Committee for Risk Assessment

RAC

Annex 1
Background document
to the 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

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 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

16 September 2021

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 alcohol

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

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

Index Number: **603-057-00-5**

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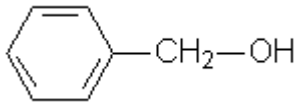
CONTENTS

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)	Phenylmethanol
Other names (usual name, trade name, abbreviation)	alpha-Hydroxytoluene Benzenemethanol
ISO common name (if available and appropriate)	
EC number (if available and appropriate)	202-859-9
EC name (if available and appropriate)	benzyl alcohol
CAS number (if available)	100-51-6
Other identity code (if available)	
Molecular formula	C_7H_8O
Structural formula	
SMILES notation (if available)	OCc1ccccc1
Molecular weight or molecular weight range	108.1378
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 alcohol CAS-No: 100-51-6	100 %		

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
-				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
-					

Table 5: Test substances (non-confidential information) (this table is optional)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used
-				

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	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 submitter's proposal					**Modify:** Acute Tox. 4 **Remove:** Acute Tox. 4 **Add:** Eye Irrit. 2 Skin Sens. 1B	 H302 H332 H319 H317	GHS07 Wng	H302 H319 H317		Oral: ATE=1570 mg/kg bw	
Resulting entry in Annex VI if adopted by RAC and agreed by Commission					Acute Tox. 4 Eye Irrit. 2 Skin Sens. 1B	H302 H319 H317	GHS07 Wng	H302 H319 H317		Oral: ATE=1570 mg/kg bw	

Table 7: 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)		
Oxidising gases		
Gases under pressure		
Flammable liquids		
Flammable solids		
Self-reactive substances		
Pyrophoric liquids		
Pyrophoric solids		
Self-heating substances		
Substances which in contact with water emit flammable gases		
Oxidising liquids		
Oxidising solids		
Organic peroxides		
Corrosive to metals		
Acute toxicity via oral route		**Yes**
Acute toxicity via dermal route	**No classification proposed**	**Yes**
Acute toxicity via inhalation route	**No classification proposed**	**Yes**
Skin corrosion/irritation	*Hazard class not assessed in this dossier*	No
Serious eye damage/eye irritation		**Yes**
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		
Reproductive toxicity		
Specific target organ toxicity-single exposure		
Specific target organ toxicity-repeated exposure		
Aspiration hazard		
Hazardous to the aquatic environment		
Hazardous to the ozone layer		

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The current acute toxicity classification for benzyl alcohol is based on Directive 67/548/EEC and translates into a minimum classification of:

Acute Tox. 4* (oral) H302: "Harmful if swallowed." and

Acute Tox. 4* (inhalation) H332: "Harmful if inhaled."

Minimum classification for category is indicated by an asterisk.

RAC general comment
Benzyl alcohol is used as a solvent for inks, paints lacquers, 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 active biocidal substance (PT6) under the BPR; however, no information is yet publicly available.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

- Change in existing entry due to changes in the criteria
- Differences in self-classification
- Disagreement by DS with current self-classification

Further detail on need of action at Community level

The current acute toxicity classification of benzyl alcohol is a minimum classification according to Directive 67/548/EEC. For certain hazard classes, including acute toxicity, the classification according to the criteria in Directive 67/548/EEC does not correspond directly to the classification in a hazard class and category under the CLP Regulation.

For benzyl alcohol in total 2414 notifications to the C&L inventory are reported on the ECHA website (last accessed 2019-02-13), but there are differences in the self-classification of a substantial number of C&L notifiers. Only one notifier has self-classified benzyl alcohol as Skin Sens. 1. However, reliable studies were

[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

identified during substance evaluation showing that benzyl alcohol may act as a moderate skin sensitizer. Around half of the notifiers self-classified benzyl alcohol as Eye Irrit. 2, 126 notifiers self-classified benzyl alcohol as Eye Dam. 1. Reliable studies were identified during substance evaluation which justify the classification of benzyl alcohol as irritating to the eye.

Based on the information given on ECHA's dissemination website significant exposure is to be expected as the substance is used as a solvent, in coating materials and paint strippers. Consumers are exposed to benzyl alcohol through various uses (wide-dispersive use). Benzyl alcohol was detected in cosmetic products and articles, air care products, washing and cleaning products, textile processing aids, and modelling clay. Harmonised classification proposal was considered as a follow-up measure to substance evaluation (CoRAP 2016).

5 IDENTIFIED USES

Benzyl alcohol is a colourless liquid with a faint, nondescript odour, which is used as a solvent, preservative, and fragrance ingredient. Benzyl alcohol is manufactured and/or imported in the European Economic Area in a volume of 10 000 – 100 000 tons per year with widespread uses by consumers and professional workers, in formulation or re-packing, at industrial sites, and in manufacturing (ECHA dissemination website):

- Professional workers:
  - Adhesives, sealants
  - Air care products
  - Biocidal products (e.g. disinfectants, pest control)
  - Coatings, paints, thinners, paint removers
  - Fillers, putties, plasters, modelling clay
  - Metal surface treatment products
  - Non-metal-surface treatment products
  - Ink and toners
  - Products such as pH-regulators, flocculants, precipitants, neutralisation agents
  - Laboratory chemicals
  - Leather treatment products
  - Lubricant, greases, release products
  - Paper and board treatment products
  - Plant protection products
  - Perfumes, fragrances
  - Pharmaceuticals
  - Photo-chemicals
  - Polishes and wax blends
  - Polymer preparations and compounds
  - Textile dyes and impregnating products
  - Washing and cleaning products
  - Cosmetics, personal care products

- Consumers:
  - Adhesives, sealants
  - Air care products
  - Coatings, paints, thinners, paint removers
  - Fillers, putties, plasters, modelling clay
  - Ink and toners
  - Leather treatment products
  - Perfumes and fragrances
  - Polishes and wax blends
  - Textile dyes and impregnating products
  - Washing and cleaning products
  - Cosmetics and personal care products

Benzyl alcohol is largely available to consumers for day-by-day use. When used in cosmetic products it may be percutaneously absorbed over more or less the entire body and/or on smaller localised skin areas. Exposure could also occur through eye contact.

5.1 Data SOURCES

In addition to the information that is available on the website of ECHA, in the IUCLID registration dossier and in the dossier submitted for the assessment as biocidal active substance, an extensive literature search was conducted in several relevant online resources (e.g. PubMed, SCOPUS, Web of Science, Wiley, Toxnet, Science Direct).

Furthermore, evaluations by EFSA and EMA were reviewed. The European Medicines Agency (EMA) summarised the data for "benzyl alcohol and benzoic acid group as excipients"[2] with the main focus on benzyl alcohol used as solubilising agent and/or preservative in medicinal products. The EFSA published a report "Re-evaluation of benzyl alcohol (E1519) as food additive"[3] which includes data on acute toxicity and a short summary on hypersensitivity. However, no relevant additional data was identified in these reports.

6 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101.3 kPa	Benzyl alcohol is a colourless liquid with a slightly aromatic odour	(Lide, 2006)	experimental
Melting/freezing point	-15.4 °C at 1013 hPa	(Lide, 2006)	experimental
Boiling point	205.31 °C	(Lide, 2006)	experimental
Relative density	1.045 g/cm^3 at 20°C	(Brühne and Wright,	experimental

[2] https://www.ema.europa.eu/en/documents/report/benzyl-alcohol-benzoic-acid-group-used-excipients-report-published-support-questions-answers-benzyl/chmp/508188/2013-t_en.pdf

[3] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2019.5876

Property	Value	Reference	Comment (e.g. measured or estimated)
		2005)	
Vapour pressure	7 Pa at 20 °C 12 Pa at 25 °C	(Apelblat et al., 1984)	experimentally measured based on an (isoteniscope) established and documented method in the temperature range of 20 - 45 °C.
Surface tension	39 mN/m at 20 °C 33 mN/m at 80 °C	(Mookherjee and Wilson, 1992)	experimental
Water solubility	40 g/L at 25 °C	(Mookherjee and Wilson, 1992)	experimental
Partition coefficient n-octanol/water	1.05 at 20 °C	(Sangster, 1989)	Shake-flask method, two values are determined with the HPLC method.
Flash point			not assessed in this dossier
Flammability			
Explosive properties			
Self-ignition temperature			
Oxidising properties			
Granulometry			A test on particle size distribution does not need to be conducted since benzyl alcohol is a liquid substance under normal conditions.
Stability in organic solvents and identity of relevant degradation products			In accordance with column 2 of REACH Annex IX, the test on stability in organic solvents and identity of relevant degradation products does not need to be conducted as the stability of benzyl alcohol is not considered to be critical.
Dissociation constant	15.4 at 25 °C Benzyl alcohol does not tend to dissociate in water under normal environmental conditions.	(Serjeant and Dempsey, 1979)	kinetic measurement
Viscosity	5.84 mPa· s at 20 °C	(Brühne and Wright, 2005)	experimental

7 EVALUATION OF PHYSICAL HAZARDS

Not assessed in this dossier.

