6%)**	(Malten et al., 1984)
5% in petrolatum	1/2261 **(0.04%)** from 1978-79 0/1934 **(0%)** from 1979-80	(Mitchell et al., 1982)
5% in petrolatum	3/991 **(0.3%)**	(Dickel et al., 2001)
5% in petrolatum	3/669 **(0.4%)**	(Katoh et al., 1995)
5% in petrolatum	0/667 **(0%)**	(van Joost et al., 1984)
5% in petrolatum	6/661 **(0.9%)**	(Itoh et al., 1988)
5% in petrolatum	9/585 **(1.5%)**	(Itoh et al., 1986)
5% in petrolatum	3/425 **(0.71%)**	(Nagareda et al., 1992)
5% in petrolatum	1/479 **(0.2%)**	(Nagareda, 1996)
5% in petrolatum	1/398 **(0.3%)**	(Sugai, 1996)
5% in petrolatum	2/200 **(1%)**	(Nethercott, 1982)
5% in petrolatum	0/241 **(0%)**	(Ferguson and Sharma, 1984)
5% in petrolatum	8/102 **(7.8%)**	(Hausen, 2001)
5% in petrolatum or 10% in alcohol	19/95 *(20%)*	(Hjorth, 1961)
5% (vehicle not reported)	0/3037 **(0%)**	(Angelini et al., 1985)
5% (vehicle not reported)	13/1206 **(1.1%)**	(Sugai, 1982)
5% (vehicle not reported)	0/574 **(0%)**	(Hirose et al., 1987)
5% (vehicle not reported)	1/457 **(0.2%)**	(Addo et al., 1982)
5% (vehicle not reported)	8/427 **(1.9%)**	(Nishimura et al., 1984)
5% (vehicle not reported)	2/242 **(1.7%)**	(Van Joost et al., 1985)
5% (vehicle not reported)	6/220 **(2.7%)**	(Ishihara et al., 1979)
5% (vehicle not reported)	0/178 **(0%)**	(Hirano and Yoshikawa, 1982)
5% (vehicle not reported)	3/167 **(1.8%)**	(Larsen et al., 1996)
5% (vehicle not reported)	0/145 **(0%)**	(Suzuki et al., 1997)
5% (vehicle not reported)	1/84 *(1.1%)*	(Takase et al., 1984)

Concentration of benzyl alcohol	Incidence	Original references
5% (vehicle not reported)	1/81 *(1.2%)*	(Haba et al., 1993)
5% (vehicle not reported)	3/78 *(3.8%)*	(Ishihara et al., 1979)
2% (vehicle not reported)	2/78 *(2.6%)*	
1% (vehicle not reported)	2/78 (2.6%)	
1% in petrolatum	7/2166 **(0.3%)**	(Schnuch et al., 2007)
1% in petrolatum	1/1082 **(0.1%)**	(Geier et al., 2003)
1% in petrolatum	1/320 **(0.3%)**	(van Oosten et al., 2009)
1% (vehicle not reported)	0/3115 **(0%)**	(Cooper and Shaw, 2000)
1% (vehicle not reported)	0/436 **(0%)**	(Penchalaiah et al., 2000)
1% (vehicle not reported)	0/422 **(0%)**	(An et al., 2005)
1% (vehicle not reported)	1/390 **(0.3%)**	(Torgerson et al., 2007)
0.2% (vehicle not reported)	18/614 **(2.9%)**	(Fuji et al., 1972)

The results of diagnostic patch tests with benzyl alcohol summarised in table 3 above showed incidences of sensitisation in 0 to 20% of the patients. However, the DS notes that the robustness of studies including less than 100 individuals may be questioned. When disregarding those studies sensitisation occurs in frequencies of 0-7.8%, with 12 negative studies, 14 studies with less than 1% of the patients reacting and 9 studies with more than 1% reactions.

The DS also reported 19 case reports from consecutive dermatitis patients reacting to benzyl alcohol. Most patients reacted strongly to patch testing with benzyl alcohol, but also mild and negative results were reported.

