Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Hydroxyisohexyl 3-cyclohexene carboxaldehyde

Reaction mass of
4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde and
3-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [1];
4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [2];
3-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [3]

EC number: - [1]; 250-863-4 [2]; 257-187-9 [3]
CAS number: - [1]; 31906-04-4 [2]; 51414-25-6 [3]

CLH-O-0000003906-67-03/F

Adopted

14 March 2014

14 March 2014

CLH-O-0000003906-67-03/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: Hydroxyisohexyl 3-cyclohexene carboxaldehyde; Reaction mass of 4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde AND 3-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [1]; 4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [2]; 3-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [3]

EC number: - [1]; 250-863-4 [2]; 257-187-9 [3]

CAS number: - [1]; 31906-04-4 [2]; 51414-25-6 [3]

The proposal was submitted by **Sweden** and received by the RAC on **5 June 2013.** All classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS); the notation of 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer given.

PROCESS FOR ADOPTION OF THE OPINION

Sweden has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **2 July 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **16 August 2013**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Marianne van der Hagen**

Co-rapporteur, appointed by the RAC: **Christine Bjørge**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling was reached on **14 March 2014** and the comments received are compiled in Annex 2.

The RAC opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion on **Hydroxyisohexyl 3-cyclohexene carboxaldehyde** that should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)	
Current Annex VI entry	No current Annex VI entry									
Dossier submitters proposal	605-040-00-8	hydroxyisohexyl 3-cyclohexene carboxaldehyde (INCI); reaction mass of 4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde and 3-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [1]; 4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [2]; 3-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [3]	- [1]; 250-863-4 [2]; 257-187-9 [3]	- [1]; 31906-04-4 [2]; 51414-25-6 [3]	Skin Sens. 1A	H317	GHS07 Wng	H317		Skin Sens. 1A; H317: ≥ 0.01 %
RAC opinion	605-040-00-8	hydroxyisohexyl 3-cyclohexene carboxaldehyde (INCI); reaction mass of 4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde and 3-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [1]; 4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [2]; 3-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [3]	- [1]; 250-863-4 [2]; 257-187-9 [3]	- [1]; 31906-04-4 [2]; 51414-25-6 [3]	Skin Sens. 1A	H317	GHS07 Wng	H317		

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)	
Resulting Annex VI entry if agreed by COM	605-040-00-8	hydroxyisohexyl 3-cyclohexene carboxaldehyde (INCI); reaction mass of 4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde and 3-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [1]; 4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [2]; 3-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde [3]	- [1]; 250-863-4 [2]; 257-187-9 [3]	- [1]; 31906-04-4 [2]; 51414-25-6 [3]	Skin Sens. 1A	H317	GHS07 Wng	H317	Skin Sens. 1A	

SCIENTIFIC GROUNDS FOR THE OPINION

HUMAN HEALTH HAZARD ASSESSMENT

RAC general comment

Any references used in the Opinion are contained in the accompanying Background Document.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) is a multi-constituent substance (reaction mass of 4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde and 3-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde) [1] composed of two isomers, i.e.:

70% of the major isomer (4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde) [2] and 30% of the minor isomer (3-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde) [3]; differing in the 4- and 3-position of the aldehyde group, respectively.

Classification as Skin Sens. 1A was proposed for both isomers, [2] and [3], as well as for the reaction mass [1]. Data on skin sensitisation is only available for the multi-constituent form [1] and for the major isomer [2], although the proposal also applies to isomer [3]. This is due to the fact that HICC is expected to bind proteins via a Schiff-base formation mechanism, which is independent of the position of the aldehyde group. Furthermore, the Dossier Submitter (DS) reported that there were no data to indicate any difference in potency between the two isomers.

The skin sensitisation properties of HICC have been demonstrated in both humans and animals. The DS summarised data from several thousand dermatitis or eczema patients showing positive patch test reactions to HICC, reported in Europe and elsewhere in retrospective descriptive analyses, patch tests and use tests published during the past decade

The EC3 value (effective concentration inducing a stimulation index of 3) resulting from the Local Lymph Node Assay (LLNA) was 17.1%, which indicates that HICC has moderate sensitising properties. However, the evidence from humans was sufficient for the DS to propose HICC as a skin sensitizer (Category 1A).