8 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Benzyl alcohol is rapidly absorbed from the gastro-intestinal tract after oral exposure in humans and animals (Chidgey and Caldwell, 1986; EMEA, 1997). In humans 75-85 % of the applied substance is excreted within 6 h (EMEA, 1997). Dermal absorption ranged from 56 to 80 % in rhesus monkeys under occluded conditions (Bronaugh et al., 1990; EMEA, 1997). Evaporative loss contributes to a lower skin penetration (approx. 30%) under unoccluded conditions in vitro and in vivo (EMEA, 1997; Miller et al., 2006). Benzyl alcohol is

an intermediate in the metabolism of Benzyl acetate and is further metabolised to benzaldehyde and finally to benzoic acid (JECFA, 1997; OECD, 2001). It is rapidly excreted as hippuric acid mainly via urine and there is no indication of a bioaccumulating potential of benzyl alcohol (Bronaugh et al., 1990; Chidgey and Caldwell, 1986; EMEA, 1997; JECFA, 1997; Miller et al., 2006; OECD, 2001).

9 EVALUATION OF HEALTH HAZARDS

9.1 Acute toxicity - oral route

Table 9: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Value LD_{50}	Reference
Acute Oral Toxicity Similar to OECD TG 401, GLP compliance not specified - No information available on purity of the substance - Only male rats were tested Reliable with restrictions as only a summary of the study was available	**Rat,** Wistar 10 male rats/dose	1 620 mg/kg bw for males	Unpublished study report (Bayer AG, 1978)
Procter and Gamble standard procedure No. 1 for toxicological evaluation (1977-11-04) Similar to OECD TG 401, GLP compliance not specified - No information available on purity of the substance - Observation period not stated Reliable with restrictions as only a summary of the study was available	**Rat,** Sprague-Dawley 5/sex/dose	1 570 mg/kg bw	Unpublished study report (Proctor & Gamble, 1980) (RIFM, 1992)
Acute Oral Toxicity Study details not available, no GLP compliance Reliability not assignable	**Rat,** Osborne-Mendel 5/sex/dose	1 230 mg/kg bw	(Jenner et al., 1964)
Acute Oral Toxicity Study details not available, no GLP compliance Reliability not assignable	**Rat,** Strain, sex and no. of animals not reported	3 100 mg/kg bw	(Smyth et al., 1951)
Acute Oral Toxicity Study details not available, no GLP compliance Reliability not assignable	**Rat,** Strain and sex not reported 5/dose group	2 080 mg/kg bw	(Graham and Kuizenga, 1945)
Acute Oral Toxicity Study details not available, no GLP compliance	**Rat,** Strain, sex and no. of animals not reported	1 400 < LD_{50} < 3 120 mg/kg bw	(Macht, 1918)

Method, guideline, deviations if any	Species, strain, sex, no/group	Value LD_{50}	Reference
Reliability not assignable			
Acute Oral Toxicity Study details not available, no GLP compliance Reliability not assignable	**Mouse,** Strain not reported 5/sex/dose	1 580 mg/kg bw	(Jenner et al., 1964)
Acute Oral Toxicity Study details not available, no GLP compliance Reliability not assignable	**Mouse,** Strain and sex not reported No. of animals/ group not specified	1 150 mg/kg bw	(Carter et al., 1958)
Acute Oral Toxicity Study details not available, no GLP compliance Reliability not assignable	**Mouse,** Strain, sex and no. of animals not reported	1 040 mg/kg bw	(Macht, 1918)
Acute Oral Toxicity Study details not available, no GLP compliance Reliability not assignable	**Rabbit,** Strain and sex not reported 9 in total	1 040 mg/kg bw	(Graham and Kuizenga, 1945)
Acute Oral Toxicity Study details not available, no GLP compliance Reliability not assignable	**Guinea pig,** Strain, sex and no. of animals not reported	1 040 < LD_{50} < 2 600 mg/kg bw	(Macht, 1918)

9.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Various studies are available in rats or mice, as well as one each in rabbits and guinea pigs. Two studies (Bayer AG, 1978; Proctor & Gamble, 1980), which were performed similar to OECD guideline 401, state comparable LD_{50} values for rats of 1 620 and 1 570 mg/kg bw.

Further studies are less reliable as essential study details are missing. The study by (Jenner et al., 1964) obtained similar LD_{50} of 1 230 mg/ kg bw and 1 580 mg/kg bw values for rats and mice. In other studies the reported LD_{50} values range from 1 040 up to 3 120 mg/kg bw. However, most LD_{50} values described are between 1 000 and 2 000 mg/kg bw. It is not clear why some values reported are > 2 000 mg/kg bw as details of these studies are limited.

9.1.2 Comparison with the CLP criteria

As described above, the lowest available LD_{50} value, taken from the studies performed similar to OECD TG 401, is 1570 mg/kg bw for rats.

According to the criteria shown in the Table 3.1.1 of Annex I, Part 3 of CLP, substances can be allocated to one of four toxicity categories based on acute toxicity by the oral route. In general, classification is based on the lowest ATE value available i.e. the lowest ATE in the most sensitive appropriate species tested. Acute toxicity values are expressed as approximate LD_{50} values (oral) or as acute toxicity estimates (ATE):

Acute oral toxicity - Category 4: 300 < ATE ≤ 2 000 mg/kg bw

9.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the results shown above, it is proposed to classify benzyl alcohol as:

Acute Tox. 4 after oral exposure (H302 – Harmful if swallowed).

An ATE value of 1570 mg/kg bw is proposed based on the most sensitive value from the two studies performed similar to OECD TG 401.

9.2 Acute toxicity - dermal route

Table 10: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Value LD_{50}	Reference
Acute Dermal Toxicity Study details not available, no GLP compliance Reliability not assignable	**Rabbit,** Strain not reported 4 male/female	> 2 000 mg/kg bw	(National Printing Ink Research Institute [Corporate Author], 1974)
	Guinea pig, Strain, sex and no. of animals not reported	< 5 000 mg/kg bw	(Opdyke, 1973)
	Cat, Strain, sex not reported 2 animals	2 930 mg/kg bw	(Graham and Kuizenga, 1945)

9.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

There is limited data on acute toxicity after dermal administration with very little details concerning study design. However, the LD_{50} values reported are all above 2000 mg/kg bw.

9.2.2 Comparison with the CLP criteria

The lowest of the available LD_{50} value was > 2 000 mg/kg bw.

Substances can be allocated to one of four toxicity categories based on acute toxicity by the dermal route according to the criteria shown in the Table 3.1.1 of Annex I, Part 3 of CLP. Acute toxicity values are expressed as approximate LD_{50} values (dermal) or as acute toxicity estimates (ATE):

'Acute dermal toxicity - Category 4: 1 000 < ATE ≤ 2 000 mg/kg bw.'

9.2.3 Conclusion on classification and labelling for acute dermal toxicity

There is no need to classify benzyl alcohol as acutely toxic after dermal application.

