Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON HYDROXYISOHEXYL 3-CYCLOHEXENE CARBOXALDEHYDE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: Hydroxyisohexyl 3-cyclohexene carboxaldehyde
EC number: -[1]; 250-863-4 [2]; 257-187-9 [3]
CAS number: -[1]; 31906-04-4 [2]; 51414-25-6 [3]
Dossier submitter: Swedish Chemicals Agency

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
13.08.2013	France		MemberState	1
Comment received				
FR agrees with the classification proposal in category 1A for skin sensitization.				
Dossier Submitter's Response				
Thanks for your support!				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2013	United States	International Flavors & Fragrances Inc.	Company-Manufacturer	2
Comment received				
Please see uploaded attachment. Following text is the attachment. IFF Lead registrant's comments, on behalf of the SIEF, on the CLH REPORT FOR HYDROXYISOHEXYL 3-CYCLOHEXENE CARBOXALDEHYDE (HICC) EC Number: 250-863-4; 257-187-9 CAS Number: 31906-04-4; 51414-25-6 Date: 9 August 2013 REACH registration number: 01-2119971808-21-0000; Submission: CX393582-06 Please find comments from International Flavors & Fragrances Inc. (IFF) on the CLH proposal for HICC. A. Summary IFF, the lead registrant responsible for the registration of HICC, CAS# 31906-04-4; 51414-25-6, is commenting on behalf of the Substance Information Exchange Forum (SIEF) on the CLH report from the Swedish Chemicals Agency for a harmonised classification of HICC as a skin sensitiser Cat 1A with a Specific Concentration Limit (SCL), herein referred to as the CLH proposal. IFF is of the opinion that the CLH proposal is not justified, because: 1) The proposal does not take into account existing key animal studies that clearly show HICC should be classified as a Cat 1B sensitiser (article 3.4.2.2.4.2 of the CLP regulation, 2011). In addition, the human repeat insult patch test (HRIPT) information indicates absence of skin sensitisation up to 15% (equivalent to 8000 µg/cm2).				

2) The CLH proposal for a Cat 1A skin sensitiser is based on diagnostic patch testing in clinics and using mainly cosmetic exposure. The prevalence in patch testing does not necessarily equate to the potency of the allergen (e.g. Basketter et al. 2005). In addition, the SCCS criteria for categorization of skin sensitisation potency for cosmetics are used whilst cosmetics are, as such, not relevant for CLP (2008/2011) and REACH (EC, 2006).
3) There is limited legal basis for such a proposal for skin sensitisers and for using Specific Concentration Limits in the CLP regulation (2008/2011). According to the CLP guidance (ECHA, 2012, 3.4.2.5), SCL should be normally based on animal studies.
4) In addition, the CLH proposal attempts to relate the positive responses in the diagnostic patch tests to the levels of HICC in cosmetic products. However, cosmetic products are complex mixtures and sensitization reactions from complex mixtures are very difficult to interpret as the exposure is to many substances, and even with the diagnostic patch test, there is still uncertainty as to the causative ingredient(s) eliciting the reaction. Also, in 'section 3.4.2.5 Setting of specific concentration limits' in the ECHA Guidance on the Application of the CLP Criteria (2012), it specifically states that "SCL are set on the basis of testing of the substance and never on the basis of testing of a mixture containing the sensitising substance (see 3.4.3.1.1 of Annex I)." Thus, establishing an SCL based on reactions observed in cosmetic products is not appropriate.
5) The CLH proposal fails to meet the requirements for the quality of a CLH dossier as adequate and reliable documentation on the presented key studies is missing as is required in Annex VI of the CLP (2008).

According to the CLH proposal, HICC has been selected for Harmonised Classification and Labelling based on Regulation (EC) 1272/2008 (CLP Regulation, Annex VI, Part 2) and the Swedish Chemical Agency is the Rapporteur. Also, the report notes that a current entry in Annex VI, CLP regulation is not available and there is no entry in the Annex I of DSD Directive (67/548/EEC).

IFF would like to point out that HICC, CAS# 31906-04-4; 51414-25-6, has been submitted to ECHA as a joint registration in May 2013 with registration number: 01-2119971808-21. The data within this dossier shows HICC to be a Cat 1B skin sensitiser following the rules of the CLP amendment of 2011 (Regulation (EU) 286/2011). The comments of IFF to the CLH proposal are detailed below but first IFF's rationale for classification is presented.

