

Committee for Risk Assessment
RAC

Annex 2
Response to comments document (RCOM)
to the Opinion proposing harmonised classification and
labelling at EU level of

cinnamaldehyde; 3-phenylprop-2-enal;
cinnamic aldehyde; cinnamal [1],
(2E)-3-phenylprop-2-enal [2]

EC Number: 203-213-9 [1], 604-377-8 [2]
CAS Number: 104-55-2 [1], 14371-10-9 [2]

CLH-O-0000006960-70-01/F

Adopted
18 March 2021

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CINNAMALDEHYDE; 3-PHENYLPROP-2-ENAL; CINNAMIC ALDEHYDE; CINNAMAL [1] (2E)-3-PHENYLPROP-2-ENAL [2]

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: cinnamaldehyde; 3-phenylprop-2-enal; cinnamic aldehyde; cinnamal [1] (2E)-3-phenylprop-2-enal [2]

EC number: 203-213-9 [1] 604-377-8 [2]

CAS number: 104-55-2 [1] 14371-10-9 [2]

Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2020	Belgium	International Fragrance Association	Industry or trade association	1
Comment received				
<p>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:</p> <ol style="list-style-type: none">1. Use of risk based IFRA Standard levels to derive hazard thresholds2. 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%. <p>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. Detailed comments are provided in the attachment.</p> <p>ECHA note – An attachment was submitted with the comment above. Refer to public attachment IFRA Comments Cinnamic aldehyde CLH final.pdf</p>				
Dossier Submitter's Response				
Thank you for your comments.				

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The IFRA standard limit is in the CLH report described as a limit by which different exposures entails a risk of sensitisation. The limit span at the time of submitting the proposal (in December 2019) was from 0.02 % to 0.4 %. The IFRA standard limits were used to indicate an exposure level and hereby finding an appropriate level for the SCL. The SCL proposed was based on animal data providing evidence of strong to extreme potency, the minimum effect levels seen in human patch test data, and the indicated exposure levels taken from the IFRA standard limit. In conclusion Dossier Submitter (DS) proposed a SCL of 0.02 %.

As stated in the CLH report, data show evidence of strong to extreme potency of cinnamaldehyde. It is noted that the expert group assessing classification criteria for skin sensitising potency by use of existing (animal) methods stated that if EC3 values are available from several studies then the lowest value should normally be used. Extreme potency was seen in two of the LLNA studies. For classification of a substance, positive data from appropriate animal studies should be used in a weight of evidence approach (CLP Annex 1, 3.4.2.2.4.1). DS is of the opinion that the RIFM studies are appropriate to use for classification in addition to setting a SCL.

The extreme potency observed in two of the LLNA studies is supported by human evidence from patch test data showing minimum effect levels of 0.02 % and 0.002 % (Bruze *et al.*, 2003 and Johansen *et al.*, 1996). The human patch test data has not exclusively been used to set the SCL of 0.02 %, rather they are used in support to the animal data to find an appropriate level for the SCL. DS is of the opinion that the GCL for strong sensitizers is not sufficiently protective for humans from the skin sensitising properties of cinnamaldehyde. The animal data does not necessarily support a SCL of 0.001 % for extreme sensitizers, for which reason the human patch test data is used to set an appropriate SCL for cinnamaldehyde.

The RAC opinion for the CLH proposal for Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), which is used for comparison to cinnamaldehyde in the attached comment, concludes that "The animal study indicates HICC to be a moderate sensitiser." Thus DS does not find this comparison of relevance, since DS's argument for setting a SCL lower than the GCL for strong sensitizers is due to the animal data providing evidence of strong to extreme potency of cinnamaldehyde supported by the human patch test data.

In conclusion DS is of the opinion that an SCL of 0.02 % is appropriate to protect humans from the sensitising properties of cinnamaldehyde.