9.3 Acute toxicity - inhalation route

Table 11: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Value LC_{50}	Reference
Acute Inhalation Toxicity According to OECD TG 403 (version 1981) and GLP compliant Reliable with restrictions as only a summary of the study was available	**Rat**, Wistar **Aerosol**, nose/head only 5/sex/dose	> 4 178 mg/m^3 (> 4.18 mg/L) Maximum technically achievable concentration	Unpublished study report (Bayer AG, 1990b)
Acute Inhalation Toxicity According to OECD TG 403 (version 1981) and GLP compliant Reliable with restrictions as only a summary of the study was available	**Rat,** albino rat of the CD strain **Aerosol**, snout only 5/sex/dose	> 5 400 mg/m^3 (> 5.4 mg/L) limit concentration	Unpublished study report (Elf-Atochem, 1993)
Acute Inhalation Toxicity Study details not available, no GLP compliance Reliability not assignable	**Rat,** Exposure to saturated **vapour** Strain, sex and no. of animals not reported	200 ppm (> 0.9 mg/L air)	(Clayton, 1982) Book chapter citing (Smyth et al., 1951) (see below) and personal communication with the author
Acute Inhalation Toxicity Non-guideline study, no GLP compliance Reliability not assignable	**Rat,** **Vapour**, 8 h exposure Strain, sex, no. of animals not reported	1 000 ppm (4.4 mg/L) for 8 h exposure Equivalent to **5.5 mg/L** for 4 h exposure Based on mortality of 3/6 rats within 14 days	(Smyth et al., 1951)
Acute Inhalation Toxicity Non-guideline study, no GLP compliance - No analytical checks on the concentration of prepared vapour Reliable with restrictions	**Rat,** Sherman **Vapour,** 4 h exposure 6/sex/dose	2 000 ppm (**8.8 mg/L**)	(Carpenter et al., 1949)

9.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

There are two studies available performed in rats according to OECD TG 403 and in compliance with GLP. The first study reports an LC_{50} value > 4.18 mg/L air (aerosol), which was the maximum technically achievable concentration in this study (Bayer AG, 1990b). There were no mortalities and only minor transient symptoms observed at this concentration. The second study reports an LC_{50} value > 5.4 mg/l (aerosol) (Elf-Atochem, 1993). Neither mortality nor clinical signs related to the exposure of benzyl alcohol were observed at this limit concentration.

Three other LC_{50} values have been reported for vapour application (Carpenter et al., 1949; Clayton, 1982; Smyth et al., 1951). The study by Smyth et al. showed an LC_{50} value of 5.5 mg/L (vapour) when extrapolated to a 4-hour exposure, whereas in the study by Carpenter et al., the LC_{50} value was 8.8 mg/L (vapour) for a 4-hour exposure. It should be noted that according to the author: "*No analytical checks were made on the concentration of the prepared vapour. The concentration is based upon empirical calculation. Experience indicates that the calculated concentrations are slightly higher than would actually be found if it were practical to determine them analytically on the exposure air.*" The third LC_{50} value described by Clayton et al. seems questionable. The value given refers to the study performed by Smyth et al. and personal communication with the author. It is unknown why the LC_{50} value in this book differs from the value reported in the original publication.

9.3.2 Comparison with the CLP criteria

There appears to be a difference between the application of aerosol and vapour. Benzyl alcohol is a low-volatile liquid. Therefore, newer studies performed according to OECD TG 403 and GLP used aerosol, whereas older studies used vapour.

For aerosols an LC_{50} value of > 5.0 mg/L seems reasonable as there are only minor transient symptoms found at 4.178 mg/L (the maximum technically achievable concentration in the other guideline-conform study).

Substances (as aerosols) can be allocated to one of four toxicity categories based on acute toxicity by the inhalation route according to the criteria shown in the Table 3.1.1 of Annex I, Part 3 of CLP. Acute toxicity values are expressed as approximate LC_{50} values (inhalation) or as acute toxicity estimates (ATE):

'Acute inhalation toxicity - Category 4 (dusts and mists): $1.0 < ATE \leq 5.0$ mg/L'.

The values for administration as vapour are somewhat different to exposure to aerosol. The described LC_{50} values are 8.8 mg/L and 5.5 mg/L (estimated value from an 8-hour exposure). The third value reported by (Clayton, 1982) seems to be questionable as described above. However, the accuracy of the given exposure values is uncertain as concentrations were not checked analytically. Moreover, MAK (Hartwig, 2017) calculated a saturation concentration of 567 mg/m^3 (≈ 0.57 mg/L and 126 ml/m^3) for benzyl alcohol at 25 °C on basis of its vapour pressure of 0.12 hPa at this temperature. Based on this data it is assumed that there is an equilibrium of benzyl alcohol aerosol and vapour above a concentration of 500-600 mg/m^3 (≈ 0.5 – 0.6 mg/L and 111-133 ml/m^3).

As vapours, substances can be allocated to one of four toxicity categories based on acute toxicity by the inhalation route according to the criteria shown in the Table 3.1.1 of Annex I, Part 3 of CLP. Acute toxicity values are expressed as approximate LC_{50} values (inhalation) or as acute toxicity estimates (ATE):

'Acute inhalation toxicity - Category 3 (vapours): $2.0 < ATE \leq 10.0$ mg/l.'

9.3.3 Conclusion on classification and labelling for acute inhalation toxicity

The estimated LC_{50} values for aerosol indicate that benzyl alcohol does not need to be classified. Taking the uncertainty of exposure concentrations of the data for vapour application into account, a classification of benzyl alcohol vapour as acutely toxic after inhalation is considered unnecessary.

There is no need to classify benzyl alcohol as acutely toxic after inhalation.

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.

Acute inhalation toxicity

Two OECD TG 403 compliant unpublished studies[4] 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

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

report quoted above is very unclear.

The DS notes that the MAK[5]-Kommission (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 and referred to RAC for a discussion on the possible use of the generic ATE.

Acute dermal toxicity:

One MSCA expressed support to 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} 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 the currently available data were included in the present proposal of no classification.

RAC concurs with the DS.

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.

The DS proposes for RAC to discuss the classification for acute inhalation toxicity, bearing

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

in mind the uncertainties of the data set.

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 substance 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.

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.

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

In conclusion, RAC recommends **to remove the existing classification for acute inhalation toxicity on benzyl alcohol**.

9.4 Skin corrosion/irritation

Not assessed in this dossier.

9.5 Serious eye damage/eye irritation

Table 12: Summary table of animal studies on eye irritation

Method, guideline, deviations if any*	**Species, strain, sex, no/group**	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Acute Eye Irritation according to OECD TG	**Rabbit,** New Zealand White	Benzyl alcohol: purity 99.99% 100 µl (104.5 µg); substance washed out	Irritating to the eyes of rabbits, but fully	Unpublished study report

Method, guideline, deviations if any*	**Species, strain, sex, no/group**	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
405 and GLP Observation for 21 days Reliable with restrictions as only a summary of the study was available	N= 3	after 24 hours Second eye served as control **Corneal opacity score: 1** 1 of max. 4; animals no. 1-3; fully reversible within 21 days **Iris score: 0.1** 0 of max. 2; animals no. 1+3 ≥0 ≤1 of max. 2; animal no. 2; fully reversible within 48 hours (mean score: 0.3) **Conjunctivae score: 2** 2 of max. 3; animals no. 1-3; fully reversible within 21 days **Chemosis score: 0.8** 1 of max. 4; animal no. 1; fully reversible within 7 days ≥0 ≤1 of max. 4; animals no. 2+3; fully reversible within 7 days (mean score: 0.7)	reversible within 21 days	(Bayer AG, 1990a)
Acute Eye Irritation according to OECD TG 405 and GLP Observation for 18 days Reliable with restrictions as only a summary of the study was available	**Rabbit,** New Zealand White N= 3	Benzyl alcohol: purity 99.98% 100 µl applied Second eye server as control **Animal no. 3 was killed on day 10 for ethical reasons (not-substance related)** **Corneal opacity score: 2** 2 of max. 4; animals no. 1-3; fully reversible within 18 days **Iris score: 1** 1 of max. 2**;** animals no. 1-3; fully reversible within 11 days **Conjunctivae score: 2.4** 2 of max. 3; animal no. 1; fully reversible within 11 days 3 of max. 3; animal no. 2; fully reversible within 11 days ≥2 ≤3 of max. 3; animal no.3 (mean score: 2.3) **Chemosis score: 2.2** ≥1 ≤2 of max. 4; animal no. 1; fully reversible within 11 days (mean score: 1.7) 3 of max. 4; animal no.2; fully reversible within 11 days 2 of max. 4; animal no. 3	Slightly irritating to the eyes of rabbits, but fully reversible within 18 days	Unpublished study report (Elf-Atochem, 1998)