B. IFF's Rationale for Classification

a. Introduction
International Flavors and Fragrances Inc. (IFF) and two joint registrants have submitted HICC under REACH for the 2013 deadline. REACH Regulation (EC) No 1907/2006 and the 2nd ATP of Regulation 1272/2008 (No 286/2011) have been followed to derive a classification and to derive DNELs. This REACH dossier contains peer reviewed data and reasoning to derive the classification and labelling (C&L) for all endpoints including the Environment using CLP (2011).

b. Skin Sensitisation
HICC is classified and labelled as a 1B skin sensitiser based on CLP (2011, Regulation (EU) No 286/2011). Per this regulation (Table 3.4.2), a substance fulfils the criteria of Sub-category 1B if the substance shows a low to moderate potency in animals. Because the animal study is considered to be the key study for classification, the starting point will be the CLP (2011) guidance on C&L on animal studies. The following reasoning has been applied to reach this conclusion:

1. Animal test results for sub-category 1B (CLP, 2011, table 3.4.4)

Local lymph node assay EC3 value > 2% - In an LLNA test a positive result was found. The EC3 was 17% and therefore the substance is classified as a 1B sensitiser. This EC3 is 8 times above the cut off value of 2%, which distinguishes 1A and 1B skin sensitisers.
2. Human evidence for subcategory 1B can include (CLP, 2011, paragraph 3.4.2.2.2.1):
a) Positive response at > 500 µg/cm2 (Human Repeat Insult Patch Test (HRIPT) (induction threshold) For HICC there is no response in a HRIPT (with 119 volunteers, reliability is Klimisch code 2) up to 15%, equivalent to 8264 µg/cm2, which is > 500 µg/cm2.
b) Diagnostic patch test data where there is relatively low but substantial evidence of reactions in a defined population in relation to relative high exposure (elicitation) IFF has used this information only for the risk characterisation and not for CLP, because there is limited guidance on the interpretation of the method and the reliability of the results as is indicated in section 3.4.3.3.4.2 of CLP (2011). In addition, some interpretation is presented in the REACH Endpoint specific guidance (EC, 2008, R.7.3.4.2) in which mainly the uncertainty of these tests are addressed. This guidance also presents that this type of information should only be used in special cases for indication of skin sensitisation.
c) Other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relative high exposure - IFF has not used this information because the epidemiological information available is from diagnostic patch testing and has already presented in (b) above.

In summary, the reliable animal data, which according to regulation should be the primary basis for classification, (Klimisch 1 score) supports HICC being classified as a 1B sensitiser (REACH HICC dossier, 2013).

c. Environment
In the REACH dossier on HICC, it is shown that HICC does not need to be classified for the environment, because the aquatic toxicity information shows that all acute and long-term effects occur at levels > 1 mg/l, the substance is readily biodegradable and has a log Kow of < 3 (2.1).

C. Comments on the CLH Proposal

a. General Comments
1) A CLH proposal should follow the requirements of the CLP regulation, Annex VI, Part 2 (2008).
a) According to CLP regulation, 2008, Article 36(1), substances for which a CLH dossier may be submitted would fulfil the criteria for classification of the following:
• Carcinogenicity, Category 1A, 1B or 2;
• Germ cell mutagenicity, Category 1A, 1B, or 2;
• Reproductive toxicity, Category 1A, 1B or 2;
• Respiratory sensitisation, Category 1.

Dermal sensitisation is not one of these hazard classes for which a dossier may be submitted. To submit for other hazard classes, the CLH proposal must justify that action is needed at the European Community level (Article 36(3) of the CLP Regulation, 2008). In the opinion of IFF, the CLH proposal does not adequately justify such action because the key argument, the claim of high frequency of sensitisation in humans based on diagnostic patch testing in clinics due to exposure of low concentration in cosmetic products, has high uncertainty. The positive diagnostic patch tests are indicative of elicitation reactions to HICC. IFFs' reasoning can be derived from CLP criteria on elicitation (2008/2011), ECHA's Guidance on the Application of the CLP Criteria (Section 3.4.2.5, 2011) and Basketter et al. (2005), for which ECHA's guidance on setting of specific concentration limits is based. The authors recognized that "Variation in elicitation thresholds between people is very large and