Despite the generally low concentrations of HICC in consumer products, varying approximately between 100 ppm (0.01%) and 6300 ppm (0.63%), the high number of positive human cases from patch testing could be attributed to the wide-spread use of HICC in different products, resulting in consumers being repeatedly exposed to this substance.

The current recommendation by the International Fragrance Association (IFRA) (2009) and the Scientific Committee on Cosmetic Products and Non-food products intended for Consumers (SCCNFP,2003) for a maximum level of 200 ppm for HICC in consumer products was considered not protective by the Scientific Committee on Consumer Safety (SCCS, 2012) and the DS. In particular, the DS stated that the generic concentration limit (GCL) for Skin Sens. 1A (≥ 0.1%) is higher than the usual concentration of HICC in consumer products which resulted in sensitisation, and that a high number of allergic reactions to HICC also occurred after the 200 ppm threshold was set by IFRA.Therefore, the DS proposes a specific concentration limit (SCL) of 100 ppm (0.01%) for HICC in consumer products.

Based on the high frequency of sensitisation by HICC shown to occur in humans, classification of HICC as Skin Sens. 1A is proposed by the DS, with an SCL of 0.01%.

A REACH registration dossier was not available at the time the CLH proposal was submitted to ECHA (see RCOM).

Comments received during public consultation

Comments from four Member State Competent Authorities (MSCAs) who supported the classification proposal for category 1A for skin sensitisation. In their detailed comments one MSCA argued that the results from patch testing of HICC fulfil the Skin Sens. 1A criteria based on both high frequency and low exposure, and that the additive exposure index (based on CLP Guidance) score = 4 when considering the use/exposure. Another MSCA found the proposal appropriate as the SCCS has already proposed the addition of HICC to Annex II to Regulation (EC) no. 1223/2009. One MSCA submitted a reference to a report from a Consumer Exposure Skin Effects and Surveillance (CESES) project reporting an 8 % positive response to HICC in patch testing performed during 2009-2012. One MSCA disagreed with an SCL of 0.01 %, as they claimed that it has not been documented that induction takes place at HICC concentrations < 0.1 %. They also questioned that an effect of the IFRA recommendation to limit the content of HICC to 200 ppm can be seen already, as products still contain 100-6300 ppm HICC. One MSCA critised the use of two risk assessment models (Johansen *et al.*, 2003; Gerberick *et al*., 2001), as the first model does not present any experimental data on HICC, and the other only provides data on elicitation, not induction. Another MSCA called for a justification on why an even lower SCL is not proposed (0.001 %), if the SCL should be based on extreme potency, but expressed doubt about whether the short time that has elapsed since the recommended concentration limit of 200 ppm has been implemented would be sufficient to already significantly influence the incidence of HICC sensitisation. One MSCA understood the concern that the GCL probably would not be sufficiently safe, but still questioned the justification for the proposed SCL.