Method, guideline, deviations if any*	Species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Acute Eye Irritation similar to OECD TG 405 and GLP Observation for 7 days	**Rabbit,** New Zealand White N= 2	Benzyl alcohol, no data on purity 100 µl applied Second eye server as control **Corneal opacity score:** 1 of max. 4; animals no. 1+2; not fully reversible within 7 days **Iris score:** ≥0 ≤1 of max. 2; animals no. 1+2; fully reversible within 7 hours **Conjunctivae score:** ≥0 ≤2 of max. 3; animals no. 1+2; fully reversible within 7 days **Chemosis score**: ≥0 ≤1 of max. 4; animal no. 1; fully reversible within 7 days ≥0 ≤2 of max. 4; animal no. 2; fully reversible within 7 days	Moderately irritating to the eyes of rabbits, but varying results between the two animals	Unpublished study report (Bayer AG, 1979)
Acute Eye Irritation	**Rabbit,** New Zealand White N= 3	No details reported	Highly irritating	(Smyth et al., 1951)
Acute Eye Irritation	**Rabbit** N= 3	0.08% aqueous solution, 2 drops; applications on 4 successive days	Not irritating	(Carter et al., 1958)
Acute Eye Irritation	**Rabbit**	4% solution	Not irritating	(Macht and Shohl, 1920)

9.5.1 Short summary and overall relevance of the provided information on serious eye damage

There are two studies available in rabbits which were performed according to OECD TG 405 and GLP (Bayer AG, 1990a; Elf-Atochem, 1998). Both studies show that benzyl alcohol is irritating to the eyes of rabbits but effects were fully reversible within 21 days. The study performed by (Elf-Atochem, 1998) generally showed higher scores and it should be noted that one animal had to be killed on day 10 due to ethical reasons (but not substance related). One more study was performed similar to OECD TG 405 (Bayer AG, 1979) which also showed moderate eye irritation in rabbits. However, only two animals were used in this study, the observation period was only 7 days after exposure and not all effects were reversible within that period.

Further studies (Carter et al., 1958; Macht and Shohl, 1920; Smyth et al., 1951) are of limited relevance as study details are missing. The results from these studies range from not irritating to highly irritating.

9.5.2 Comparison with the CLP criteria

The two studies performed according to OECD TG 405 and GLP (Bayer AG, 1990a; Elf-Atochem, 1998) both showed eye irritation of benzyl alcohol with values for corneal opacity ≥1 and for conjunctival redness ≥2 for all three animals in each study. The values for iritis and chemosis are ≤1 and ≤2, respectively in the

study by (Bayer AG, 1990a) and ≥1 and ≥2, respectively, in the study by (Elf-Atochem, 1998) and the effects vary between the animals used. All effects were reversible within 21 days.

According to the Table 3.3.2 of Annex I, Part 3 of CLP a substance should be classified as category 2, if

"Substances that produce in at least in 2 of 3 tested animals, a positive response of:
(a) corneal opacity ≥1 and/or
(b) iritis ≥ 1, and/or
(c) conjunctival redness ≥ 2 and/or
(d) conjunctival oedema (chemosis) ≥ 2
calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days"

9.5.3 Conclusion on classification and labelling for serious eye damage

Based on the results shown above, it is proposed to classify benzyl alcohol as

Eye Irrit. Cat. 2 (H319 – Causes serious eye irritation).

This conclusion is also in line with the current self-classification.

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.**

9.6 Respiratory sensitisation

Not assessed in this dossier

9.7 Skin sensitisation

Benzyl alcohol is used as a solvent, preservative, and fragrance ingredient with a widespread use in cosmetic products, toiletries, perfumes, inks and paints, household cleaners and detergents. According to the Cosmetics Regulation (EC) No 1223/2009 Annex III, benzyl alcohol has to be labelled as an ingredient when its concentration exceeds 0.001 % in leave-on products and 0.01 % in rinse-off products, respectively. As a preservative, benzyl alcohol shall not exceed 1 % in a ready-for-use preparation.

This CLH report summarises relevant animal, human and other data on skin sensitisation. Detailed summaries can be found in Annex I of this CLH report.

9.7.1 Animal data

Animal studies on benzyl alcohol are summarised in the review publication by (Scognamiglio et al., 2012). The studies include a local lymph node assay (LLNA) in mice as well as various tests in guinea pig (Table 13).

Table 13: Summary table of animal studies as summarised by (Scognamiglio et al., 2012)

Method, guideline, deviations if any*	Species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
LLNA According to OECD TG 429, GLP compliance not specified - Higher doses should have been tested according to OECD TG 429 Reliable with restrictions as only a summary of the study was available	**Mouse**, CBA, female 8-12 weeks N = 4/group	Benzyl alcohol: purity 99.8 % Vehicle: diethyl phthalate:EtOH (3:1) 0, 2.5, 5, 10, 25, 50 % w/v Stimulation index: 1, 0.9, 0.5, 0.6, 1.2 EC_3 > 50 % corresponds to > 12 500 µg/cm^2 M = > 4.62	No skin sensitisation at the doses applied	(RIFM, 2005a)
Modified Freund's Complete Adjuvant (FCA) test Study details not available, no GLP compliance Reliability not assignable	**Guinea pig,** 10 per dose No further details reported	Benzyl alcohol Purity not specified Challenge dose 3 % in acetone	Weak sensitiser	(Hausen et al., 1992)
Guinea Pig Maximisation Test (GPMT) Study details not available, no GLP compliance Reliability not assignable	**Guinea pig,** No further details reported	Benzyl alcohol Purity, vehicle and test concentrations not specified No further details provided	Negative	(Ishihara et al., 1981) Article in Japanese
Freunds Complete Adjuvant (FCA) test Study details not available, no GLP compliance Reliability not assignable	**Guinea pig,** No further details reported	Benzyl alcohol Purity, vehicle and test concentrations not specified No further details provided	Positive	
Draize guinea pig sensitization test Study details not available, no GLP compliance Reliability not assignable	**Guinea pig,** No further details reported	Benzyl alcohol Purity, vehicle and test concentrations not specified No further details provided	Negative	
Open epicutaneous test Study details not	**Guinea pig,** No further details	Benzyl alcohol Purity, vehicle and test	Positive	

Method, guideline, deviations if any*	Species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
available, no GLP compliance Reliability not assignable	reported	concentrations not specified No further details provided		
Open epicutaneous test Study details not available, no GLP compliance Reliability not assignable	**Guinea pig,** No further details reported	10 % benzyl alcohol Purity and vehicle not specified	Negative	(Klecak, 1979; Klecak, 1985)
Guinea Pig Maximisation Test (GPMT) Similar to OECD Guideline 406, no GLP compliance Reliable with restrictions	**Guinea pig**, Himalayan 10 per dose Sex not reported	Benzyl alcohol Purity and vehicle not specified 5 % intradermal induction 25 % epicutaneous induction Challenge: subirritant concentration (value not shown)	Negative	(Klecak et al., 1977)
Freund's Complete Adjuvant (FCA) test Similar to OECD Guideline 406, no GLP compliance Reliable with restrictions	**Guinea pig**, Himalayan Sex and no. of animals not reported	Benzyl alcohol Purity not specified Induction: Undiluted test substance mixed with Freund's Complete Adjuvant (FCA) Challenge: subirritant concentration in petrolatum	Positive	
Draize guinea pig sensitisation test Similar to OECD Guideline 406, no GLP compliance Reliable with restrictions	**Guinea pig**, Himalayan Sex and no. of animals not reported	Benzyl alcohol Purity and vehicle not specified Induction: 0.05 ml of a 0.1 % solution, 10 intradermal injections on alternate days Challenge: 0.05 ml of a 0.1 % solution	Negative	
Open epicutaneous test Similar to OECD Guideline 406, no GLP compliance Reliable with restrictions	**Guinea pig**, Himalayan 6-8 per dose Sex not reported	Benzyl alcohol Purity and vehicle not specified Induction: 0.1 ml undiluted test substance, up to several diluted concentrations, challenge with lowest irritant and non-irritant concentration	Positive	
Guinea Pig Maximisation Test (GPMT) Study details not available, no GLP compliance	**Guinea pig,** No further details reported	Benzyl alcohol Purity and vehicle not specified 10 % for induction and challenge	Positive	(Ishihara et al., 1986)