depends on many factors, of which sensitizing potency is only one. Other factors affecting elicitation include the duration, extent and site of exposure, status of the skin and degree of specific sensitization. For this reason, the Expert Group considered that it would be inappropriate to define elicitation thresholds as a function of skin sensitizing potency". This statement indicates that potency, and thus the establishment of a concentration limit, should not be based on elicitation.
b) Annex VI of the CLP (2008) refers to the relevant part of sections 1, 2 and 3 of Annex 1 of the REACH regulation (2006) considering the methodology and format of the dossier. The Rapporteur has not presented how they fulfil these requirements of the REACH regulation Annex 1 and which they consider relevant parts. A requirement mentioned in the CLP regulation is the need for providing information as robust study summaries (RSSs). This requirement is also presented in the REACH regulation (Annex 1, 1.1.4 and in 3.1.5, 2006). Further guidance regarding how to document such study is given in ECHA (2010): Practical guide 3 on RSS. In IFFs view the Rapporteur has not provided their information using RSS format (e.g. Table 16 in the CLH proposal). When documenting the information, the reliability of the information also needs to be presented to help distinguish key data from supporting data. No such reliability has been indicated in the proposal (e.g. Table 16 in the CLH proposal). Therefore, based on the documentation of the information of the Rapporteur, the conclusion can only be that HICC is a 1B skin sensitiser, because information to support more severe classification is not well documented (CLP, Annex VI, 2008 and REACH, Annex 1, 2006).
c) An IUCLID 5 technical dossier is only available to the RAC and member states, which makes the information of the key studies and their reliability difficult to interpret.
2) The CLP regulation is a specific framework under the REACH regulation. The applicability, considering transparency and justification, of the Rapporteur's information on skin sensitisation for the CLH proposal is not well addressed.
a) The referenced SCCS Opinion used by the Rapporteur is on "Fragrance Allergens in Cosmetic Products" (SCCS, 2012). The labelling of Cosmetic Products in the EU follows the EU Cosmetics Regulation 1223/2009, as the labelling according to the CLP regulation is not applicable to Cosmetic Products. Furthermore, the safety of cosmetic products is not governed by the REACH regulation (see Article 2, 6(b) of the REACH regulation).
b) Most if not all human hazard information presented by the Rapporteur is related to cosmetic exposure and it is unclear how this should be interpreted under REACH (e.g. CLH proposal 'Chapter 3 and section broad use of low concentrations'). IFF, therefore, would ask the Rapporteur to distinguish between cosmetic and non-cosmetic products and disagrees with the use of the SCCS Opinion as a starting point for a CLH proposal.
c) The Rapporteur presents Specific Concentration Limits (CLH report, page 34, iv), assuming that a reference is made to CLP, 2008, Annex I, Section, 1.1.2. Such limits should normally be applied on animal data considering skin sensitisation (ECHA guidance on CLP regulation, 2012, 3.4.2.5, page 275). As discussed above, based on animal data the substance should be classified as a 1B skin sensitiser. In addition, according to the CLP, concentration limits may be used for elicitation (CLP, 2011, Table 3.4.6); however, the Rapporteur has not explained how these elicitation concentrations have been derived. Furthermore, in this section of the Guidance document, it states "SCLs shall be set when there is adequate and reliable scientific information available showing that the specific hazard is evident below the GCL", 1%, for classification. As such, the SCL should normally be used as suggested in Table 3.4.2.5. The concentration limits for skin sensitisers categorized according to their sensitization potency in the Table 3.4.2.5 are recommendations from an EU expert group on skin sensitization (Basketter et al., 2005). The additional comment in the ECHA guidance on CLP (2012), that reliable human data could be included from e.g. workplace, has not been presented by the Rapporteur.
d) In table 16c, in vitro studies on phototoxicity are presented. Phototoxicity is outside the scope of the CLP regulation (CLP, 2008, 2011) and does not provide justification for HICC

being a 1A skin sensitiser.

b. Specific Comments on the CLH Proposal, Chapter 4, Section 4.6.1.4 Comparison with Criteria
1) page 32 - i) HICC is a widely used fragrance ingredient that causes skin sensitisation.
IFF fully agrees on the first sentence in this section.
The Rapporteur then starts with the European clinical studies. According to CLP Regulation (2011), the decision on the type of skin sensitiser is derived based on table 3.4.2 AND on the basis of reliable and good quality evidence from human cases or epidemiological studies AND/OR the guidance criteria set out for Human evidence and animal studies. (see article 3.4.2.2.1.3 for full text). In IFF's view, there is sufficient reliable information (Klimisch code 1 and 2) on animals to draw the conclusion that HICC is a 1B sensitiser. In addition, in the HRIPT test up to 15% (circa 8000 µg/cm2), no skin sensitisation was seen.