International Flavors & Fragrances Inc. (IFF) (on behalf of the SIEF for REACH registration) claimed that HICC should be classified as a skin sensitiser in sub-category 1B based on key animal studies, and that this key animal study (LLNA) was described in the REACH registration dossier. In addition IFF stated that the human repeat insult patch test (HRIPT), also provided in the REACH registration dossier, indicated absence of skin sensitisation up to 15 % (equivalent to 8000 $\mu g/cm^2$, i.e. > 500 $\mu g/cm^2$). With reference to Basketter *et al*. (2005) IFF, stated that the prevalence in diagnostic patch testing does not necessarily equate to the potency of the allergen, as they are indicative of elicitation and not induction of sensitisation. IFF further stated that the concentration of HICC applied in the reported diagnostic patch testing exceeds the concentration in consumer cosmetic products by far (1-5 % vs. maximum 0.63 %), and that the DS should discuss this in relation to the severity of the effect. IFF questioned the relevance of the CLP and REACH Regulations for cosmetics, and suggested that the DS distinguish between cosmetic and non-cosmetic products and that it should not use the SCCS opinion as the basis for a CLH proposal. They stated that SCL should normally be based on animal data according to the CLP Regulation, and not on human studies of elicitation. They noted that cosmetic products are complex mixtures and that there is uncertainty as to the causative ingredient(s) eliciting the reaction, and opposed the use of these mixtures as a basis for setting an SCL. Finally, IFF stated that the CLH proposal fails to meet the quality requirements for a CLH dossier, as robust study summaries are missing, and transparency and justifications are not well addressed. IFF questioned whether the REACH Endpoint specific guidance (Chapter R.7a), section R.7.3.4.2 (Human data on skin sensitisation) has been applied to address the uncertainty of the information in the clinical trials, and they considered that the validity of the diagnostic patch test has not been adequately described. Further, they provided their rationale for classification in sub-category 1B, based on animal data (the same study as reported by the DS, with an EC3 value > 2 %). IFF finds support for this sub-category in Human Repeat Insult Patch Test (HRIPT). In IFFs view, data from diagnostic patch testing can only be used for risk characterisation, and not for CLP because of the limited guidance. IFF questioned the DS justification that action is needed at community level. IFF denoted the data on HICC and phototoxicity as outside the scope of the CLP Regulation. IFF claimed that the timeline between IFRA (2009) recommending lower HICC concentration in consumer products and the latest publications (2012) is too short to show an increase or decrease in skin sensitisation from HICC. IFF agreed that the individual isomers of HICC as well as the reaction mass should be classified consistently for skin sensitisation, but in sub-category 1B and not in 1A. IFF agrees that HICC has a structural alert for skin sensitisation.

IFRA disagreed with the use of the SCCS opinion (SCCS/1459/11) as a basis for deriving conclusions under the the CLP Regulation, as CLP addresses hazards while SCCS addresses risks,

and because cosmetic products are excempted from CLP. They stated that cosmetic products have different exposure scenarios from consumer products such as household and detergent products which are covered by the CLP Regulation. They also stated that the IFRA standard on HICC includes elements of elicitation, and not only induction, and thus is inadequate for concluding on an SCL to prevent induction. Finally they stated that according to CLP Guidance (3.4.2.5, ECHA 2012), an SCL should normally be based on animal studies. AISE (the International Association for Soaps, Detergents and Maintenance Products) fully supported IFRA.

Assessment and comparison with the classification criteria

Relevant information from human data with respect to skin sensitisation is available for HICC from multiple population studies (mostly diagnostic patch test studies, several multicentre patch test studies), and case studies of allergic contact dermatitis. Relevant information from animal data with respect to skin sensitisation is available for HICC from a key LLNA study. *In vitro* studies of the phototoxic properties of HICC were also submitted, but RAC considered that the relevance of these studies for classification was low.

Structural alert data/SAR: As stated by the DS, the aldehyde HICC is a lipophilic turpentine-based molecule with a high capability of penetrating the skin. Structurally, HICC is a simple aliphatic aldehyde (class 1 aldehyde) in which the carbonyl group is a hard electrophile, and is expected to react with the amino groups of lysine residues on proteins via Schiff base formation (Patlewicz *et al*., 2003). RAC agreed with the DS that this property makes HICC more reactive in the skin resulting in further subsequent interactions with proteins and provoking allergic reactions.

According to the CLP Regulation, Annex I, Table 3.4.2, skin sensitisers shall be assigned to Category 1 if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons, or if there are positive results from an appropriate animal test. Based on the frequency of occurrence in humans and/or the potency in animals as well as severity of reaction substances may be assigned to sub-category 1A or 1B, if data are sufficient.

For HICC, the DS presented over 40 patch test studies involving several thousand dermatitis patients from various countries in Europe and other parts of the world. Most of the studies were diagnostic patch test studies. Due to its strong sensitising properties, HICC has been included in the base line series of such patch test studies. There are also four ROAT studies (Repeated Open Application Tests, use tests), in which the patch test results were confirmed, i.e. the contact allergy which has been diagnosed by patch testing was verified to be caused by HICC. In the ROAT tests, an increased positive response at increasing HICC concentrations was observed (dose-response studies). In use tests with the patients' own products and with various concentrations of HICC, the threshold for elicitation was found to be lower than the recommended content limit from industry.