Method, guideline, deviations if any*	Species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Reliability not assignable				
Closed epicutaneous Test Study details not available, no GLP compliance Reliability not assignable	**Guinea pig,** 10 per test Sex and strain not reported	Benzyl alcohol Purity and vehicle not specified 30 % for induction and 1 % for challenge	Negative	
Freund's Complete Adjuvant (FCA) test Study details not available, no GLP compliance Reliability not assignable	**Guinea pig,** No further details reported	Benzyl alcohol Purity and vehicle not specified 10 % challenge concentration	Moderate sensitiser	(Hausen et al., 1992)
Modified Draize guinea pig sensitisation test Non-guideline study, induction and challenge protocol differ from OECD TG 406, no GLP compliance Reliable with restrictions	**Guinea pig,** Hartley, male and female N = 10	Benzyl alcohol Purity and vehicle not specified 0.25 % injection challenge concentration 10 % application challenge concentration	Negative	(Sharp, 1978)
Delayed contact hypersensitivity test (modified cumulative contact enhancement test) Non-guideline study, no GLP compliance Reliable with restrictions	**Guinea pig,** female Strain not reported N = 5	Benzyl alcohol Purity and vehicle not specified 30 % induction concentration, 10 % benzyl alcohol in ethanol challenge concentration	Weak sensitiser	(Kashima et al., 1993)

* Information on studies is available as short summaries of unpublished studies or studies are not available in English only.

An LLNA test according to OECD TG 429 was negative up to 50 % benzyl alcohol (RIFM, 2005a). No higher doses were tested, therefore possible sensitisation at doses > 12 500 µg/cm^2 cannot be ruled out. It is unclear why higher doses were not tested. In a study on Acute Dermal Irritation according to OECD TG 404 using albino rabbits, benzyl alcohol was evaluated as not irritating to the skin (unpublished study report, (Bayer AG, 1990b)).

The available guinea pig tests show equivocal results: Only one out of the three Guinea Pig Maximisation Tests (GPMT) described caused a positive skin reaction. Further tests on guinea pigs showed that benzyl alcohol is a weak sensitiser in Freund's Complete Adjuvant (FCA) test but non-sensitising in the Draize guinea pig sensitisation test. The open epicutaneous tests described show ambiguous results (2/3 positive).

Nevertheless (Scognamiglio et al., 2012) list benzyl alcohol as a weak sensitiser in a potency classification based on animal data.

9.7.2 Human data

A substantial human database is available for benzyl alcohol. The available studies include human repeated insult patch tests (HRIPT) and a human maximisation test (HMT) in presumably healthy human volunteers,

patch test results in consecutive dermatitis patients as well as a number of case studies. There are no details regarding the selection process for the volunteer studies, therefore it is assumed that the volunteers are healthy individuals rather than dermatitis patients.

Table 14: Human volunteer studies on the potential of benzyl alcohol to induce sensitisation in either a maximisation test or repeated insult patch tests (HRIPT); data taken from (Scognamiglio et al., 2012)

Relevant information about the study	Test substance, concentration	Number of volunteers	Results	Reference*
Human repeat insult patch test (HRIPT) Induction with 0.3 ml benzyl alcohol onto an occlusive patch applied to the upper arm or back for 24 h 9 induction applications on alternate days during a 3 week period 10-14 day rest period Challenge patch applied on previously unexposed site for 24 h Reactions scored at 24, 48, 72 and/or 96 h after application Information available as short summaries of unpublished studies No information available on - composition of the study populations, (only "human volunteers" mentioned) - purity of the substance Reliable with restrictions as only a summary of the study was available	20 % benzyl alcohol Diethyl phthalate:EtOH (3:1) 23 622 µg/cm²	56	5 subjects with oedematous reactions during induction, patching was continued for 1 subject with transient reactions Challenge: 2 with '2+' oedema (3.6 %) 3 with '1+' oedema (5.4 %) Other subjects exhibited transient (±/1) reactions Re-challenge: 1 with '2+' oedema (1.8 %) 1 with '1+' oedema (1.8 %) 1 with low level (+/-) reaction at both occlusive and semi-occlusive test sites (1.8 %) 1 with low level (+/-) reaction at occlusive test site (1.8 %) No reactions under „normal use" conditions	(RIFM, 2002)
	15 % benzyl alcohol Diethyl phthalate:EtOH (3:1) 17 717 µg/cm²	46	5 subjects with oedematous reactions during induction, patching was continued for 1 subject with transient reactions Challenge: 4 subjects with '2+' oedema (8.7 %) 1 with '1+' oedema (2.2 %) 1 with transient (±/1) reactions (2.2 %) The level 2+ and 1+ reactions indicative for skin sensitisation according to the author.	(RIFM, 2003)
	7.5 % benzyl alcohol Diethyl phthalate:EtOH (3:1) LOEL (induction): 8 858 µg/cm²	110	1 subject with severe irritation during patching (induction) Challenge: 1 with (2+) oedema, still existent 96 h after challenge (0.9 %) 2/110 with reaction upon challenge (1.8 %) Re-challenge indicated sensitisation in 1/ 3 (positive with occlusive, semi-occlusive and antecubital fossa sites) but not in the others (only minimal erythema)	(RIFM, 2004b)

Relevant information about the study	Test substance, concentration	Number of volunteers	Results	Reference*
	5 % benzyl alcohol in Diethyl phthalate:EtOH (3:1) NOEL (induction): 5 906 µg/cm^2	101	2 subjects with oedematous reactions during induction, patching was discontinued for both subjects one with low level reaction Challenge: 1 with '3+' oedema (1 %) 1 with '1+' oedema (1 %) **indicative of pre-sensitisation for 2 subjects according to the authors**	(RIFM, 2005b)
	3 % benzyl alcohol in Diethyl phthalate:EtOH (3:1) 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 48 h periods Patch sites pre-treated for 24 h with 5% aqueous sodium lauryl sulphate (SLS) under occlusion, 10-14 day rest period Challenge for 48 h – reactions read upon removal and again at 48 and 72 h Reliable with restrictions as only a summary of the study was available	10 % benzyl alcohol in petrolatum NOEL (induction): 6 900 µg/cm^2	25	Negative	(RIFM, 1970)

* Full references can be accessed from the original publication

The results of human repeated insult patch tests with doses ranging from 3 543 µg/cm^2 to 23 622 µg/cm^2 (3 to 20% benzyl alcohol for induction and challenge) show that increasing doses of benzyl alcohol (above 8 858 µg/cm^2 or 7.5% benzyl alcohol) led to increasing numbers of sensitised subjects (0 – 11%). Since results stem from separate studies, reproducibility of a skin sensitising effect can be inferred. Some volunteers reacted with oedematous reactions during the induction phase. As benzyl alcohol is considered to be non-irritating, it could be speculated that these volunteers are already sensitised to benzyl alcohol due to its ubiquitous presence in a large number of cosmetic products.

A human maximisation test (HMT) on 25 volunteers was negative for 10% benzyl alcohol. However, it should be noted that according to (Kligman, 1966): "*There is a greater variability in the borderline group especially with substances which are recognized as occasional sensitisers.*" This means that for occasional sensitisers more accurate and reproducible results can be obtained by using larger numbers of test subjects and in this specific case a higher concentration of the test substance would be needed to produce a positive result.

In addition to the studies in human volunteers, there are various retrospective analyses of hospital statistics regarding the number of dermatitis patients reacting to benzyl alcohol in all tested patients over a certain period of time.

