Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

isoeugenol; [1];
(E)-2-methoxy-4-(prop-1-enyl)phenol; [2];
(Z)-2-methoxy-4-(prop-1-enyl)phenol; [3];

EC Number: 202-590-7; [1]; 227-678-2; [2];
227-633-7; [3];
CAS Number: 97-54-1; [1]; 5932-68-3; [2];
5912-86-7; [3];

CLH-O-0000001412-86-98/F

Adopted

10 March 2016

ANNEX 2 – COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON ISOEUGENOL; [1]; (E)-2-METHOXY-4-(PROP-1-ENYL)PHENOL; [2]; (Z)-2-METHOXY-4-(PROP-1-ENYL)PHENOL; [3];

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public 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 public 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 public 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.

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Substance name: **isoeugenol; [1]; (E)-2-methoxy-4-(prop-1-enyl)phenol; [2]; (Z)-2-methoxy-4-(prop-1-enyl)phenol; [3];**
EC number: **202-590-7; [1]; 227-678-2; [2]; 227-633-7; [3];**
CAS number: **CAS Number: 97-54-1; [1]; 5932-68-3; [2]; 5912-86-7; [3];**
Dossier submitter: **the Netherlands**

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2015	Germany		MemberState	1
Comment received				
Overall, the current proposal for harmonised classification of Isoeugenol as Skin. Sens. 1A is supported by the German CA. However, in the section 'comparison with criteria' some amendments are proposed (see specific comments). In the reference substance data set for Isoeugenol in the IUCLID file in the subsection "Molecular and structural information" only the molecular formula is given, the other fields (molecular weight, SMILES notation, InChI code and structural formula) are left empty. The corresponding information should be added. In IUCLID section 1.2 one composition of the substance is given. Neither from the reference substance data set nor from the substance composition can be concluded that the substance is a mixture of two diastereomers and that both corresponding isomers should be covered with this CLH-Dossier. The IUCLID file should be amended accordingly. At least a remark should be added in the IUCLID file clarifying the present case. In Part A, section 1.1, table 1 of the CLH report three tables are given referring to the substance identity of Isoeugenol (mixture of two diastereomers) and both individual diastereomers. In all three tables in the first row on the substance name "Isoeugenol" is stated. In order to make the tables more readable it might be reasonable to mention the E-Z notation for the two diastereomers (CAS No 5932-68-3: (E)-Isoeugenol; CAS No 5912-86-7: (Z)- Isoeugenol). In Part B, section 1.1, table 4 of the CLH report in the row "CAS number" the corresponding				

information is missing and should be added. In Part B, section 1.3, table 5 of the CLH report on the physical chemical properties of the substance for the "Partition coefficient n-octanol/water" a value of 3.04 is given. In order to make the report more comprehensible please replace the given value using "log Pow = 3.04" instead.
Dossier Submitter's Response
The comments are noted. However, the CLH report or IUCLID-file cannot be updated anymore at this stage of the CLH-process. In future, we will pay better attention to these issues.
RAC's response
Thank you for the comments. RAC agrees with the proposed amendments.

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2015	Denmark		MemberState	2
Comment received				
The Danish CA supports the proposal to classify Isoeugenol as a skin sensitizer in Category 1A. Both animal and human data demonstrate that isoeugenol is a potent sensitizing substance and that classification in sub-category 1A is justified. The proposal is also in line with the findings in the SCCS opinion on Fragrance allergens in cosmetic products from 2012 (http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf) where Isoeugenol is identified as an established contact allergen in humans with more than 100 positive cases reported.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you for your comments.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
28.07.2015	Finland		MemberState	3
Comment received				
The Finnish CA supports the proposed classification and labelling as Skin Sens. 1A; H317 for isoeugenol;(E)-2-methoxy-4-(prop-1-enyl)phenol;(Z)-2-methoxy-4-(prop-1-enyl)phenol. There is clear and strong animal and human evidence supporting this classification. Finland would like to thank Netherlands for this thorough and well justified CLH proposal.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you for the comment.				

ANNEX 2 – COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON ISOEUGENOL; [1]; (E)-2-METHOXY-4-(PROP-1-ENYL)PHENOL; [2]; (Z)-2-METHOXY-4-(PROP-1-ENYL)PHENOL; [3];

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2015	Germany		MemberState	4

Comment received

Section 4.6.1.4, page 53:
The part concerning the results of the LLNAs should be amended as follows:
"Several LLNA studies with Isoeugenol have been reported. All of them showed positive results (sensitising effects described or SI values ≥ 3 reported). In nine cases an EC3 value ≤ 2% was obtained (Wright et al., 2001; RIFM 2001; Basketter et al., 2002; Basketter and Cadby 2004). Hence, the LLNA criteria for the 1A classification of Isoeugenol are fulfilled in a number of LLNA studies."
Please instead delete the sentence on page 53: "The results of animal tests have showed that in LLNAs EC3 values of isoeugenol is between 0.5 and 3.8 at applied concentrations, and a SI of three or more has been observed in LLNA of isoeugenol from the test concentration of 1.3% (Kimber et al, 1991; Basketter and Scholes, 1992; Hilton et al., 1996, Bertrand et al., 1997; Dearman et al., 1999; Basketter et al., 1999; Takeyoshi et al., 2008)." No EC3 or SI values have been reported in the document (Table 16) for the cited studies of Kimber et al., 1991; Basketter and Scholes, 1992 and Hilton et al., 1996.