***Table 4**: Case reports of sensitisation*

Study description	Results	References
30 year-old facial dermatitis patient Patch testing with Benzyl alcohol (no test concentration reported) produced	Macular erythema	Case reports cited by (Johnson et al., 2017)
38 year-old eczema patient 1% aqueous Benzyl alcohol Prick test and intradermal injection	Negative prick test result Positive (++) intradermal injection test result. (injection test were negative in 10 healthy controls)	
39 year-old female with pruritic erythema of foot 5 % Benzyl alcohol in petrolatum Patch test and Repeated open application test	Weak (+) reaction in patch test Strong positive reaction in repeated open application test	
67 year-old male with leg dermatitis Occlusive patch test with 1% benzyl alcohol in petrolatum Prick test with 0.9% benzyl alcohol in saline	Positive (+ +) occlusive patch test reaction. Negative prick test reaction at 0.5 hours reading, but marked induration and proximal spread over arm at days 3 to 8	

Study description	Results	References
53 year-old with stasis dermatitis Patch test with 1% Benzyl alcohol in petrolatum	Redness and swelling at 1 hour after patch application, wheal 1 day later, and mild urticaria at day 5	
16 year-old female with possible anaphylactic reaction after injection with B12 preparation containing 0.9 % Benzyl alcohol Prick test and intradermal test with benzyl alcohol preparation (concentration not reported)	Negative in prick test, Positive in intradermal test	
57 year-old female with pruritic dermatitis Patch testing with Benzyl alcohol (concentration not reported)	Allergic contact dermatitis after patch testing	
40 year-old female with dermatitis Patch test using 9.5% benzyl alcohol in petrolatum	Positive patch test reaction (+++)	
65 year-old female with eyelid dermatitis Patch testing with benzyl alcohol (concentration not stated)	Macular erythema	
30 year-old female with eyelid dermatitis Patch testing with benzyl alcohol (concentration not stated)	Positive (+) patch test reaction	
46 year-old man with atopic excema Patch testing with 5% Benzyl alcohol in petrolatum	Positive (+ +) reaction at day 2 and day 3	(Corazza et al., 1996)
43 year-old patient with recurrent right leg ulceration Patch testing with 0.1% Benzyl alcohol in aqueous solution	Strong positive (+ + +) reaction at day 1 and day 3	(Jager et al., 1995)
63 year-old woman Patch testing with 5% Benzyl alcohol (vehicle not reported)	Positive (+ +) reaction	(Li and Gow, 1995)
37 year-old woman with acute excema Patch testing with 1% Benzyl alcohol in petrolatum	Strong positive (+ + +) reaction at day 2 and 4	(Aguirre et al., 1994)
50 year-old man Patch testing with 5% Benzyl alcohol in petrolatum	Strong positive (+ + +) reaction after 48 and 96 hours	(Wurbach et al., 1993)
28 year-old metal grinder with patchy rash Patch testing with 1% Benzyl alcohol in petrolatum	Positive (+ +) reaction at day 2 and 3	(Mitchell and Beck, 1988)
41 year-old Japanese women Patch testing with 5% Benzyl alcohol (vehicle not reported)	Positive reaction (+ +) after 48 and 72 hours in patch test Negative in open patch test	(Shoji, 1983)
80 year-old man Patch testing with 5% Benzyl alcohol in petrolatum	Positive reaction at days 2 (+) and 4 (++)	(Kleyn et al., 2004)
36 year-old female and 43-year old male with contact dermatitis Patch testing with 1% Benzyl alcohol in petrolatum Scratch, intradermal and subcutaneous injections of 1% Benzyl alcohol in saline solution	Strong positive reaction in patch test. Negative in intradermal and subcutaneous injections	(Fisher, 1975)

DS conclusion on human data

A large database from human studies including HRIPTs, one HMT, and several patch test studies from dermatological hospitals and case reports was available on benzyl alcohol.