Table 15: Human patch test studies performed with benzyl alcohol on dermatitis patients

Relevant information about the study	Test substance, concentration	Number of patients	Results	Reference
Human patch test Retrospective study on data from all eczema patients routinely tested with the fragrance series and the European baseline series (2011-2012) retrieved from the database at St John's Institute of Dermatology at St Thomas' Hospital, London. Patch test reactions to the fragrance series include 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).	**10 %** benzyl alcohol in petrolatum Purity not specified	1 951	4 subjects with positive reactions **(0.21 %)** Co-reactions with any fragrance marker (% of reactions to fragrance series substance) 3/4 (75 %) Co-reactions with FM I (% of reactions to ingredient): 1/4 (25) Co-reactions with FM II (% of positive reactions to ingredient): 2/4 (50)	(Mann et al., 2014)
Human patch test Prospective study of 93 consecutive patients suspected of having allergic contact dermatitis tested with the European standard series and cosmetic series at the Dermatology Department, Baskent University Faculty of Medicine, Ankara, Turkey (2005-2006).	**10%** benzyl alcohol Purity and vehicle not specified	93	1 subject with positive reaction **(1.1 %)**	(Ada and Seckin, 2010)
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	79 770	258 subjects with positive reactions (**0.28 %)** **(64 men (0.18 %), 194 women (0.34 %))** Association with leg dermatitis reported	(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	23 257	51 subjects with positive reactions **(0.22 %)**	(Uter et al., 2010)
Human patch test Retrospective study on patients with suspected allergic contact dermatitis tested with a preservative series, data collected from 24 departments participating in the German Information Network of Departments of Dermatology (IVDK, 1990-1994).	**1 %** benzyl alcohol in petrolatum Purity not specified	11 373	46 subjects with positive reactions **(0.4 %)**	(Schnuch et al., 1998)

Relevant information about the study	Test substance, concentration	Number of patients	Results	Reference
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).	**1%** benzyl alcohol in petrolatum Purity not specified	5 183 (atopic) 14 722 (non-atopic)	15 atopic patients with positive reactions **(0.28 %)** 44 non-atopic patients with positive reactions (**0.3 %)** (standardised for age and sex, patients with current leg ulcer/stasis dermatitis were excluded)	(Jappe et al., 2003)
Human patch test First 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	4 552	18 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. During 4 periods of 6 months, from 1 January 2003 to 31 December 2004, 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.	**1 %** benzyl alcohol Purity and vehicle not specified	2 166	7 subjects with positive reactions **(0.3 %):** 3 subjects +, 3 subjects + +, 1 subject + + +) 12 irritant or doubtful reactions Sensitisation to Benzyl alcohol associated with leg dermatitis (29 %). Low frequency, but some strong allergenic reactions are indicative of Benzyl alcohol to be an – albeit rare – sensitiser	(Schnuch et al., 2007)
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. Responses were categorised in terms of the following categories: Positive (++/++/+), doubtful (+?) or irritant reactions (IR).	**1 %** benzyl alcohol Purity and vehicle not specified	1 508	2 subjects with positive reaction **(0.1 %)** In addition: - 3 subjects with doubtful reaction - 1 subject with irritant reaction	(Heisterberg et al., 2011)

Relevant information about the study	Test substance, concentration	Number of patients	Results	Reference
Human patch test 4-year retrospective study of patients tested with the Spanish baseline and/or fragrance series (2004-2008). A fragrance series has been tested in a selected group of 86 patients. Patients selected were either positive to baseline series (54 patients) or there was clinical suspicion (32 patients).	**1 %** benzyl alcohol in petrolatum Purity not specified	86	2 subjects with positive reactions **(2.3 %)**	(Cuesta 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	17 740	31 subjects with positive reactions (**0.17 %)**	(Schnuch et al., 2011b)
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	4 922 (1995-1996) 6 125 (2000-2002)	1995-1996: 1 subject with positive reaction **(0.02 %)** 2000-2002: **No** allergic reactions	(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	5 202 (with known contact dermatitis)	48 subjects with positive reactions **(0.9 %)**	(Broeckx et al., 1987)
Human patch test Risk of sensitisation to fragrances estimated on the basis of patch test data and exposure according to use volumes. 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 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)

Relevant information about the study	Test substance, concentration	Number of patients	Results	Reference
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 previous six years are discussed (2010–2015). The data were retrieved from and evaluated with a patient database developed in-house.	Benzyl alcohol Purity, vehicle and test concentrations not specified	147	1 subject with positive reaction **(0.68 %)**	(Goossens, 2016)
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 data from collectives of consecutive dermatitis patients tested with a concentration of 1% benzyl alcohol show sensitisation rates ranging from 0.1 % to 2.3 %, two studies performed with 10% benzyl alcohol show rates of 0.21 % and 1.1 %. The studies, in which the concentration of benzyl alcohol used is not specified, lie within the same range (up to 2% positives). Out of these 18 studies there is only one study (Mitchell, 1977) reporting a higher incidence of sensitisation (6 %) and one study with no positive or 0.02 % positive reactions during the two time periods reported (Hasan et al., 2005). The largest collective of patients (79 770 patients in total) was evaluated by (Schnuch et al., 2011a) who performed a retrospective analysis on consecutive dermatitis patients from 1996 to 2009. The authors list benzyl alcohol as rare contact allergen with an association to leg dermatitis and report a higher incidence in women (0.34 %) compared to men (0.18 %). Overall studies with > 100 patients show sensitisation rates > 0.1 and < 1 %.

Further human patch test studies, mainly studies in consecutive dermatitis patients in clinical departments of dermatology, have been summarised in the review by (Scognamiglio et al., 2012).

Table 16: Summary of human diagnostic patch test studies performed with benzyl alcohol as reported by (Scognamiglio et al., 2012). The purity of benzyl alcohol was not reported for these studies.

No.	Concentration	Incidence	References
1	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)
2	10 % in petrolatum	0/501	(De Groot et al., 1986)
3	10 % (vehicle not reported)	3/182 **(1.6 %)**	(Malten et al., 1984)
4	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	
5	5 % in petrolatum or 10% in alcohol	19/95 **(20 %)**	(Hjorth, 1961)
6	5 % in petrolatum	1/2261 **(0.04 %)** from 1978-79 0/1934 from 1979-80	(Mitchell et al., 1982)
7	5 % in petrolatum	3/991 **(0.3 %)**	(Dickel et al., 2001)
8	5 % in petrolatum	3/669 **(0.4 %)**	(Katoh et al., 1995)
9	5 % in petrolatum	0/667	(van Joost et al., 1984)
10	5 % in petrolatum	6/661 **(0.9 %)**	(Itoh et al., 1988)
11	5 % in petrolatum	9/585 **(1.5 %)**	(Itoh et al., 1986)
12	5 % in petrolatum	1/479 **(0.2 %)**	(Nagareda, 1996)
13	5 % in petrolatum	3/425 **(0.71 %)**	(Nagareda et al., 1992)
14	5 % in petrolatum	1/398 **(0.3 %)**	(Sugai, 1996)
15	5 % in petrolatum	0/241	(Ferguson and Sharma, 1984)
16	5 % in petrolatum	2/200 **(1 %)**	(Nethercott, 1982)
17	5 % in petrolatum	8/102 **(7.8 %)**	(Hausen, 2001)
18	5 % (vehicle not reported)	0/3037	(Angelini et al., 1985)
19	5 % (vehicle not reported)	13/1206 **(1.1 %)**	(Sugai, 1982)
20	5 % (vehicle not reported)	0/574	(Hirose et al., 1987)
21	5 % (vehicle not reported)	8/427 **(1.9 %)**	(Nishimura et al., 1984)
22	5 % (vehicle not reported)	1/457 **(0.2 %)**	(Addo et al., 1982)
23	5 % (vehicle not reported)	2/242 **(1.7 %)**	(Van Joost et al., 1985)
24	5 % (vehicle not reported)	6/220 **(2.7 %)**	(Ishihara et al., 1979)
25	5 % (vehicle not reported)	0/178	(Hirano and Yoshikawa, 1982)
26	5 % (vehicle not reported)	3/167 **(1.8 %)**	(Larsen et al., 1996)
27	5 % (vehicle not reported)	0/145	(Suzuki et al., 1997)

No.	Concentration	Incidence	References
28	5 % (vehicle not reported)	1/84 **(1.1 %)**	(Takase et al., 1984)
29	5 % (vehicle not reported)	1/81 **(1.2 %)**	(Haba et al., 1993)
30	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 %)**	
31	1 % in petrolatum	7/2166 **(0.3 %)** Association with leg dermatitis	(Schnuch et al., 2007)
32	1 % in petrolatum	1/1082 **(0.1 %)**	(Geier et al., 2003)
33	1 % in petrolatum	1/320 **(0.3 %)**	(van Oosten et al., 2009)
34	1 % (vehicle not reported)	0/3115	(Cooper and Shaw, 2000)
35	1 % (vehicle not reported)	0/436	(Penchalaiah et al., 2000)
36	1 % (vehicle not reported)	0/422	(An et al., 2005)
37	1 % (vehicle not reported)	1/390 **(0.3 %)**	(Torgerson et al., 2007)
38	0.2 % (vehicle not reported)	18/614 **(2.9 %)**	(Fuji et al., 1972)

The studies described were performed with concentrations ranging from 0.2 to 20 % benzyl alcohol. The observed frequency of skin reactions ranged from 0 to 20 %. Considering studies with > 100 patients only, the sensitisation rates range from 0 up to 7.8 % (14 studies < 1 % and 9 studies > 1 %), whereas 12 of the studies did not show any positive reactions.