The CLP Regulation, Annex I, section 3.4.2.2.2.1 states that human evidence for sub-category 1A can include diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure. In the CLP Guidance (Table 3.4.2-b), the frequency of occurrence of skin sensitisation in human diagnostic patch test data from dermatitis patients (unselected, consecutive) is described as high if it is ≥ 1.0 %, and as low/moderate if it is < 1.0 %. The frequency is also described as high if the number of published cases of skin sensitisation is ≥ 100 cases, and as low/moderate if it is < 100 cases.

In most of the diagnostic patch test studies ≥ 2 % had positive reactions to HICC. The number of cases are clearly > 100. In one study, HICC is even described as the most common sensitiser in Europe at a rate of 1.5 - 3 %. Seven case studies of allergic contact dermatitis are reported by the DS, with positive reactions to HICC in six studies. In one of the two key studies a positive reaction was seen when the patient was tested with 0.075 % HICC.

Furthermore, in the CLP Guidance (Table 3.4.2-c), criteria for low and high exposure are given, and the sub-categorisation decision (CLP Guidance, Table 3.4.2-d) provides a matrix of exposure vs. frequency.

In consumer products HICC varies from 0.0036 to 0.63 %, with two exceptions (3.8 and 6.2%, respectively). Thus the score would be 0 for concentration/dose. HICC is used in consumer products that may be used more than once per day (score for repeated exposure = 2) and the number of exposures may be assumed to be ≥ 100 (score for number of exposures = 2). Thus the additive exposure index would be 0+2+2 = 4, which is described as low according to the CLP Guidance (Table 3.4.2-c and text below the table).

According to the CLP Regulation (Annex I, Table 3.4.3), a substance may be assigned to sub-category 1A if the EC3 value ≤ 2 % in a LLNA (the EC3 value is the percentage of test chemical required to elicit a stimulation index of 3 in the standard LLNA). As the EC3 value was 17.1 % in the LLNA key study for HICC (Patlewicz *et al*., 2002), sub-category 1A is not warranted based on the animal test, but fulfils the criteria for sub-category 1B, since the EC3 value was > 2 %.

Summary of the weight of evidence determination
Positive data from patch testing is available for HICC from several dermatology clinics indicating that ≥ 2 % of the tested patients (and up to 17 %) had a positive reaction to HICC. In addition to this there are four ROAT studies and six case studies where HICC was identified as the causative agent of allergic contact dermatitis. Positive data are also available from a key LLNA study, where the EC3 value was 17.1. The molecular structure of the aldehyde HICC is an alert for sensitising properties. The DS denoted the key studies in the tables and explained in the RCOM that these were considered to be key studies in the CLH proposal, as the selection of individuals tested as well as the number of individuals tested is clarified in the study reports.

Based on all available information submitted by the DS, RAC concluded that HICC should be classified as a skin sensitiser in sub-category 1A.

Specific concentration limits (SCL)
In the CLP Guidance (Table 3.4.2-f), substances are considered to have moderate, strong or extreme skin sensitisation potency, based on the LLNA. The CLP Guidance (Table 3.4.2-i) recommends that SCLs are established for substances of extreme potency and that the GCL should apply to substances of strong and moderate potency. According to the result from the key LLNA study with an EC3 value of 17.1, no SCL is warranted. However, the DS argues that a SCL is necessary because of the continued high frequency of sensitised people in the last decade, persisting even after an IND recommended maximum level of HICC in consumer products of 200 ppm (0.02 %). The DS proposed that this SCL be set at 100 ppm (0.01 %). The GCL is 0.1 % for sub-category 1A substances.

RAC agreed with the DS that HICC is a potent sensitiser. However, although the CLP Regulation offers the possibility to assign a SCL based on human studies, RAC considered that the human data on HICC did not provide adequate and reliable scientific justification to set an SCL. The animal study indicates HICC to be a moderate sensitiser.

Conclusion
RAC recommended that HICC should be classified as a skin sensitiser in sub-category 1A, with the general concentration limit 0.1%.

RAC also noted that because HICC is classified as Skin Sens. 1A, the supplemental label element EUH208 is obligatory on the packaging of mixtures not classified as a skin sensitiser but containing HICC at a concentration ≥ 0.01 % (CLP Annex II, section 2.8), to protect already sensitised individuals.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and rapporteurs' comments (excl. confidential information).