RAC's response

Noted. RAC is of the opinion that, in a weight of evidence assessment, an SCL of 0.01% is justified for cinnamaldehyde.

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2020	Germany		MemberState	2

Comment received

In section 1, table 1 the first CAS and EC number belong to the unspecific Cinnamaldehyde, whereas the second CAS and EC number belong only to the trans-isomer of Cinnamaldehyde. The EC number 604-377-8 is only a list number and should not be used. Furthermore, the cis-isomer has no big significance and we assume that it is

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not in the scope of this CLH dossier. This assumption is underlined by the substance name (2E)-3-phenylprop-2-enal. Nevertheless, we propose to make it more clear, if the unspecific CAS and EC number indicate that also the cis-isomer is in the scope of the CLH dossier or not.
Dossier Submitter's Response
Thank you for your comments.
We apologize for the confusion about including the list number of the specific trans-isomer of cinnamaldehyde. We agree that the list number, for the specific identifier CAS 14371-10-9, should not be included in the dossier.
The unspecific CAS and EC number does not specify any configurational isomerism. However, since the substance actually corresponds to the trans-isomer, both the generic identifiers and the identifiers specific for the trans-isomer are included in the CLH dossier.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
20.05.2020	France		MemberState	3
Comment received				
Ecotoxicity - The report states that environmental hazards have not been assessed in this dossier. However, data from REACH registration dossier indicates endpoints values potentially leading to an environmental classification of the substance cinnamic aldehyde. FR CA is of the opinion that reasons for no environmental classification should be clearly explained.				
Dossier Submitter's Response				
Thank you for your comment.				
Skin sensitisation is a prioritized concern for Denmark for which reason the substance has been assessed for this hazard. As ecotoxicity is not mandatory according to CLP Article 36, this hazard has not been assessed for the current CLH proposal. Denmark is eager to have cinnamaldehyde assessed for skin sensitisation and for this reason the current proposal has been submitted prior to the assessment under Biocidal Product Regulation (BPR), which Poland has undertaken from the UK.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2020	Belgium	International Fragrance Association	Industry or trade association	4
Comment received				
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.				

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<p>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%</p> <p>ECHA note – An attachment was submitted with the comment above. Refer to public attachment IFRA Comments Cinnamic aldehyde CLH final.pdf</p>
Dossier Submitter's Response
<p>Thank you for your comment and support on the proposed classification of Cinnamaldehyde as Skin Sens. 1A.</p> <p>On the comment on the proposed specific concentration limit please refer to the answer given to comment number 1.</p>
RAC's response
<p>Noted. RAC is of the opinion that, in a weight of evidence assessment, an SCL of 0.01% is justified for cinnamaldehyde.</p>

Date	Country	Organisation	Type of Organisation	Comment number
20.05.2020	Sweden		MemberState	5

Comment received
<p>The Swedish CA agrees with the proposed classification of cinnamaldehyde as Skin Sens 1A, H317 based on evidence of skin sensitizing properties in animals as well as in humans, with evidence of strong to extreme potency from animal studies.</p> <p>The Swedish CA suggests reviewing the basis for the proposed SCL. For example, the IFRA standards for cinnamaldehyde, which was in part used as justification by the DS for the proposed specific classification limit of 0.02, have recently been amended (January 2020, amendment 49). The DS seems to refer to the IFRA Standards from 2013 (amendment 47). With amendment 49, maximum levels range from 0.014 to 1.8% in products with various degree of skin contact (0.15% in mouthwash).</p>
Dossier Submitter's Response
<p>Thank you for your comments and support on the proposed classification of cinnamaldehyde as Skin Sens. 1A.</p> <p>DS was not aware of the updated IFRA standard limits for cinnamaldehyde from January 2020. The CLH proposal was submitted in December 2019, and has therefore not been updated with this information. However, DS is still of the opinion to keep the proposed SCL of 0.02 %.</p> <p>Evidence from animal studies show that cinnamaldehyde is more potent than a strong sensitiser, borderline to having extreme sensitising effects. Extreme potency is observed in two of the LLNA studies. This is supported by human evidence from patch test data. The data show minimum effect levels of 0.02 % and 0.002 % (Bruze <i>et al.</i>, 2003 and Johansen <i>et al.</i>, 1996). DS is of the opinion that the GCL for strong sensitisers is not sufficiently protective for humans from the skin sensitising properties of cinnamaldehyde, hence DS suggests a SCL of 0.02 % based on the human patch test data.</p>