In addition to the patch test studies on consecutive dermatitis patients a number of case reports of patients, reacting to benzyl alcohol can be found.

Table 17: Case reports of patients reacting to benzyl alcohol.

Relevant information about the study (as applicable)	Observations	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: Negative prick test results and positive (++) intradermal injection test results. (Negative injection test results in 10 healthy controls)	
39 year-old female with pruritic erythema of foot	5 % benzyl alcohol in petrolatum: Weak (+) reaction in patch test and strong positive reaction in repeated open application test	
67 year-old male with leg dermatitis	1 % benzyl alcohol in petrolatum: + + occlusive patch test reaction. 0.9 % benzyl alcohol in saline: Negative prick test reaction at 0.5 hours reading, but marked induration and proximal spread over arm at days 3 to 8	
53 year-old with stasis dermatitis	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 reactions after IM	Benzyl alcohol preparation (concentration not reported):	

Relevant information about the study (as applicable)	Observations	References
injection with B12 preparation containing 0.9 % benzyl alcohol	Negative in prick tests, but positive in intradermal tests	
57 year-old female with pruritic dermatitis	Allergic contact dermatitis after patch testing with benzyl alcohol (concentration not reported)	
40 year-old female with dermatitis	9.5 % benzyl alcohol in petrolatum: Positive patch test reaction (+++)	
65 year-old female with eyelid dermatitis	Macular erythema after patch testing with benzyl alcohol (concentration not stated)	
30 year-old female with eyelid dermatitis	Positive (+) patch test reaction to benzyl alcohol (concentration not stated)	
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 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: Strong positive reaction in patch test. Scratch, intradermal and subcutaneous injections of 1 % benzyl alcohol in saline solution: negative	(Fisher, 1975)

Available case reports describe positive reactions to benzyl alcohol to a varying degree.

Overall, the results on human volunteers or consecutive dermatitis patients show that benzyl alcohol has the potential to cause skin sensitisation in humans with a relatively low frequency of occurrence as described in the studies. However, the experimental and clinical studies described above do not allow for a reliable estimate of the level of exposure to benzyl alcohol. Given the ubiquitous presence of benzyl alcohol in a broad range of cosmetic products, exposure can be assumed to be relatively high according to section 3.4.2.2.3.1 of the Guidance on the application of the CLP criteria (ECHA, 2017). Johnson et al., 2017 supported this view in the publication: *"Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin, nails, or hair for variable periods following application. Daily or occasional use may extend over many years*". This means with respect to Table 3.3 of the Guidance on the Application of the CLP Criteria (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 largely unknown (leading to an intermediate score of 1). This results in an overall score of 5 reflecting high exposure (ECHA, 2017).

9.7.3 Other data relevant for skin sensitisation

Traditionally the skin sensitising potential of a substance has been evaluated using animal testing. However, recently a battery of in vitro, in chemico, and in silico tests for evaluation of skin sensitisation have been developed. A number of methods have been validated and are described in OECD guidelines 442C, 442D and 442E (updated in June 2018). As each of the current test methods address only one specific key event involved in the adverse outcome pathway (AOP) leading to skin sensitisation, they cannot be used as stand-alone methods but have to be used in combination.

Table 18: Summary table of other studies relevant for skin sensitisation

	Type of test	Test substance	Result	Reference
Key event 1 Peptide/ protein binding	DPRA (in chemico) Direct peptide reactivity assay	Benzyl alcohol Purity and test concentrations not reported as detailed study reports are unpublished)	Negative	(Urbisch et al., 2015)
Key event 2 Keratinocyte response	KeratinoSens™ (in vitro) ARE-Nrf2 luciferase assay		Negative	
	LuSens (in vitro) ARE-Nrf2 luciferase assay		Positive	
Key event 3 Monocytic/ Dendritic cell response	h-CLAT (in vitro) Human cell line activation test		Positive	

The assays shown in Table 18 address three different key events of the skin sensitisation AOP as indicated in row 1. Detailed summaries of these studies can be found in Annex I to this dossier.

The DPRA assay addressing key event 1 shows a negative result whereas the h-CLAT assay addressing key event 3 shows a positive result. Metabolic activation of benzyl alcohol to benzaldehyde is possible (Urbisch et al., 2015), however, some of the assays such as the DRPA assay lack the required metabolic competence and therefore might lead to false negative results. It is not entirely clear why the KeratinoSens™ and the LuSens™, which are both ARE-Nrf2 luciferase assays, show differing results. The most likely explanation for this phenomenon might be that benzyl alcohol elicits a rather low sensitisation potency and is, thus, a borderline skin sensitiser based on in-vitro testing. Having in mind that the two assays exhibit different sensitivities, the differing results, hence, might be attributable to the low sensitising potency of the test chemical. Nevertheless, overall data point towards a sensitising potential of benzyl alcohol.

Currently, the CLP regulation does not yet include criteria for how to use these data in the context of classification and labelling for skin sensitisation or for sub-categorisation. Therefore, the available publications on in vitro and in silico data were reviewed, but were only considered as supportive evidence in the overall assessment.

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

A large number of human studies was identified which consist of reports on HRIPT and HMT data in human volunteers, patch tests of consecutive dermatitis patients in dermatological hospitals as well as a number of case reports. The results of HRIPT tests in presumably healthy volunteers show that increasing doses of benzyl alcohol (3 – 20 %) led to increasing numbers of sensitised subjects (0 – 11 %). According to section 3.4.2.2.3.1 of the Guidance on the Application of the CLP Criteria (ECHA, 2017) positive responses at > 500 µg/cm^2 for HRIPT studies should be considered for classification in category 1B.

In contrast to these results, a human maximisation test in 25 healthy volunteers was negative for 10 % benzyl alcohol, but given the absence of details regarding experimental conditions, the small number of volunteers, as well as the fact that only one dose was tested, it is difficult to judge the reliability of this result.

The retrospective analyses from multicentre studies support the conclusion from the HRIPT studies as they show sensitisation rates ranging from 0.1 to 2.3 % in collectives of consecutive dermatitis patients reacting to 1 or 10 % benzyl alcohol. Additional data from human patch test studies performed with 0.2 – 20 % benzyl alcohol show frequencies of skin reactions ranging from 0 (in 1/18 studies) up to 20 %. In general, most studies on collectives > 100 patients show a frequency of sensitisation of < 1 %. According to section 3.4.2.2.3.1 of the Guidance on the Application of the CLP Criteria (ECHA, 2017), positive responses from diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure should be considered for classification. A percentage of < 0.2 % of skin sensitising incidences in general population studies and a percentage of < 1 % in consecutive, unselected dermatitis patients is considered to reflect a low to moderate frequency of occurrence of skin sensitisation. Given the ubiquitous presence of benzyl alcohol in cosmetic products, a relatively high frequency of exposure can be assumed as described in section 9.7.4.

There is no clear outcome from the available animal data. The available studies in guinea pigs investigating the skin sensitisation potential of benzyl alcohol show equivocal results: 1 out of 3 positive in the Guinea Pig Maximisation Test, 2 out of 3 in the Open Epicutaneous Test, a weak sensitiser in Freund's Complete Adjuvant Test and non-sensitising in the Draize Guinea Pig Sensitisation Test.

A guideline compliant LLNA showed no sensitisation up to 50 % benzyl alcohol. No higher doses were included in the test, although the substance should have been tested at higher concentrations as well according to OECD TG 429. Therefore, a possible sensitisation at doses > 12 500 µg/cm^2 cannot be ruled out. It should be noted that a retrospective analysis of LLNA data in comparison to human and/or guinea pig data performed by ICCVAM (2011) revealed that of 27 strong sensitising substances analysed, approximately half were underclassified in the LLNA based on an EC3 cut-off value of < 2 % (ECHA, 2017).

