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16 December 2020

RE: Comments on dossiers proposing harmonised classification and labelling of substances – Benzyl Alcohol (EC 202-859-9/CAS 100-51-6)

Emerald Performance Materials is a global company who manufactures benzyl alcohol in the European Union (EU), as well as in the United States (US). As a chemical manufacturer, our general approach to health and safety is that we are committed to utilizing the most sound science to evaluate the potential health concerns with products we manufacture.

Emerald is a member of the Benzyl Alcohol Consortium, where the Lead Registrant is Lanxess. Emerald supports the comments submitted by Lanxess on behalf of the consortium, and believes that these comments clearly support the idea that the currently available human and animal data are inconsistent. In addition to the Consortium comments, Emerald would like to provide the following comments. We will be specifically addressing the proposal for classification of benzyl alcohol as Skin Sens. 1B.

In nearly 50 years of manufacturing (including our EU and US facilities, during and prior to Emerald ownership), Emerald has had no allegations of skin sensitization from benzyl alcohol exposure from workers and/or outside parties.

As recently as 2018, the German Authorities evaluated the German regulations on worker exposure, and in setting worker exposure maximum levels, concluded the following:

“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.”

(Hartwig, A./MAK Commission, 2018)

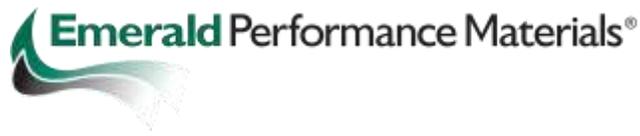
In this review, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area evaluated the same data set cited in the CLH proposal, and reached a different conclusion. In our commitment to providing guidance on safe use, we are also concerned that overly conservative classification will have a significant impact on our product, and the products manufactured

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by our customers using our material. While the German authorities have provided a detailed view of the available data, we would like to point out that the data regarding skin sensitization potential derived from human studies is inconsistent, and coupled with the low frequency of positive responses does not support the conclusion that benzyl alcohol presents a dermal sensitization risk to the general population.

Given the inconsistency in both the animal and human data regarding skin sensitization potential, Emerald disagrees with the proposed classification as Skin Sens. 1B. Emerald does not dispute the addition of Eye Irrit. 2 (carrying the H319 Hazard Phrase), and also does not dispute updating the Acute Tox. 4 classification to only carry the H302 Hazard Phrase.

As a manufacturer of a substance that has many downstream uses, we understand that overly conservative classification of a substance can have unintended impact in the marketplace. In this particular case, if the data showed a higher Risk (R) of causing dermal sensitization (we feel that both the Hazard and Exposure components of the "R = H x E" equation support a finding of low risk), the classification might be warranted. However, where the data suggest both a low Hazard, and low Exposure, unwarranted classification can cause a misperception of the actual Risk.

Our comments will be addressing the following Key Points:

- Overly conservative interpretation of existing data by the German Authorities
- Inconsistency in the human and animal datasets regarding the skin sensitisation potential of benzyl alcohol
- Misinterpretation of the *in vitro* data on skin sensitisation
- Lack of consideration of "Severity of Reaction" in the proposal
- Need for further information before coming to a conclusion

Regarding statements made and data cited in the CLH report and Annexes, we would like to provide the following comments:

- **Regarding the following statement in the CLH report:**

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

We feel that this statement incorrectly implies that this "classification" was performed in the context of a Hazard Classification under a Regulatory Framework. This was not the case, as the review by the RIFM Expert Panel was performed in an overarching Risk Assessment. The use of Scognamiglio alone does not tell the entire story, which is substantiated by the following statement at the end of Scognamiglio *et al.* (2012):

"Please refer to the Toxicologic and Dermatologic Assessment of Aryl Alkyl Alcohols (Belsito et al., 2012) for an overall assessment of this material."