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RAC's response
Noted. RAC is of the opinion that, in a weight of evidence assessment, an SCL of 0.01% is justified for cinnamaldehyde.

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2020	Germany		MemberState	6

Comment received
<p>The proposed classification of cinnamaldehyde for Skin Sens. 1A is supported. The classification is based on data from animal studies (22 LLNAs, 2 LLNA BrdU-ELISA tests, 2 ex vivo LLNA:BrdU-ELISA and 3 GPMTs) as well as human data (46 patch test studies, 2 human repeated open application tests, 14 human repeat insult patch tests, 2 human maximisation tests and 3 case studies).</p> <p>The data show that a classification as Skin Sens. 1A is justified and that cinnamaldehyde has a strong, borderline to extreme skin sensitisation potency based on the data from LLNA studies.</p> <p>An SCL of 0.02 % is proposed. The SCL setting is based on calculated limits from the International Fragrance Association (IFRA) in various product types. However, the SCL setting based on uses is unusual. Furthermore, a new version of the IFRA standards (2020) point to lower calculated limits in some product types. Data from human repeated open application tests and patch test data (Bruze et al. 2003; Johansen et al., 1996) should rather be considered for SCL setting. The data show minimum effect levels of 0.002 % and 0.02 %, respectively. The human data would support the extreme skin sensitisation potency observed in two of the LLNA tests.</p>

Dossier Submitter's Response
<p>Thank you for your comments and support on the classification of cinnamaldehyde for Skin Sens. 1A and the proposed SCL of 0.02 %.</p> <p>DS agrees with setting the SCL based on the human data and refers to the answer given to comment number 5.</p>

RAC's response
Noted. RAC is of the opinion that, in a weight of evidence assessment, an SCL of 0.01% is justified for cinnamaldehyde.

Date	Country	Organisation	Type of Organisation	Comment number
20.05.2020	France		MemberState	7

Comment received
<p>The guideline and reliable animal and human studies available in the literature confirm the sensitising properties of cinnamic aldehyde. According to the CLP criteria, the results of these tests are directly applicable for classification and sub-categorisation of skin sensitisation.</p> <p>Based on the available animal studies (22 LLNAs and 3 GPMTs) there is clear evidence for classification in sub-category 1A. This result is supporting by the high frequencies of skin sensitisation observed in 46 human patch tests leading to consider the active substance as a strong skin sensitizer in sub-category 1A.</p> <p>Besides, considering the limits 0.02%-0.4% by which different exposures entails a risk of sensitization (IFRA data), an SCL of 0.02% of the cinnamic aldehyde can be set.</p>

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To conclude, FR agrees with the proposal classification Skin Sens 1A, H317 and the specific concentration of 0.02% for the active substance cinnamic aldehyde.

Dossier Submitter's Response

Thank you for your comments and support.

Even with the new IFRA standard limits for cinnamaldehyde from January 2020, with a limit span from 0.014 % to 1.8 % between product types, DS stays with the SCL of 0.02 % based on the animal and human evidence, and refers to the answer given to comment number 5.

RAC's response

Noted. RAC is of the opinion that, in a weight of evidence assessment, an SCL of 0.01% is justified for cinnamaldehyde.

PUBLIC ATTACHMENTS

1. IFRA Comments Cinnamic aldehyde CLH final.pdf [Please refer to comment No. 1, 4]