2) page 32 - Human data
The first criterion in the CLP regulation (2011), in the section human evidence, is based on the HRIPT studies. The HRIPT for HICC did not demonstrate any adverse effects up to 15%, with a reliability Klimisch code 2, as has been presented in the submitted REACH HICC dossier (2013). Therefore IFF is of the opinion that HICC should be classified as a 1B skin sensitiser (which is corroborated by the EC3 value of 17%).
The information presented by the Rapporteur on the positive responses in diagnostic patch testing should receive Klimisch code 4, because the information is not adequately and reliably documented using RSSs. There is no reference presented on the methodology of this test and the uncertainty of the results is not addressed as is required according to CLP section 3.4.2.2.4.2 and EC's 'Endpoint specific guidance' R.7.3.4.2 (EC, 2008), which says that information from such patch testing should be used with care. Also a discussion is missing on how to interpret the wording in the CLP 3.4.2.2.2.1/2 relatively high/low and substantial evidence, what is a defined population and that prevalence/high number of patch test positives does not necessarily equate to high potency of an allergen.
The information provided on the epidemiological evidence is also not presented as RSSs. It is not clearly laid out how incidence and prevalence should be interpreted. For example, in epidemiological studies, statistical significance is of main importance to interpret the results (Wijnhoven, 2008). This has not been well presented. In addition, the epidemiological evidence is mainly based on the diagnostic patch testing and therefore the epidemiological argument cannot be distinguished from the diagnostic patch testing.

3) page 33 - Animal data
IFF agrees with the result of the animal data, but notes that there is no RSS supporting the result in the CLH proposal.

4) page 33 – ii. According to table 3.4.2 substances showing high frequency and/or high potency in animal can be presumed to have the potential to produce significant sensitisation in humans". Such substances shall be classified in sub-category 1A.
IFF's view is that the potency in animals results in a 1B sensitiser (the EC3 is 8 times higher than the required criterion: EC3 is 17.1 versus 2%) and that this information is the key study with a Klimisch code 1. The supporting information is from a HRIPT with a reliability of Klimisch 2, showing no skin sensitisation up to 15%. This concentration is equivalent to a dose of circa 8000 µg/cm2, which is 16 times above the threshold of 500 µg/cm2 for classification as a 1A skin sensitiser. This HRIPT information has been presented in the REACH dossier on HICC (2013).
IFF agrees with the statement that the frequency of sensitised subjects reacting to HICC, when they are tested during diagnostic patch testing, is substantial. It should, however, be noted that the exposure levels of HICC in most patch tests is 1to 5%, and mostly 5% (Table

16a in the CLH proposal). These concentrations are higher than the highest concentration of 0.63% in consumer products (excluding one product) as being presented by the Rapporteur. When applying HICC at such high concentrations (at least 5 times above the concentration in consumer products) the severity of the reaction should also be considered (CLP, 2011, Table 3.4.2). In view of sensitisation being an immunological reaction a distinct reaction should be evident at lower concentrations. The Rapporteur does not present information on severity and evidence of reactions at lower concentrations. Therefore in the view of IFF the 1B skin sensitisation classification does not have to be changed.
In addition, this maximum 0.63% concentration in consumer products (as being presented by the Rapporteur) has not been specified considering cosmetics and personal care products versus other consumer products that need to be assessed under REACH.
The Rapporteur does not adequately put the reported frequencies of HICC sensitivity (as obtained from diagnostic patch testing at a dosage of 2.7%) into perspective.
For example, in the CLH proposal (4.6.1.4, ii, at point 2) the 1500 cases of skin sensitisation since 1999 (as presented earlier) has not been put into perspective compared to the number of people being tested, nor was this done for prevalence for HICC of 0.28% in the German population. IFF questions whether the information of the REACH Endpoint specific guidance (R.7.3.4.2, EC, 2008) has been used to address the uncertainty of the information on these clinical cases.