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Belsito *et al.* (2012) summarizes the toxicological and dermatological assessment of aryl alkyl alcohols (as a general category) when used as fragrance ingredients. Regarding skin sensitization, the overall conclusion was:

“AAA fragrance ingredients should not induce sensitization. However, for those individuals who are already sensitized, there is a possibility that an elicitation reaction may occur because the relationship between the no effect level for induction and the no effect level for elicitation is not known for this group of materials.”

- **Regarding the following statement in the CLH report:**

“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.”

This is not the case, as the RIFM Expert Panel review was explicitly performed as a Risk Assessment, which clearly takes exposure into consideration. In fact, the RIFM QRA 2 is considered to be highly conservative, as a conservative approach was implemented with numerous aspects of the model.

- **Regarding the citation of Urbisch *et al.* (2015) in the CLH report and the Annex to the report, in the report, it is stated:**

“Purity and test concentrations not reported as detailed study reports are unpublished)”

However, the Annex to the report gives significant detail on the assays. Furthermore, there is detailed information on the outcome of the assays in the Supplementary Table to the publication (Supplementary Table is a separate document). The assays are presented as “positive” or “negative”, with no concentration context given. From the various sources, it can be determined that:

- For the DPRA, the Annex to the CLH report states:
 - *“The final reaction, containing 0.5 mM of the peptide and 5 or 25 mM of the test chemical, representing 1:10 and 1:50 M ratios.”*
 - The Supplementary Table to Urbisch *et al.* (2015) does not mention the concentration, but assuming that the assay followed the guideline, it can be assumed that appropriate ratios were used.
- For the KeratinoSens™ Assay, the Annex to the CLH report states:
 - *“Each test substance was subsequently tested at 12 twofold dilutions (0.98–2000 μM).”*

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- The Supplementary Table to Urbisch *et al.* (2015) gives the following:
 - Concentration for 1.5-fold luciferase induction [μM] as “4000”
 - Concentration for 2-fold luciferase induction [μM] as “4000”
 - Concentration for 3-fold luciferase induction [μM] as “4000”
 - Overall, this means that the assay included a concentration that was actually twice the maximum concentration required in the OECD 442D guideline, and was still negative.
- For the LuSens Assay, the Annex to the CLH report states:
 - “Following the range finder experiment, a main experiment was set up using six concentrations of test substance (in triplicates), the highest tested concentration was 1.2x CV75 (or 2000 μM if no cytotoxicity was observed).”
 - The Supplementary Table to Urbisch *et al.* (2015) gives the following:
 - Concentration for 1.5-fold luciferase induction [μM] as “< 964.51 μM ”
 - Concentration for 2 fold luciferase induction as > 2400
 - Concentration for 50% cytotox as > 2400
 - While the top concentration was not stated, the assay included a concentration higher than the 2000 μM maximum concentration required in the OECD 442D guideline.
- For the h-CLAT Assay, the Annex to the CLH Report states:
 - “THP-1 cells were treated with eight different concentrations, decided based on dose finding cytotoxicity test, for 24 h.”
 - The Supplementary Table to Urbisch *et al.* (2015) gives the following:
 - CV75 [$\mu\text{g}/\text{mL}$] as “1000”
 - EC150 (CD86) [$\mu\text{g}/\text{mL}$] as “766.60”
 - Interestingly, the Supplementary Table gave the following for MIT, a substance characterized as an “extreme” sensitiser:
 - MIT [$\mu\text{g}/\text{mL}$] as 766.60
 - This implies that benzyl alcohol, consistently described as “weak sensitiser” giving a similar response as an “extreme” sensitiser in this assay.