The HRIPTs available on benzyl alcohol are considered to be valid, although the reporting is lacking some information. Three of the studies including 47-110 subjects resulted in sensitisation in 2.7%-11% of subjects occurring from increasing doses (0-11%) benzyl alcohol from 7.5% (8858 µg/cm^2). The HMT showed no sensitisation from exposure to 10% benzyl alcohol in 25 volunteers. Due to the low number of subjects tested and that only one dose was applied, the reliability of the results is uncertain.

Multicenter patch testing studies of collective of dermatitis patients show sensitisation rates from 0.1 to 2.3% when tested with benzyl alcohol from in concentrations 1 to 10%. Short reports from further patch test studies performed with 0.2-20% benzyl alcohol show sensitisation rates from 0 up to 20%, with studies with more than 100 patients generally showing sensitisation of <1%, perceived as a low to moderate sensitisation rate according to the Guidance (the ECHA Guidance on the Application of the CLP criteria, 2017).

The information on exposure to benzyl alcohol from both experimental and clinical studies is however scarce, and no reliable estimate of the level exposure is possible. The DS points especially to the ubiquitous presence of Benzyl alcohol in a broad range of cosmetic products that may be applied several times per day and result in a prolonged or repeated exposure over years. Applying the criteria for scoring exposure set in the Guidance, table 3.3, the DS concludes that exposure to benzyl alcohol is relatively high.

Animal data

The animal studies presented include results from one LLNA test and a number of guinea pig tests, three being maximisation tests, and others including older test protocols such as the Draize test, the open and closed epicutaneous test (OET and CET), and one Freund's complete adjuvant (FCA) test. The studies are only available as short summaries of unpublished reports, and one is in Japanese.

The LLNA test from 2005, conducted according to OECD TG 409 with 99.8% pure benzyl alcohol in diethyl phthalate:ethanol (3:1), using 4 animals and 5 treatment groups up from 2.5 to 50% w/v was negative. The stimulation indices (SI) were 0.5-1.2% and EC_3 >50%.

In a GPMT conducted in a protocol similar to OECD TG 406 and deemed reliable with restrictions, 5% intradermal and 25% epicutaneous induction did not result in sensitisation (Klecak et al. 1977).

Another article reported a GMPT using 10% benzyl alcohol for induction and challenge to be positive (Ishihara et al. 1986), whilst the same main author had earlier reported a GMPT to be negative (Ishihara et al. 1981). However, it was not possible to assess the reliability of these results.

Kashima and coworkers reported benzyl alcohol to be a weak sensitiser in a non-standard "modified cumulative contact enhancement test" using 30% for induction and 10% benzyl alcohol for challenge (Kashima et al. 1993). The DS considered the report reliable with restrictions based on the level of detail available.

A negative modified Draize sensitisation test conducted prior to OECD TG regarded to be reliable with restrictions was reported to have used the challenge concentration of 0.25 and 10% intradermally and epidermally, respectively (Sharp 1978).

The paper by Klecak et al. (1977) also reported a FCA test, an OET, and a Draize test stated to be a conducted according to OECD TG 406 comparable protocols. The FCA test, in which undiluted

benzyl alcohol for induction was used, gave a positive result with a "non-irritating challenge dose". The OET using several dilutions up to undiluted benzyl alcohol for induction also resulted in sensitisation after challenge with a "non-irritating challenge dose", whilst the Draize test using 5 doses of 0.1% at induction over 10 days for induction and 0.1% at challenge was negative (Klecak 1977). The information from the studies in this article is considered reliable with restrictions.

Two later papers from Klecak (1979, 1985) reported a negative result from an OET using 10% benzyl alcohol, but reliability could not be attributed due to lack of detail.

Hausen et al. (1992) reported benzyl alcohol (component of Balsam of Peru) to be a moderate sensitiser in a FCA test and a weak sensitiser in a modified FCA test. However, very few study details were given and reliability therefore not assessed.

Overall, the animal studies are of variable quality, their reporting is poor, and the results are contradictory. One out of three GPMTs and two out of three OETs were positive, the FCA tests showed benzyl alcohol to be a weak to moderate sensitiser whilst the Draize tests were negative. The LLNA test was negative, however it is noted that the maximum concentration tested was 50%, and no justification not using a higher concentration was offered in the summary available.