5) page 33 - iii) According to 3.4.2.2.2.1 human evidence for subcategory 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 relative low exposure.
In the first bullet point in this section the Rapporteur presents exposure information to show that people are reactive to relatively low exposures when they already have been sensitised.
The inconsistency between the percentages used as a criterion for classification of skin sensitization and the dose/cm2 used here creates a lack of clarity. The relation between these two criteria should be highlighted as the low dose/cm2 exposure to consumer products is in contradiction to the high concentrations used in the diagnostic patch testing (mostly 5%). In IFF's view, the combination of high diagnostic patch testing exposure of 1 to 5% required to evoke a mild reaction does not support the 1A skin sensitisation classification for HICC.
In the second bullet point in this section (page 34) the Rapporteur shows that the concentration in the products is < 1% and that this has not resulted in absence of a reaction in diagnostic patch testing. In IFF's view the high concentrations used in the diagnostic patch tests (1-5%) may be of concern also because skin irritation may have interfered with the reading of the result (Belsito et al., 2006).

6) page 34 - iv The current general concentration limit for classification in sub-category 1A, 0.1%, is not sufficiently protective for induction of sensitisation to HICC.
In IFF's view the concentration limits are not applicable for skin sensitisers according to ECHA's guidance on CLP (2012). Though this guidance does not take into account the CLP, 2011 information on 1A and 1B sensitisers, it is presented here that Specific Concentration Limits for skin sensitisers should only be based on animal studies (ECHA's guidance on CLP (2012), section 3.4.2.5, page 275). This justifies the 1B skin sensitisation C&L for HICC.
In IFFs view the results of the diagnostic patch testing since 2009 should be documented using RSS (as required by the CLP regulation, Annex VI and EC, 2006) to be able to interpret these data considering the level of increase or decrease of skin sensitisation to HICC. In addition, the time lines to present such an increase or decrease are too short between the onset of the decrease in HICC concentration in consumer products as a result of the RMMs of IFRA, 2009 and the latest publications in 2012. Furthermore no distinction is made between patients already sensitised before the concentration limits have been

implemented and individuals which are sensitised after this implementation.

c. Additional Comments on the CLH Proposal
1) Section 1.1. Substance. Page 5, last sentence of the paragraph below Table 1
"According to the notifications to the Inventory both isomers, with the different CAS numbers, have been self-classified as either Skin Sens. 1 or Skin Sens. 1B. The difference in structure between the two isomers is in the 3- and 4-position of the aldehyde group. Generally, binding to proteins is a key step in the sensitisation process and HICC is expected to do this by a Schiff base formation (Patlewicz, et al, 2002), which is independent of the position of the aldehyde group in HICC. Further, there is no data to indicate any difference in potency between the two isomers. Therefore, the same classification, Skin Sens. 1A is proposed for both isomers, [2] and [3], as well as for the reaction mass [1]."
IFF agrees to classify the individual isomers of HICC as well as the reaction mass for skin sensitisation consistently. However, although the structure-activity relationship arguments of the Rapporteur do indicate skin sensitisation, they do not lead to a Skin Sens. 1A. Therefore attempting to propose a 1A for both isomers as well as the reaction mass is not appropriate, as only a 1B classification can be justified.
2) Section 1.2. Table 3: The current annex VI entry and the proposed harmonised classification
IFF suggests include a reference to the REACH HICC dossier submitted in 2013.
3) Section 2.1. History of the previous classification and labelling
The SCCS (2012) referenced in 2.1 and the literature presented in 2.2 is on clinical cases (i.e. diagnostic patch testing). This type of information should be used in a weight of evidence (WoE) approach because these are not standard tests. According to REACH regulation (2006) Annex I (1.1.4 and 3.1.5) and according to Annex XI, 1.2, such information should be adequately and reliably documented (see also ECHA's Practical guide 2 on WoE, 2010). The validity of the diagnostic patch test has not been adequately described and whether it is equivalent for a non-validated test set following REACH, Annex XI is not presented. In the introduction of Table 16 a (i), this type of testing is "performed according to international standards by dermatologists". According to Wijnhoven (2008) this is not necessarily a valid method. For an independent evaluation the reliability of the results should be well documented as well as their relevance for C&L.
4) Section 2.2. Short summary of the scientific justification for the CLH proposal
The concentration of HICC in consumer products is presented as being low (0.63%). IFF proposes to make a distinction between cosmetics and non-cosmetics because CLP does not apply to cosmetics according to the REACH regulation (EC, 2006).
The Rapporteur presents information that: "recent evaluations have demonstrated that the incidence of skin sensitisation due to HICC has not shown a considerable change".
IFF is aware of these results, but considered these to be of limited relevance for identification for C&L.
When for CLP diagnostic patch testing and epidemiological data are used, the incidence and prevalence relation should be shown to be able to evaluate the CLP criteria for human evidence under b and c. Information on incidence and prevalence is presented by e.g. Wijnhoven (2008) in section 4.1:

"The prevalence/incidence of contact dermatitis specifically due to allergens in consumer products is also unknown, since the data from general practitioners include both occupational and non-occupational contact dermatitis. In addition, it is unclear in which cases the contact dermatitis is validated by a dermatologist and in which cases irritation can be excluded".

In addition, following the CLP (2011) section 3.4.2.2.4 Specific considerations are only applicable when no decision can be derived based on the criteria in the sections above. In

IFFs opinion this section is not applicable because a 1B skin sensitisation for HICC can be appropriately derived based on animal data as well as reliable HRIPT data.
5) Chapter 3: Broad use at low concentrations
IFF agrees that the substance is widely used in various consumer products in low concentrations <1%. Almost all information (3rd paragraph) provided is from cosmetics and personal care products, which are not assessed under REACH. Can the Rapporteur distinguish between cosmetic products and consumer products which needs to be evaluated under REACH e.g. detergents? Can the Rapporteur define what he understands by 'causal products'? Also the information from earlier studies (4th paragraph) is not presenting concentration in non-cosmetic products. Therefore the relevance of this exposure information for REACH and CLP is not substantiated and does not support a change the 1B skin sensitiser classification of HICC.
6) Chapter 3: High frequency of sensitisation in humans
According to the Heisterberg study (2012) and the German study of Schnuch et al. (2012) the national rate (question to the Rapporteur is this Germany?) remains at 2.5% over the last decade which means that the sensitised population to HICC remains constant over the last years and possibly a slight decrease.
In IFF's view the conclusion of the Rapporteur that there is 'still wide public exposure to the potent allergen' is true for the 'wide exposure' and the substance being an allergen. However, the substance being called a potent allergen is not defined, or justified.
Also there is no discussion by the Rapporteur on the justification of the high concentrations used in the patch testing. These concentrations are up to 5 times above CLP labelling concentration of 1%, and whether this is justifiable when performing diagnostic patch testing on humans. Related to this the Rapporteur has not discussed the severity of the effect during patch testing. In view of the high HICC concentrations used during patch testing and skin sensitisation being an immunological reaction, the severity of the effect in these patch tests should be discussed as well as given in the CLP (2011), Table 3.4.1.
The comment of the Rapporteur in the 4th paragraph that HICC has strong additive/synergistic effects according to Bonefeld et al. (2011) is not relevant because under CLP (2011) and under REACH the focus is on a specific substance and additive effects are not considered for classification.
7) Chapter 3: Self-classification is not satisfactory
The self-classification as a 1B skin sensitiser proposed in December 2010 is fully supported by the Industry as has been presented in 2.4 by the Rapporteur. However, it has to be noted that the C&L notifications do not reflect the quality of the data and are therefore of doubtful relevance for the CLH proposal.
8) Part B, Section 1: Identity of the substance, 1.3. Physico-chemical properties
IFF proposes to include the missing physico-chemical properties using the ones that have been presented in the REACH HICC dossier, 2013.

9) Part B, Section 2, Manufacture and Uses, 2.1 Manufacture
The comment of the Rapporteur that the production/marketed volume in Europe, has increased since 2000, is not correct. The HICC volumes in Europe have declined from just over 350 MT annual usage in 2000 to approximately 260 MT annual usage in the latest survey (2011). These marketed tonnage values of HICC areis based on figures from periodic IFRA global volume of use surveys.

10) Part B, Section 4, Human health assessment, 4.1 Toxico-kinetics
IFFs first comment is that the absorption and reactivity is only relevant under the section 'specific consideration' (CLP, 2011, 3.4.2.2.4) and for a yes/no skin sensitisation classification not for assessing a substance being a 1A or a 1B skin sensitiser.
Having said this, IFF agrees that HICC has a structural alert for skin sensitisation. To underpin its case the Rapporteur presents Citral as a read across substance but without

presenting the REACH required justification for read across (ECHA's practical guide 6, 2010). In addition, though both Citral (assuming that CAS no 141-27-5 is meant) and HICC have an aldehyde as a structural alert for skin sensitisation, the mechanisms of action are different between the two, which is not discussed by the Rapporteur.