Overall, the CLH Report presents the *in vitro* data as evidence of potential for sensitization, but the Supplementary Table to Urbisch *et al.* (2015) states in the “Overall Result” summary:

- “‘2 out of 3’ WoE (black: DPRA, KeratinoSens, h-CLAT; red*: LuSens / MUSST included) – ‘1’ indicates >2 positive test results.” as “0”.
- Urbisch *et al.* (2015) considers the fact that the discordance in assays evaluating Key Event 2 in the Adverse Outcome Pathway (AOP) for skin sensitisation gives an overall Weight of Evidence result of “not sensitising”

Furthermore, the presentation of these data as coming solely from Urbisch *et al.* (2015) mask the fact that these results come from 4 different laboratories, and do not account for inter-laboratory variation in the results.

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- To the broader point of Classification Criteria, in the CLH report, the German Authorities have stated:

“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.”

In their quotation of the Criteria for Sub-category 1B in Table 3.4.2 of the CLP regulation, they have omitted one key phrase. The Criteria for Sub-Category 1B in the most current consolidated version of the CLP regulation is as follows (bolding added for emphasis):

*“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.**”*

The German Authorities have acknowledged the inconsistencies in both the animal and human datasets for benzyl alcohol, but do not appear to have considered the severity of the reaction.

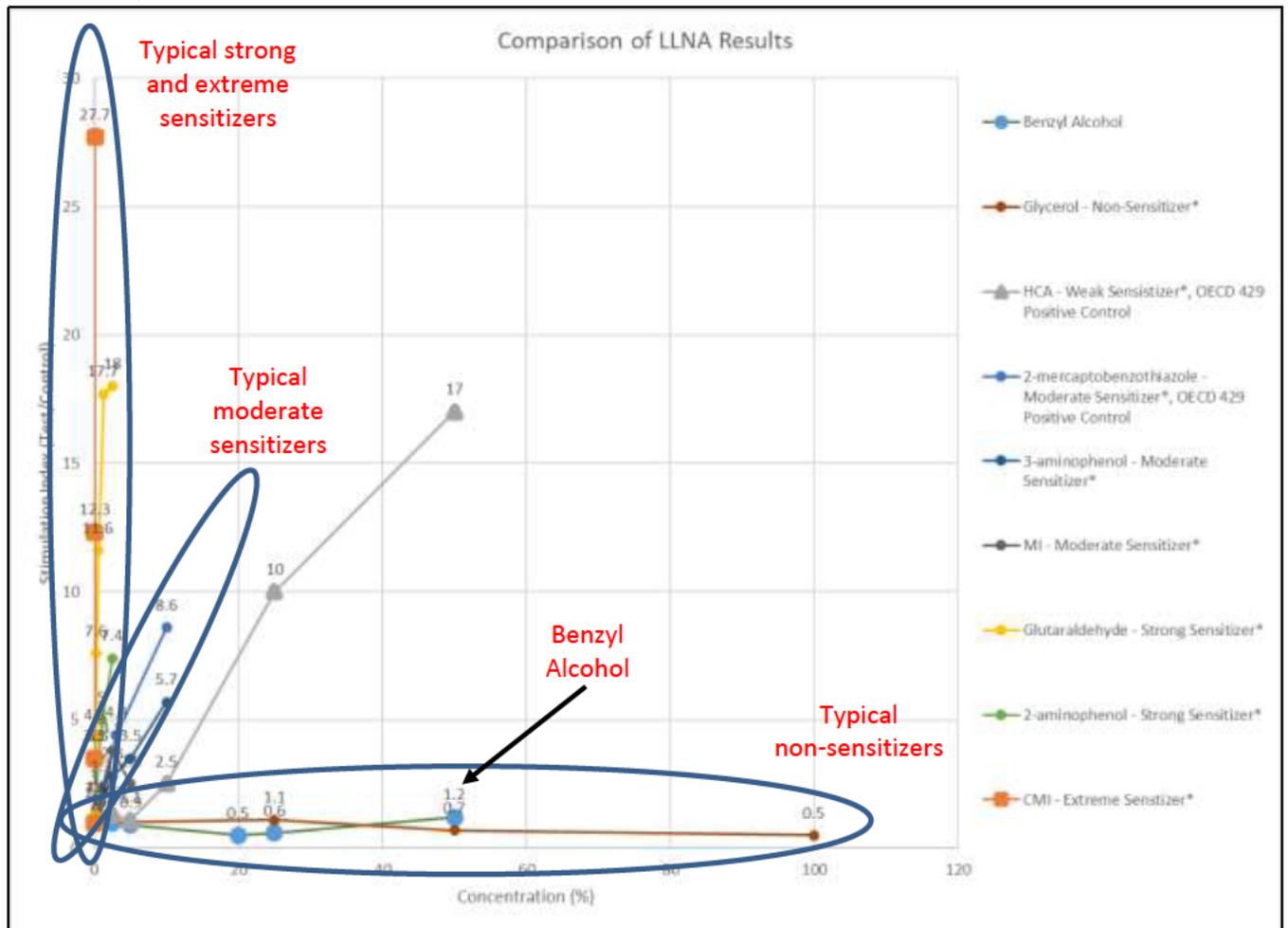
As these criteria are not quantitative, but are rather qualitative, we feel it is important to consider the sensitization potential in a relative sense. For example, when the LLNA Stimulation indices for benzyl alcohol are compared to those of substances categorized as “non-sensitizers”/“weak sensitizers”/“moderate sensitizers”/“strong sensitizers”/“extreme sensitizers” (Gerberick *et. al.*, Compilation of Historical Local Lymph Node Data for Evaluation of Skin Sensitization Alternative Methods, *Dermatitis*, 16(4): 157-202, 2005), it is clear that the response to benzyl alcohol (as shown by shape and slope of dose response curve) is in alignment with “non-sensitizers”. It should also be noted that the example substance for “weak sensitiser”, hexyl cinnamic aldehyde (HCA) is the positive control recommended in the OECD 429 Test Guideline. In addition to the response of benzyl alcohol being well below that of a “weak sensitiser”, this also implies that the threshold for “positivity” in the OECD 429 TG is already significantly low:

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In the second compilation of LLNA data (*Kern et. al.*, Local Lymph Node Data for the Evaluation of Skin Sensitization Alternatives: A Second Compilation, *Dermatitis*, 21(1): 8–32, 2010), benzyl alcohol itself is categorized as “non-sensitizing”.

It is clear that the overall consensus on benzyl alcohol is that while there have been some indications of the potential for skin sensitisation in humans, these data point to a very small subpopulation. In fact, the majority of data on human subjects comes from retrospective studies, where patients were already presenting with existing, unknown dermatological issues. The CLH report even states:

“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.”

and (bold added for emphasis):

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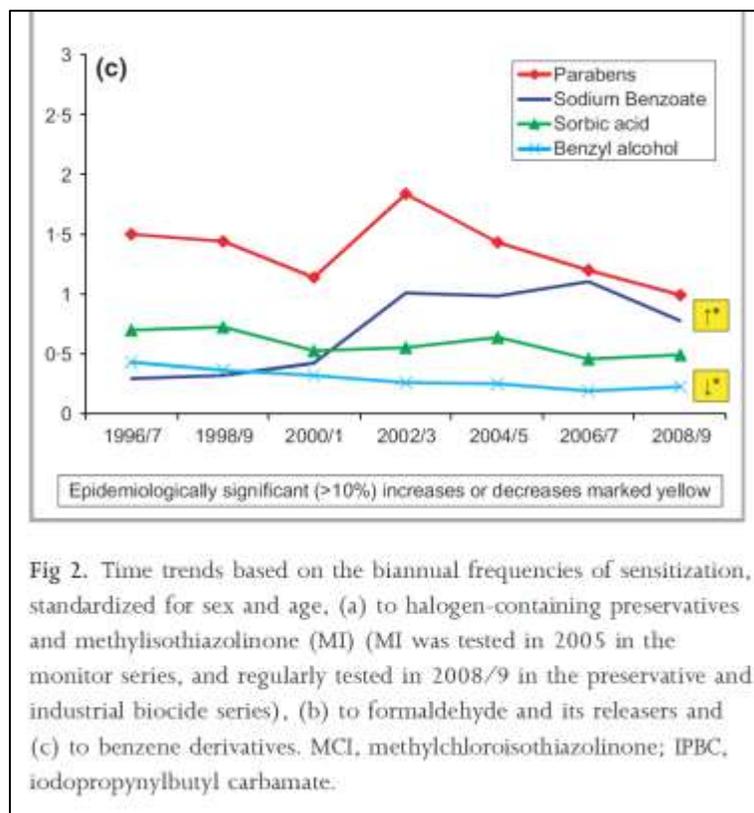
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*“The largest collective of patients (79 770 patients in total) was evaluated by (Schnuch et al., 2011a) who performed a retrospective analysis on consecutive dermatitis patients from 1996 to 2009. **The authors list benzyl alcohol as rare contact 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 %.”*