Some of the studies found in the literature also assess the skin sensitising potential of benzyl alcohol. The publication on benzyl alcohol by (Api et al., 2015) states: "Based on the available data, summarised in the current IFRA (International Fragrance Association) Standard, benzyl alcohol is considered to be a weak skin sensitizer". The Scientific Committee on Consumer Safety (SCCS) lists benzyl alcohol as "established contact allergen in humans" (SCCS, 2012). Furthermore, the International Fragrance Association (IFRA) recommends limiting the use of benzyl alcohol depending on the product (leave-on or rinse-off products) (IFRA, 2007).

In contrast earlier publications conclude that benzyl alcohol is an insignificant or questionable contact allergen based on clinical human data, negative human experimental data and positive as well as negative animal data (Schlede et al., 2003). However, it remains unclear which data was used for the evaluation, thus, possibly only the HMT and not the HRIPT data was considered. In a classification based solely on LLNA data and including reaction mechanistic domains (Safford et al., 2011) benzyl alcohol was classified in the non-reactive domain. According to the author, "*some chemicals classified into the non-reactive domain have been shown to be skin sensitisers in the LLNA. This sensitisation potential may be attributed to the presence of contaminants in the samples tested, formation of oxidation products or some other biological processes although this has not been categorically proven*". However, it is not clear how the authors concludes that contaminants or oxidation products could be the cause of the sensitisation potential of these chemicals or why the data based on the mechanistic domain of the substances should be given preference over the experimental LLNA data. Relating the relative frequency of sensitisation and the relative frequency of use, benzyl alcohol is included in the group of less important or even unimportant allergens (Schnuch et al., 2011b).

However, according to the Guidance on the Application of the CLP Criteria (ECHA, 2017), all data sources have to be considered in a weight-of-evidence approach when assessing the skin sensitising potential of a chemical: *"Since the data used in hazard or risk assessment should be relevant, reliable and sufficient for the regulatory purpose, it is necessary to base the assessment on the totality of available information, i.e. to apply Weight of Evidence (WoE) considerations"* (ECHA, 2017).

Overall, the data from HRIPT studies on benzyl alcohol, data from dermatitis patients, as well as diverse animal data clearly point to a weak to moderate skin sensitising potential of benzyl alcohol. Thus, although data of a recently conducted LLNA performed according to OECD TG 429 indicated no sensitizing potential of benzyl alcohol up to 50 %, the other available animal studies (even if documentation is sometimes limited) and especially data regarding the sensitising potential of benzyl alcohol in humans cannot be overruled by the LLNA test result only, especially since it is not clear why higher concentrations were omitted in the LLNA test design.

9.7.5 Comparison with the CLP criteria

The Guidance on the Application of the CLP Criteria (ECHA, 2017) states that *"positive effects seen in either humans or animals for skin sensitisation will normally justify classification. Evidence from animal studies on skin sensitisation is usually more reliable than evidence from human exposure, although adequate reliable and representative human data are usually more relevant. In cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to decide on the classification on a case-by-case basis".* Therefore, all data sources are compared to the criteria of the CLP regulation, which is summarised in Table 19.

Table 19: Comparison of experimental results confirming the skin sensitisation potential with benzyl alcohol in 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
Human data			
HRIPT	Annex I: 3.4.2.2.2.1. **Human evidence for sub-category 1A can include**: (a) positive responses at ≤ 500 µg/cm^2 (HRIPT, HMT–induction threshold); (b) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure; (c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure. Annex I: 3.4.2.2.2.2. **Human evidence for sub-category 1B can include:** (a) positive responses at > 500 µg/cm^2 (HRIPT, HMT–induction threshold); (b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure; (c) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.	NOAEL: 5 906 µg/cm^2 LOAEL : 8 858 µg/cm^2	**Skin Sens. 1B**
HMT	Criteria as above	Negative	**No classification**
Consecutive dermatitis patients	**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. 1A:** relatively high frequency (≥ 1.0 %) and "relatively low exposure"	Low/moderate frequency, presumed relatively high exposure	**Skin Sens. 1B**

Reference(s)	Criteria acc. to CLP regulation, as laid out in detail in (ECHA, 2017)	Relevant result	Resulting Classification
	Skin Sens. 1B: relatively low/moderate Frequency (< 1.0 %) and "relatively high exposure"		
Case reports	**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"	< 100 cases and presumed relatively high exposure	**Skin Sens. 1B**
Animal data			
LLNA test	**Skin Sens. 1A:** EC3 ≤ 2 % **Skin Sens. 1B:** EC3 > 2 %	EC3 > 50 % corresponds to > 12 500 µg/cm^2	**No classification**
Guinea Pig Maximisation Test		1 out of 3 tests positive	**No classification**
Freund's Complete Adjuvant Test		Positive	**Sensitiser**
Draize Guinea Pig Sensitisation Test		Negative	**No Classification**
Open Epicutaneous Test		2 out of 3 tests positive	**Sensitiser**

The evidence for classification of benzyl alcohol can be summarised as follows. Human evidence for classification into sub-category 1B include positive responses at > 500 µg/cm^2 (induction threshold) in several HRIPT studies, multiple diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population (< 1 %) in relation to a relatively high exposure, as well as various case reports showing positive reactions to benzyl alcohol. It is not possible to identify individual exposures to benzyl alcohol but given the ubiquitous presence of benzyl alcohol in cosmetic products a high exposure can be assumed as discussed above. The animal data described including LLNA test and guinea pig assays, on the other hand, do not allow for classification and sub-categorisation, as reported data is sometimes limited and the results are overall ambiguous.

Similarly the available in chemico and in vitro data are ambiguous, but collectively point towards a skin sensitising potential of benzyl alcohol. In weight of evidence of all available data, benzyl alcohol has to be considered a weak skin sensitiser.

With regard to classification and sub-categorisation according to the Guidance on the Application of the CLP Criteria, table 3.4.3 (ECHA, 2017):"Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitisation in humans" and should therefore be considered for classification into sub-category 1B.

9.7.6 Conclusion on classification and labelling for skin sensitisation

Based on the results shown above, it is proposed to classify benzyl alcohol as skin sensitiser, subcategory 1B (Skin Sens. Category 1B, H317 - May cause an allergic skin reaction). In line with (ECHA, 2017) table 3.9 no Specific Concentration Limit (SCL) is proposed as classification for benzyl alcohol is largely based on human data.

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 1994 from 24 departments participating in the German Information Network of Departments of Dermatology (IVDK).	**1 %** Benzyl alcohol in petrolatum Purity not specified	11373	46/11373 subjects with positive reactions **(0.4 %)**	(Schnuch et al., 1998)
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%) of reactions to ingredient. Co-reactions with fragrance mix II (FM II) 2/4 (50%) of positive reactions to ingredient.	(Mann et al., 2014)
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	Benzyl alcohol	244	5 subjects with positive reactions	(Trattner et

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.	Purity, vehicle and test concentrations not specified		(**2.0 %**)	al., 2002)
Human patch test Frequency of cosmetics as causal factors of allergic contact dermatitis are reported and the cosmetic allergens identified during the previous six years are discussed (2010–2015). The data were retrieved from and evaluated with a patient database developed in-house.	Benzyl alcohol Purity, vehicle and test concentrations not specified	147	1 subject with positive reaction (**0.68 %**)	(Goossens, 2016)
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 including 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)
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	
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)

<u>DS conclusion on human data</u>

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	≥100 exposures	≥100 exposures

	(score 0)	(score 2)	(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 the animal data 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 Reliable with	**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. 1A:** Relatively high frequency (≥ 1.0	**Skin Sens. 1B**

	restrictions	%*) 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 restrictrions	**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)
	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 KeratinoSens™ 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.

9.8 Germ cell mutagenicity

Not assessed in this dossier.

9.9 Carcinogenicity

Not assessed in this dossier.

9.10 Reproductive toxicity

Not assessed in this dossier.

9.11 Specific target organ toxicity-single exposure

Not assessed in this dossier.

9.12 Specific target organ toxicity-repeated exposure

Not assessed in this dossier.

10 EVALUATION OF ENVIRONMENTAL HAZARDS

Not assessed in this dossier.

11 EVALUATION OF ADDITIONAL HAZARDS

Not assessed in this dossier.

12 ADDITIONAL LABELLING

Not applicable.

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14 ANNEXES

Detailed summaries of all studies can be found in Annex I.