The DS concluded that the animal data indicate that benzyl alcohol is a weak sensitiser in animal studies of variable quality.

Other data

Summaries from reports from *in vitro* tests relating to key events an adverse outcome pathway (AOP) leading to skin sensitisation were available on benzyl alcohol.

Table 5*: Summary table of in vitro / in chemico data*

Key event **Type of test**	**Result**	**Remarks from study author or DS**	**Reference**
Key event 1: Peptide/ protein binding Test: Direct peptide reactivity assay (DPRA) *in chemico*	Negative	Metabolic activation of benzyl alcohol may be necessary, according to author.	(Urbisch et al., 2015)
Key event 2: Keratinocyte response ARE-Nrf2 luciferase assay Test 1: KeratinoSens™ (*in vitro*)	Negative	The DS notes that the different results may be due to differences in sensitivity in detecting a weak sensitising potential	
Key event 2: Keratinocyte response ARE-Nrf2 luciferase assay Test 2: LuSens (*in vitro*)	Positive		
Key event 3: Monocytic/ Dendritic cell response Test: Human cell line activation test (h-CLAT (in vitro))	Positive		

Based on the results and remarks included in the table above the DS regards that the *in vitro/in chemico* data point towards a sensitising potential of benzyl alcohol.

In conclusion, regarding all the data in a weight of evidence assessment, from the HRIPT studies on Benzyl alcohol, from dermatitis patients, animal data, and indications o sensitisting potential

from *in vitro/in chemico* assays, the results all point to a weak to moderate skin sensitising potential of benzyl alcohol. A classification as Skin Sens. in category 1B is proposed by the DS.

Comments received during consultation

A total of 10 organisations or individuals filed detailed comments, often including public and confidential comments in the public consultation.

Two MSCAs supported the proposed classification based on weight of evidence.

Six Industrial organisations, including one industrial expert group commented that the quality of the database was not satisfactory. Several organisations questioned whether the status of the patched tested individuals, pointing to the possibility of the patients being selected rather that unselected. The commenters also commented on the low to insignificant sensitising potential of benzyl alcohol. Considering classification in category 1B to overestimate the hazard from benzyl alcohol.

The academic organisation IVDK provided additional information on patch test results from several dermatology departments performed from 2010 to 2019 with benzyl alcohol. The largest resulted in incidences of positive results of 146/70867 (0.21%) and 99/54062 (0.18%). They provided analyses to demonstrate that a number of patch tested patients had previous sensitisation history or some reactions were irritative rather than sensitisation response to benzyl alcohol. Comparison with other sensitizer led IVDK to conclude that benzyl alcohol is a very rare skin sensitiser not meriting classification.

One individual commented on the animal and *in vitro* data, stating that only OECD TG studies should be used for classification and considered the outcome of the *in vitro* tests negative

The DS stressed that the CLP criteria rules that a weight of evidence approach using all available and suitable animal, *in vitro* and human data should be performed in order to reach a conclusion on classification. The DS further explained that the human data were evaluated in accordance with CLP criteria and supplemented by the Guidance, inter alia in the evaluation of frequency of effect and exposure.

Assessment and comparison with the classification criteria

Human data

The numerous human data available for benzyl alcohol include experimental and clinical studies. RAC notes that conducting experimental studies in humans such as HRIPT and HMT, as underlined in the CLP regulation, is not allowed for ethical reasons. Information from existing studies may however be considered for classification purposes, and therefore criteria for the use of such data are also included in the classification criteria.