Furthermore, in citing Schnuch *et al.* (2011), the German Authorities did not include the finding that:

“Epidemiologically relevant decreases (> 10%) were seen in chloroacetamide, benzyl alcohol and MDBGN.”

The following is Figure 2 from Schnuch *et al.* (2011), where panels (a) and (b) have been omitted for lack of relevance:



That is, there was a decrease in reactions over time, within one test population, which is contrary to the idea of sensitisation (where subsequent reactions to exposure are stronger than the initial reaction).

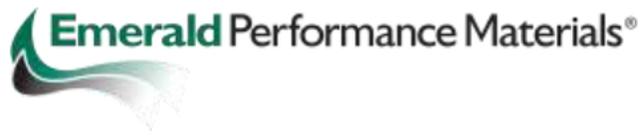
Emerald understands and appreciates the inconsistencies in the overall dataset on benzyl alcohol. We urge caution in making a decision on classification given these inconsistencies, with the understanding

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that overly conservative estimates of Hazard can have the earlier mentioned unintended consequences on end-users. We are committed to helping to resolve these inconsistencies, and are planning on repeating the *in vitro* Skin Sensitisation assays (OECD 442C, 442D and 442E) discussed earlier in our comments. As this would be the required pathway in the current approach to determining Hazards under (EC) 1907/2006 (the “EU REACH Regulation”), which is inextricably linked to the CLP regulation, obtaining more clear results from GLP studies performed in a single lab, to current OECD Guidelines, would help strengthen the overall dataset.

We therefore ask that the Committee not make any decision on benzyl alcohol until these new data can be generated.

Respectfully,



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References:

Belsito *et al.* (2012) A toxicological and dermatological assessment of aryl alkyl alcohols when used as fragrance ingredients. *Food Chem. Toxicol.* 50: S52-S99.

Gerberick *et al.* (2005) Compilation of Historical Local Lymph Node Data for Evaluation of Skin Sensitization Alternative Methods, *Dermatitis*, 16(4): 157-202.

Hartwig, A./MAK Commission (2018) Benzyl alcohol [MAK Value Documentation, 2017], The MAK-Collection for Occupational Health and Safety: Annual Thresholds and Classifications for the Workplace, Vol. 3, Iss. 3.

Kern *et al.* (2010) Local Lymph Node Data for the Evaluation of Skin Sensitization Alternatives: A Second Compilation, *Dermatitis*, 21(1): 8-32.

Schnuch *et al.* (2011) Contact allergy to preservatives. Analysis of IVDK data 1996–2009, *British J. Dermatol.*, 164: 1316-1325.

Scognamiglio *et al.* (2012) Fragrance material review on Benzyl alcohol. *Food Chem. Toxicol.* 50: S140-S160.

Urbisch *et al.* (2015) Assessing skin sensitization hazard in mice and men using non-animal test methods. *Regulatory Toxicol. Pharmacol.*, 71: 337-351.

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