Comments on CLH report Proposal for Harmonised Classification and Labelling, Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2 for Resorcinol EC Number: 203-585-2; CAS Number: 108-46-3; Index Number: 604-010-00-1

Skin Sensitisation evaluation:

In association with the proposed CLH report, Proposal for Harmonised Classification and Labelling on resorcinol (CAS 108-46-3), the Resorcinol Task Force (RTF) has evaluated the proposal and has the following comments on skin sensitisation proposal.

Skin Sensitisation:

Since the original submission of the EU REACH dossier on resorcinol, several subsequent evaluations have occurred on resorcinol including the recent (October 2020) *Scientific Committee on Consumer Safety (SCCS) OPINION on Resorcinol.* As part of the SCCS evaluation, a re-evaluation occurred of the existing data set on resorcinol including the endpoint of skin sensitisation. As part of this re-evaluation, it was determined that an error existed in the calculation of the EC3 value from the LLNA (Anonymous (Sire), 2005) study. This study was the key study, reliability of 1, in the resorcinol EU REACH dossier for the skin sensitisation endpoint and was considered as an important factor in the overall weight of evidence for the Lead Registrants classification proposal as a Skin sensitiser Category 1B.

Based on the detailed evaluation of the key LLNA study (Sire, 2005) the EC3 value of 1.4% as previously presented in the EU REACH Lead Registrant's dossier and in *Table 10.7 of the CLH report and section 10.7.1, Table 17, Skin sensitisation potential of resorcinol in the first and second main tests (LLNA study 1., Anonymous (Sire), 2005),* is not accurate. The re-evaluation of the study by the Lead Registrant, Resorcinol Task Force members, SCCS and other professionals' results in an EC3=3.67 based on the stimulation index (SI) from the second experiment from the study (the first main test was equivocal with no clear dose-related increase in SI. We have revised the Lead Registrant's dossier on that condition.

Calculation of EC3 from Sire, 2005.

The EC3 value (theoretical concentration resulting in a SI value of 3) was determined by linear interpolation of points on the dose-response curve, immediately above and below the 3-fold threshold. The equation used for calculation of EC3 was: $EC3 = c + [(3 – d)/(b-d)] \times (a – c)$
Where a = the lowest concentration giving stimulation > 3; b = the actual stimulation index caused by a; c = the highest concentration failing to produce a stimulation index of 3; and d = the actual stimulation index caused by c.

Test concentration	0.1%	0.5%	1%	5%	25%
Stimulation Index (SI)	1.58	2.87	1.97	3.51	5.74

In the second experiment, a dose-related increase in the stimulation index (except at the concentration of 1%) was noted and the threshold positive value of 3 was exceeded at the concentrations ≥ 5%.

EC3=1 +[(3-1.97)/3.51-1.97)] x (5-1) = 3.67

1+[1.03/1.54]x4= 1+[0.6688x4]= 3.67

The same conclusion is documented in Section 3.4.2 of the SCCS report, in which the EC3 value is noted as being 3.67.

It appears that the study author did not use the correct departure point in calculating the EC3 value resulting in the discrepancy of the final EC3 that is presented in the study 1.4 verse 3.67.

This is highly relevant, as in terms of relying on GHS classification criteria and ECHA *Guidance on the Application of the CLP Criteria Version 5.0 – July 2017,* a combination of human evidence and animal studies can be used for classification criteria. Sub-categories are not required but can be used.

If relying strictly on the findings from the LLNA study (EC3=3.67) then following the criteria outlined above, resorcinol would be classified as a moderate skin sensitiser**, Category 1B.**

Human data on Skin sensitisation:

More emphasis, however, should be placed on the findings from actual human experience due to professional or consumer exposure. A summary of the human experience was provided in the *CLH report for resorcinol, Table 15*, *Summary table of human data on skin sensitisation* in which several evaluations were cited. The findings undoubtably indicate that although there is a small incidence of irritation/skin sensitisation which is not necessarily associated with resorcinol itself but as part of use as in hair dye application (or other formulations) in which resorcinol is present at a very low percentage (up to 1.25% in oxidative dyes for hair and eyelashes) and in which other known and documented sensitisers are present such as e.g. Hydroxyethyl-3,4-Methylenedioxyaniline HCl and m-Aminophenol. As a result, relying on data in which resorcinol is present in a formulation or mixture in which other sensitisers may be present or in which a population is routinely exposed to other sensitisers is erroneous as it provides a misperception that any positive effects are solely related to resorcinol. On the other hand, the data show that despite the wide use of resorcinol in hair dyes, the frequency of contact sensitisation in humans is low.

When reviewing the remainder of the human data in Table 15, it appears that most studies were conducted on patients that had abraded skin in some manner, i.e., dermatitis, eczema, paint formulation, ulcers, psoriasis, inflammatory acne. These data cannot therefore be used to evaluate the sensitisation potential of resorcinol.

It should be noted that dose/concentration levels that are exhibiting sensitisation are typically greater than 2-5%, which is the greater than the concentration of resorcinol present in consumer and medicinal products. During manufacturing/formulation operations with resorcinol, gloves should be worn to prevent dermal exposures.

The most relevant and telling findings were noted in *Abbate et al, 1989,* in which skin test were negative in all subjects at a motorcycle tyre plant.

Conclusions

Animal data:

Given the discrepancy noted in the findings from the anonymous (Sire) 2005, all animal data supports a proposed skin sensitisation classification of **Category 1B** in accordance with ECHA *Guidance on the Application of the CLP Criteria Version 5.0 – July 2017*.

LLNA: EC3 value >3.0% (anonymous, (Sire) 2005) and (Basketter *et al*, (2007) – 2A

GPMT: 70% response at 2% intradermal induction dose

Human data:

We disagree with the total number of positive patch test and positive cases identified in the Summary of Human Data as 117 patch-test positive cases for a variety of reasons. For instance, they are not necessarily associated with resorcinol itself but with hair dye application or other formulations in which other known sensitisers are present. The workplace study of 42 workers at the motorcycle tyre (Abbate *et al*, 1989) with negative skin test to resorcinol was not included in the total number of workplace studies which would increase the number of total workers evaluated thus substantially altering the median positive % rate. Furthermore, there is no distinction in the concentration of resorcinol present during the various evaluations to discern positive responses.

Overall, we are aligned with the conclusion that *the available human data altogether indicate a low to moderate frequency of occurrence of skin sensitisation for resorcinol*.

Overall Conclusion:

Based on the available data, including the re-evaluation of the EC3 value from the anonymous (Sire), 2005 study, the proposed classification for skin sensitisation should be **Category 1B.**