RAC notes that specific information on the exposure levels of the patients tested are often missing in clinical data from diagnostic patch tests, as it is also the case for benzyl alcohol. However, in view of the broad use pattern of benzyl alcohol and especially its use in cosmetics, exposure is expected to occur repeatedly and over longer periods of time. The Guidance (ECHA 2017) includes a scoring system to evaluate the size of exposure qualitatively in table 3.4 applied below:

Table: *Level of exposure*

Exposure data	Relatively low exposure	Relatively high exposure	**Benzyl Alcohol**
Concentration/ dose criteria	<1.0% or <500µg/cm^2 (score 0)	≥1.0% or ≥500µg/cm^2 (score 2)	Unknown (score 1[1])
Repeated exposure	< once daily (score 1)	≥ once daily (score 2)	≥ once daily (score 2)
Number of exposures	< 100 exposures (score 0)	≥100 exposures (score 2)	≥100 exposures (score 2)
Total score	1-3	4-6	**5**

[1]An intermediate score of 1 is attributed as the exposure concentration is not reported in the available studies.

The resulting total score achieved for benzyl alcohol of 5 is regarded as reflecting a high exposure. RAC notes that IFRA use recommendations for different product groups in rinse-off and leave-on cosmetics indicate that concentrations over 1% might occur (IFRA standards 2020) indicating that the overall score in the estimation of the level of exposure to benzyl alcohol could be higher than 5.

The criteria relating to diagnostic patch tests data further distinguishes between "*a relatively high and substantial incidence of reactions*…" and "*a relatively low but substantial incidence of reactions*…" (category 1A and sub-category 1B). Table 3.2 on Frequency of occurrence of skin sensitisation in the Guidance (ECHA 2017) considers test data in unselected, consecutive dermatitis patients resulting in incidences above ≥ 1.0% to be of high frequency, and incidences <1.0% of low/moderate frequency. The results of patch testing studies reported in table 1. Experimental data in humans testing consecutive, unselected patients and using standard series fall under category of high frequency.

If the dermatitis patients are selected, and the testing aimed, the limit between high and low/moderate frequency is 2.0%. Due to the scarce information available for the studies reported in table 3 on human diagnostic patch test data, it cannot be excluded that the some of the studies included selected patients, and the information is thus difficult to assess under this part of the criteria.

Animal data

Only few details are available from the animal study summaries on benzyl alcohol. One LLNA study from 2005 conducted according to OECD TG 429 and GLP for which a robust study summary is available can be considered as reliable with restrictions, although there appears to be no justification available for the lower concentration used is relation to the OECD TG 429 requirements. The reporting of the majority of adjuvant and non-adjuvant studies in guinea pigs carried too few details to enable evaluation of their reliability. The results are often only listed as positive or negative, and application of sub-categorisation criteria is not possible as the condition of induction are not reported. Overall, the animal data are insufficient for classification on their own. However, the results are included in the table below on the weight of evidence assessment for the classification of benzyl alcohol.

Other data

There are as yet no specific criteria in CLP on the use of *in vitro/in chemico* data for classification for skin sensitization. The CLP regulation and the Guidance recommends to include the information from *in vitro* methods in a weight of evidence approach with other data. OECD TGs have in the recent years included *in vitro* methods describing key event steps relating to an Adverse Outcome Pathway (AOP) approach for skin sensitisation, developed by the OECD in 2016

including three key events to investigated in *in vitro* tests. These tests are referred in the Guidance on Information Requirements and Chemical Safety Assessement, Chapter R.7a: endpoints specific guidance (2017). Most recently, a defined approach for skin sensitisation (DASS) was adopted by the OECD WNT (May 2021) including a refined Integrated Testing Strategy (ITS) v2 (OECD 2021a, 2021b). The data from key events tests related to skin sensitisation performed on benzyl alcohol are therefore also included in the table below on the weight of evidence approach for the classification of benzyl alcohol. RAC notes that benzyl alcohol is one of the substances included in the OECD database (OECD 2021b) supporting the new defined approach on skin sensitisation adopted by OECD (OECD 2021a). Application of the OECD ITS v2. approach (Integrated Testing Strategy including use of OECD toolbox for *in silico* data scoring) gives total score of 2 (1 from OECD Toolbox and 1 from the positive hCLT) which is considered to warrant sub-categorisation as Skin Sens. 1B.

