

Benzyl Alcohol Classification as Sensitizing under EU CLP

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Introduction:

- **Benzyl alcohol has been in commerce for decades, and LANXESS has been manufacturing benzyl alcohol for more than 50 years**
- **The European Commission recently harmonized benzyl alcohol as Skin Sens. 1b under the EU CLP regulation (Regulation on Classification and Labeling)**
- **The CLH (Harmonised Classification and Labeling) dossier was submitted by Germany**
- **The conclusion of the CLH report was inconsistent with numerous statements that were within the report**
- **Comments were submitted by LANXESS during the evaluation process, expressing concern that this harmonized classification would be overly conservative, and did not take into consideration the whole of the database on benzyl alcohol**

Statements in the CLH Report:

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.

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.



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Benzyl alcohol / phenylmethanol

MAK Benzyl alcohol is not regarded to be genotoxic or carcinogenic. Sensitization is not expected as benzyl alcohol was not a contact sensitizer in a local lymph node assay and there were no conclusive positive clinical findings of sensitizing effects on the skin. Skin contact is expected to contribute significantly to the systemic toxicity. Therefore, benzyl alcohol is designated with an “H”.

A. Ha
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Abstract

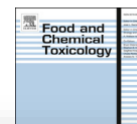
The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated benzyl alcohol [100-51-6] to derive a maximum concentration at the workplace (MAK value), considering all toxicological endpoints. Available publications and study reports are described in detail.



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RIFM fragrance in
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10.1.7. Skin sensitization

Based on the available data, summarized in the current IFRA Standard, benzyl alcohol is considered to be a weak skin sensitizer with a defined NESIL of 5900 $\mu\text{g}/\text{cm}^2$.

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JEADV

ORIGINAL ARTICLE

Is benzyl alcohol

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Results Of 70 867 patients patch tested with benzyl alcohol 1% pet., 146 (0.21%) showed a positive reaction, most of them (89%) only weakly positive. The number of doubtful and irritant reactions significantly exceeded the number of positive reactions. Reproducibility of positive test reactions was low. Among benzyl alcohol-positive patients, compared to benzyl alcohol-negative patients, there were significantly more patients with leg dermatitis (17.8% vs. 8.6%), more patients aged 40 years or more (81.5% vs. 70.5%) and more patients who were tested because of a suspected intolerance reaction to topical medications (34.9% vs. 16.6%). Concomitant positive reactions were mainly seen to fragrances, preservatives and ointment bases.

Conclusions Sensitization to benzyl alcohol occurs very rarely, mainly in patients with stasis dermatitis. In view of our results, benzyl alcohol cannot be regarded as a significant contact allergen, and therefore marking it as skin sensitizer 1B and labelling it with H 317 is not helpful.

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Safety Assessment of Benzoic Acid and Benzoate

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Both positive and negative results were reported for benzyl alcohol in animal skin sensitization studies. A maximum skin sensitization incidence of 1% was reported for benzyl alcohol in human patch tests. Occupational exposure to benzyl alcohol, benzoic acid, or sodium benzoate has not resulted in skin sensitization over a period of decades.

A. Forreryd et al.

Table 2

Conformal predictions on external test dataset.

Treatment	Non-sensitizer (p-value)	Sensitizer (p-value)	Conformal classifications: significance level (ϵ)	
			$\epsilon = 0.15$	$\epsilon = 0.20$
Non-sensitizers				
1-Brombutane	0.227	0.114	NS	NS
α -Glucosylrutin	0.400	0.000	NS	NS
Benzoic acid	0.190	0.125	NS	Empty
Benzyl alcohol	0.355	0.000	NS	NS
Citric acid	0.209	0.133	NS	NS
Dextran	0.167	0.125	NS	Empty

Benzyl alcohol was included as “non-sensitizing” in the Learning Set of the newly implemented OECD Test Guideline (OECD 442E)

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.

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Table 3.4.2

Hazard category and sub-categories for skin sensitisers

Category	Criteria
Category 1	Substances shall be classified as skin sensitisers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria: (a) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons; or (b) if there are positive results from an appropriate animal test (see specific criteria in section 3.4.2.2.4.1).
Sub-category 1A:	Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered.
Sub-category 1B:	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. Severity of reaction may also be considered.

“Severity of reaction may also be considered”

Summary:

- Action taken in the EU does not appear to agree with the whole of the available data
- Given the discordance and ambiguity in the data, and the rare, weak response, classification as a sensitizer was not warranted
- The most recently added OECD Guideline *in vitro* assay for skin sensitization would conclude that benzyl alcohol is non-sensitizing
- The criteria under CLP were used selectively, with specific parts not taken into consideration
- Inconsistent approaches to classification can lead to inappropriate conclusions on the Hazard

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