Section 4.6.1.4, page 54:
In the part concerning the HRIPT discussion please recheck the sentence "In human tests, a number of HRIPT…" as follows:
The cited references RIFM 1964, 1973, 1979d, 1987b and Marzulli and Maibach, 1980 should be rechecked as for those no documentation of positive responses at ≤ 500 µg/cm2 can be found in the document (Table 23). Positive results at ≤ 500 µg/cm2 were only found to be documented for RIFM 1980b and Johansen et al., 1996.

Information for the studies by Kligman and Gollhausen, 1986; Johansen et al., 1996 and Andersen et al., 2001 given on page 34 and 35 are sufficient to achieve an exposure index (comp. with Table 3.4.2-C of the Guidance on the Application of the CLP Criteria) and to decide for sub-categorisation according to Table 3.4.2-d of the Guidance. For the three studies a relatively low exposure (score 1-4) and a relatively high frequency of occurrence of skin sensitisation was determined. Hence, the decision criteria for Sub-category 1A are fulfilled (according to Table 3.4.2-d of the Guidance). This fact should be added to Section 4.6.1.4 in the document.

Section 4.6.1.4, page 54:
Please clarify the phrase "As human data is considered more relevant than animal data ...". If not further specified this phrase is in conflict with Annex I: 3.4.2.2.4.2. of the Guidance on the Application of the CLP Criteria "Evidence from animal studies is usually much more reliable than evidence from human exposure".

Table 23, page 33:
The given information for the studies of Johansen et al., 1996 and Andersen et al., 2001 in the text (page 34) and the Table 23 are not similar. Please clarify this issue.

Dossier Submitter's Response

The comments are noted. However, the CLH report or IUCLID-file cannot be updated anymore at this stage of the CLH-process.

See below for our response:

1. With respect to the LLNA data and the comparison with the criteria, the dossier

submitter supports the suggested replacement.

2. The dossier submitter agrees that positive results at ≤ 500 µg/cm^2 were only observed in RIFM (1980b) and Johansen et al. (1996). In RIFM 1964, 1973, 1979d and 1987b, Marzulli and Maibach (1980), positive results were observed at >500 µg/cm^2.

3. The dossier submitter agrees that the human studies of Kligman and Gollhausen (1986), Johansen et al. (1996), Andersen et al. (2001) would also support sub-clasification in Category 1A.

4. The dossier submitter acknowledges that human data should be assessed carefully, and in most cases animal data regarding skin sensitisation are more reliable than evidence from human exposure based on the issues mentioned in the CLP-guidance. However, as also stated in the CLP-guidance, "in cases where evidence is available from both sources, and there is conflict between the results, the quality and reliability of the evidence from both sources must be assessed in order to resolve the question of classification on a case-by-case basis". As human data on skin sensitisation is available for isoeugenol with well known exposure information, this information is considered more relevant for the classification for skin sensitisation. The dossier submitter agrees that for clarity, this could have been better phrased.

5. The ROAT-test data of Johansen et al. (1996) as described in the text on page 34 does correspond to information in Table 23 of the CLH-report: a positive result of 63% was obtained when exposed to isoeugenol in ethanol. The HRIP-test data of Johansen et al. (1996), as presented in table 23, were however not described in the text on page 34.
   With respect to the data of Andersen et al. (2001), the table below (taken from Andersen et al. (2001)) provides some additional data which were used for Table 23 of the CLH-report. A 67% (=16/24) positive response was observed with a 0.2% concentration of isoeugenol in ethanol, and a 42% (=10/24) positive response was observed with a 0.05% concentration of isoeugenol in ethanol. Further, the authors stated that "the amount of isoeugenol applied during each application during the ROAT procedure was calculated to be 9 µg/cm^2 for the 0.2% solution and 2.2 µg/cm^2 for the 0.05 % solution".

TABLE 1
Results of ROAT with 0.2 and 0.05% Isoeugenol in Ethanol in 24 Patients with a Positive Patch Test to Isoeugenol

	ROAT concentration	
	0.2%	0.05%
Patients with positive ROAT	16/24	10/24
No. of days to positive ROAT (median)	7	15
Range (days)	2–26	3–28
Mean ± SD (days)	8.4 ± 6.2	15.2 ± 8.8

RAC's response

Thank you for the comments. Your detailed analysis of the CLH Report is highly appreciated. We agree that the two human HRIPT studies (RIFM, 1980b and Johansen et al., 1996) and the HMT by Kligman and Gollhausen (1986) support a classification in sub-category 1A as

the exposure in these studies is ≤ 1.0% or ≤ 500 μg/cm^2. However, it is considered that care should be taken in the assessment of the study by Johansen et al. (1996) since it is described in the study that the eczema patients participating in the study had a positive patch test to a fragrance mix 8% or 16% in petrolatum and either a doubtful or positive patch test to isoeugenol. Therefore less weight should be put on the results from this study. The patch testing and ROAT by Johansen et al. (1996) and the ROAT by Andersen et al. (2001) however, are not applicable for sub-categorisation as these types of studies (dose response studies) are performed solely on sensitised individuals and does not measure the induction but rather elicitation. Patch test serial dilution and ROAT provide an indication of the degree of sensitivity and of safe limits of exposure (CLP Guidance, Table 3.4.2-a Types of Human Studies).