Conclusion

The table below includes all the available human data from volunteer studies (HRIPT and HMT), diagnostic patch test in consecutive patients, diagnostic patch tests where information on the history of the patients is unavailable, and human patch test cases. With respect to animal data available in the dossier, the table includes the LLNA, 3 GMPTs, 3 FCA tests, 3 OETs, one closed epicutaneous test, one delayed contact hypersensitivity test, and 3 Draize tests available in the classification report. Finally, the table also includes the 4 available *in vitro/in chemico* tests. A short mention on reliability of the studies and RACs evaluation on the contribution to classification from the individual results in order to facilitate the weight of evidence based conclusion on the classification of benzyl alcohol are included.

Table : *Weight of evidence approach for the classification of benzyl alcohol*

Study type	Result /Reliability	CLP criteria, and detail from the Guidance on the Application of classification criteria	RAC evaluation on classification outcome of each individual study[a]
Human data			
HRIPT	3 positive results at 8 858 µg/cm^2 and above in studies including >100 volunteers Reliable with restrictions	**Sub-category 1A**: (a) positive responses at ≤ 500 µg/cm^2 (HRIPT, HMT–induction threshold) (Annex I: 3.4.2.2.2.1.) **Sub-category 1B:** (a) positive responses at > 500 µg/cm^2 (HRIPT, HMT–induction threshold); (Annex I: 3.4.2.2.2.2)	**Skin Sens. 1B**
HMT	Negative Uncertainty due to low number of volunteers. Not reliable	**Sub-category 1A:** (a) positive responses at ≤ 500 µg/cm^2 (HRIPT, HMT–induction threshold) (Annex I: 3.4.2.2.2.1.) **Sub-category 1B:** (a) positive responses at > 500 µg/cm^2 (HRIPT, HMT–induction threshold); (Annex I: 3.4.2.2.2.2)	**Not considered suitable for classification in this case**
Diagnostic patch tests in consecutive dermatitis patients	Overall sensitisation rate of <1% Low/moderate frequency, Relatively high exposure	**Skin Sens. 1:** Relatively high frequency (≥ 1.0%*) and "relatively high exposure" or Relatively low/moderate frequency (< 1.0%*) and "relatively low exposure"	**Skin Sens. 1B**

Study type	Result /Reliability	CLP criteria, and detail from the Guidance on the Application of classification criteria	RAC evaluation on classification outcome of each individual study[a]
	Reliable with restrictions	**Skin Sens. 1A:** Relatively high frequency (≥ 1.0 %*) and "relatively low exposure" **Skin Sens. 1B:** Relatively low/moderate frequency (< 1.0 %*) and "relatively high exposure"	
Diagnostic patch tests Conditions of testing unclear	Sensitisation rates 0-7 %. Most studies with >100 patients <2% Reliable with restrictions	**Skin Sens. 1:** Relatively high frequency (≥ 1.0%* or ≥ 2.0%**) and "relatively high exposure" or Relatively low/moderate frequency (< 1.0%* or < 2.0%**) and "relatively low exposure" **Skin Sens. 1A:** Relatively high frequency (≥ 1.0 %* or ≥ 2.0%**) and "relatively low exposure" **Skin Sens. 1B:** Relatively low/moderate frequency (< 1.0 %* or <2.0%**) and "relatively high exposure"	**Skin Sens. 1B**
Case reports	< 100 cases Relatively high exposure estimated above (score 5) Reliable with restrictions	**Skin Sens. 1:** Relatively high frequency (Number of published cases ≥ 100) and "relatively high exposure" or Relatively low frequency (number of published cases < 100) and "relatively low exposure" **Skin Sens. 1A:** Relatively high frequency (Number of published cases ≥ 100) and "relatively low exposure" **Skin Sens. 1B:** relatively low frequency (Number of published cases < 100) and "relatively high exposure"	**Skin Sens. 1B**
Animal data			
LLNA test	EC3 > 50 % Maximum used concentration. Uncertainty as justification on choice of dose levels unavailable Reliable with restrictions	**Skin Sens. 1A:** EC3 ≤ 2 % **Skin Sens. 1B:** EC3 > 2 %	**No classification**
Guinea Pig Maximisation Test	1 positive reliability unknown		(Skin sensitiser)
	1 negative reliability unknown		(No classification)

