

## IFRA Comments on the CLH report Proposal for Harmonised Classification and Labelling of Cinnamic aldehyde

IFRA in general agrees with the overall conclusion of classifying Cinnamic aldehyde as SS1A, which is in line with already existing industry policy, without specifically endorsing all the rationale provided in the classification dossier.

On the other hand, IFRA strongly disagrees with the proposed specific concentration limit (SCL) of 0.02% instead of the generic concentration limit (GCL) for a strong sensitizer of 0.1%, in particular on the following subjects:

1. Use of risk based IFRA Standard levels to derive hazard thresholds
2. Assumption that all data indicate that cinnamic aldehyde is an extreme skin sensitizer.
3. Human diagnostic patch test data cannot be used to establish the SCL of 0.02%.

We would also like to note that, consumer exposure related information (labelling) under the scope of the CLP Regulation does exclude cosmetic products, which are solely covered by the Cosmetic Regulation and this exposure is the focus of the SCCS opinion. The consumer products affected by the CLP regulation are mainly household and detergent products, with a completely different exposure scenario compared to cosmetic products. It is therefore questionable to use the SCCS opinion and exposure information from cosmetic products as basis for conclusions on other product categories.

### 1. The IFRA Standards do not represent hazard levels

It is stated (page 34 section 10.7.5.4) that the high number of reported clinical cases, meaning positive patch test reactions, demonstrates the sensitizing capacity of Cinnamic aldehyde under normal exposure conditions and the IFRA Standard limits are referenced as describing those.

This wording gives the wrong impression that the IFRA Standards are hazard thresholds. This is incorrect. The methodology applied by the industry, the quantitative risk assessment for skin sensitization (QRA) involves the derivation of a No-expected sensitization induction level (NESIL) from all available human, animal, in vitro and QSAR data. This value (590 µg cinnamic aldehyde/cm<sup>2</sup> skin) can be considered to be a hazard threshold. To the NESIL several product-specific safety factors are applied totalling between 30 and 300 in order to derive IFRA Standards which are the maximum allowed use concentrations. As with other risk assessment derived values, such as DNEL, ADI or TDI values these are orders of magnitude below an actual hazard threshold.

Moreover, the use of the limits of the IFRA Standard ranging from 0.02 to 0.4% (mouth wash) to assume that *“For most of the product types exposures above 0.02%-0.05% are regarded to constitute a risk of sensitization”*, is incorrect. Given the ample safety factors applied, it is incorrect to conclude that any exceedance of IFRA standard concentrations carries a risk of induction of skin sensitization.

Therefore, IFRA Standards are inappropriate to be used for SCL derivation.

### 2. Cinnamic aldehyde is not an extreme sensitizer



From the LLNA studies presented in the report, 18 out of 21 showed Cinnamic aldehyde to be a strong sensitizer ( $EC3 > 0.2 - < 2\%$ ), and only two studies demonstrated a borderline extreme response ( $EC3 = 0.2\%$ ). These two are unpublished RIFM studies. For a weight of evidence approach it is considered not acceptable to cite unpublished data from secondary or tertiary sources and later on rely heavily on the  $EC3$  value cited. Therefore, the preponderance of LLNA data indicate it is a strong sensitizer, and in this case, there is little technical basis to default to extreme potency. In the two studies with  $EC3 = 0.2\%$  cited, the  $EC3$  value for positive control hexyl cinnamic aldehyde used in these two studies was reported to be smaller than  $1\% (w/v)$ . The vehicle used for hexyl cinnamic aldehyde was acetone, a defatting solvent which is not a standard solvent in the OECD 429. Hexyl cinnamic aldehyde is a proficiency positive control substance in the OECD 429 and the acceptable  $EC3$  range has been reported as  $0.5x$  mean  $EC3$  to  $2x$  mean  $EC3$ , that is  $4.4-14.7\%$ . The reported  $EC3$  value of  $<1\%$  indicates that the test system - supposedly due to the wrong choice of solvents - was overly sensitive reporting too low  $EC3$  values. Further, taking the vehicle used into account, the lowest LLNA  $EC3$  value coming from an OECD TG compliant study was  $0.5\%$ , which is well above the  $EC3$  range that may be considered 'extreme'. Consequently, there are no reliable animal studies that suggest that Cinnamic aldehyde is an extreme sensitizer and any statements suggesting the contrary are misleading. If there is no case to determine Cinnamic aldehyde is an extreme sensitizer, then under CLP there is only the GCL of  $0.1\%$  for SS1A.

### **3. Human diagnostic patch test data cannot be used to establish the SCL of $0.02\%$**

The dossier states that for skin sensitizers SCLs are normally set based on the results of animal studies, but reliable human data where exposure is defined can also be used. The human data cited in the CLH dossier do not allow arriving to a clear conclusion regarding the induction exposure levels and conditions of the patients in the studies showing a high frequency of reactions to Cinnamic aldehyde. Patch tests do not provide specific information on the previous exposure regime for these patients and cannot be used to establish a SCL. This missing causal relationship between a positive patch test to a material and the exposure conditions leading to sensitization represents a major shortcoming of the clinical patch tests for the use in any kind of classification decision. Reliable data on the exposure conditions that led to induction of skin sensitization in patients who later on test positive in elicitation assays are not available. Moreover, historical data from human repeated insult patch tests listed in the CLH dossier did show skin reactions after dermal application at or above  $1\%$  test substance concentration and do not support the proposed SCL of  $0.02\%$ . In contrast to the human diagnostic patch test data cited, these human repeated insult patch test studies were performed under clearly defined induction exposure conditions. Moreover,  $1\%$  cinnamic aldehyde is the concentration used by dermatologists in patch test clinics and it does not seem to induce active sensitization in the subjects being tested.

The same argumentation as provided above against the use of human diagnostic patch test data in support of a SCL apply to the rationale provided in the respective section of the CLH dossier making reference to the material being considered as a substance of special concern by the SCCS, as this categorization is nearly also exclusively based on patch test data.

Moreover, there is no reference on the use of human patch test data from the dermatological clinics for setting SCLs. Human data can be used, though under caution according to article 3.4.2.2.2 of Annex 1 of the CLP regulation, to classify for sensitisation. The ECHA CLP Guidance mentions in article 3.4.2.2.5: "SCLs for skin sensitisation can be set based on the results from animal testing". Therefore, there is no mention on the use of human data in the setting of SCLs in the ECHA CLP Guidance or CLP Regulation.

Noteworthy, the human data in the HICC<sup>1</sup> CLH proposal by Sweden could be regarded as more relevant for this approach. In that case, the request for an SCL was not accepted by the ECHA RAC, (see ECHA Opinion

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<sup>1</sup> Hydroxyisohexyl 3-cyclohexene carboxaldehyde



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reference CLH-O-0000003906-67-03/F: at <https://echa.europa.eu/documents/10162/c9ddf299-7883-47e6-07ed-369df33f468d>).

It is stated that elicitation reactions have been described down to 0.002% (by patch testing) (Bruze et al., 2003). Elicitation thresholds are not relevant for setting SCLs for induction of skin sensitization.

All data indicate that Cinnamic aldehyde is a strong, but not an extreme skin sensitizer, so the GCL is clearly applicable and should apply to this substance.