Study type	Result /Reliability	CLP criteria, and detail from the Guidance on the Application of classification criteria	RAC evaluation on classification outcome of each individual study[a]
	1 negative reliable with restrictions		**No classification**
Freund's Complete Adjuvant Test	1 positive reliable with restrictions		**Skin sensitiser**
	1 positive reliability unknown		(Skin sensitiser)
	1 weakly positive reliability unknown		(Skin sensitiser/ no classification)
Open Epicutaneous Test	2 positive reliability unknown		(Skin sensitiser)
	1 positive reliable with restrictions,		**Skin sensitiser**
	1 negative reliability unknown		(No classification)
Closed epicutaneous test	negative reliability unknown		(No classification)
Delayed contact hypersensitivity test	positive reliable with restrictions		**Weak sensitiser**
Draize Guinea Pig Sensitisation Test	1 negative reliable with restrictions		**No classification**
	1 negative reliable with restrictions		**No classification**
	1 negative reliability unknown		(No classification)
		***In vitro* data[1]**	
Key event 1 protein binding: Direct peptide reactivity assay	Negative Reliable without restrictions	**Skin sensitiser when 2 out of 3 key events confirmed in test**	**Inconclusive result: 1 or 2 out of 3 key events are positive**
Key event 2: ARE-Nrf2 luciferase assay KeratinoSensTM Keratinocyte response	Negative Reliable without restrictions		
Key event 2: ARE-Nrf2 luciferase assay LuSens (in vitro) Keratinocyte response	Positive Reliable without restrictions		
Key event 3: h-CLAT (in vitro)	Positive Reliable without restrictions		

[a] Text in bold refers to a reliable study (with or without restrictions), text in brackets to study with unknown reliability, which are not considered in the WoE. The WoE gives preference to reliable results.
[*] Limit applies to unselected dermatitis patients
[**] Limit applies to selected dermatitis patients
[1] One *in vitro* test cannot stand alone, but overall build up to an AOP on skin sensitisation.

The data base on benzyl alcohol is very large, albeit of varying reliability and suitability for classification purposes. In the weight of evidence assessment above, the human data from HRIPTs and from diagnostic patch tests and case reports are regarded as suitable for classification, and all point to benzyl alcohol being a low-moderately potent skin sensitiser.

The most reliable animal data is the LLNA although there is uncertainty whether the maximum dose of 50% was sufficiently high to detect an apparently weak sensitiser as benzyl alcohol. The rest of the animal results are contradictory, and the reliability and suitability for classification is low, as details of exposure are unavailable.

Finally, data included in the AOP (OECD 2016a, referred in IR&CSA 2017) do not point to a clear conclusion, as there is both a positive and a negative result for one of the three key events of this AOP, but indicate activity that can lead to sensitisation.

In conclusion RAC agrees with the DS that the weight of evidence assessment including all human, animal, *in silico* and *in vitro* data available on benzyl alcohol, with the extensive human data from HRIPT and diagnostic patch test data as the most important evidence, leads to the conclusion that benzyl alcohol should be **classified as Skin Sensitiser, subcategory 1B; H317 - May cause an allergic skin reaction**.

RAC further agrees with the DS that attribution of SCL is not warranted.

Additional references

IFRA standards (2020) amendment 49 – benzyl alcohol (https://ifrafragrance.org/standards/IFRA_STD_008.pdf)

OECD (2021a): OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects - Guideline No. 497: Defined Approaches on Skin Sensitisation. Organisation for Economic Co-operation and Development. https://www.oecd-ilibrary.org/environment/guideline-no-497-defined-approaches-on-skin-sensitisation_b92879a4-en

OECD (2021b). Supporting document to the OECD Guideline 497 on Defined Aproaches for Skin Sensitisation- Series on Testing and Assessment No. 336. Organisation for Economic Co-operation and Development. ENV/CBC/MONO(2021)11. https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/CBC/MONO(2021)11&docLanguage=En

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).