Citral HICC
Citral has an alpha-beta conjugated bond with the aldehyde, which is considered to be more reactive compared to an isolated aldehyde group as in HICC. This difference in reactivity may contribute to a decreased potency that is reflected in the EC3 value of the LLNA: 6.8% for Citral and 17.1% for HICC (REACH dossier, 2013).Therefore IFF is of the opinion that Citral is not a proper substance to present a similar mode of action compared to HICC. (Citral on the REACH dissemination website: http://apps.echa.europa.eu/registered/data/dossiers/DISS-bde0fe36-30e2-693a-e044-00144f67d031/AGGR-559f7645-6b15-432c-b7b9-6eaf83f61669_DISS-bde0fe36-30e2-693a-e044-00144f67d031.html#AGGR-559f7645-6b15-432c-b7b9-6eaf83f61669).
11) Part B, Chapter 4, Section 4.1, Toxicokinetics. Second paragraph.
According to the Rapporteur, HICC is found to be phototoxic. However, the information presented is not relevant for CLP regulation, because the hazard as such is not mentioned and no classification criteria are presented in this regulation (CLP, 2008, 2011).
12) Part B, Chapter 4, Section 4.6.1, Skin sensitisation, Table 16a, (i) Population studies
Most studies in table 16a are presented as key studies. Could the Rapporteur present these as RSSs for IFF to interpret these data? In IFF's view the information lacks adequate and reliable documentation and these studies receive Klimisch code 4. In relation to CLP; the relevance of the individual studies or of all studies together, is not well presented and therefore, in IFF's view, the information is of limited relevance for CLP. Furthermore, in these studies potentially other modes of actions, e.g. irritation, are not indicated.

13) Part B, Chapter 4, Table 16 b Animal studies; Reference Bonefeld, 2011
In the result section of the table, the Rapporteur mentions a 130% ear thickness as compared to the control. According to OECD TG 442B (2010) ear thickness may also be an irritant reaction instead of an allergic reaction when ear thickness is > 25%. Therefore, in IFFs view the result of the Bonefeld study indicates a skin irritation reaction instead of a skin sensitisation reaction.
14) Part B, Chapter 4, Section 4.6.1.1, pag.29: Non-human information
At first some structure-activity relationships (SARs) are presented. The Rapporteur presents two types of reaction mechanisms to substantiate their case of C&L. In IFFs view SAR information does not distinguish a skin sensitiser 1A from 1B. Most SAR information is based on animal studies and therefore the SAR presented is supporting the 1B C&L of HICC.

References
Basketter, D.A., Andersen, K.E., Liden, C., Loveren van, H., Boman, A., Kimber, I., Alanko, K., Berggren, E., 2005, Evaluatation of the skin sensitizing potency of chemicals by using existing methods and consideration of relevance for elicitation, Contact Dermatitus, 52, 39-43 (Expert group opinion on behalf of the Technical Committee on Classification and Labelling dealing with harmonized classification of substances and classification criteria under Directive 67/548/EED on behalf of the European Commission)
CLP, 2011, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:083:FULL:EN:PDF
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ECHA, 2010, Practical guide 2, How to report Weight of Evidence
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ECHA, 2010, Practical guide 6, How to report Read across
ECHA, 2012, Guidance on application of the CLP criteria,
http://echa.europa.eu/documents/10162/13562/clp_en.pdf)
ECHA, 2013, Citral, Dissemination website,
OECD, 2010, OECD Test Guideline, 442B, Local Lymph node assay BrdU-Elisa:
http://iccvam.niehs.nih.gov/SuppDocs/FedDocs/OECD/OECD-TG442B.pdf
REACH HICC dossier 2013, submission to ECHA
SCCS, 2012, OPINION on Fragrance allergens in cosmetic products
http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf
Wijnhoven, 2008, Allergens in consumer products:
http://www.rivm.nl/bibliotheek/rapporten/320025001.pdf

ECHA note: Attachment provided as a separate document (with figures)

Dossier Submitter's Response

Response to IFF comments

The Guidance to the CLP criteria is currently subject to an update due to the ATP 2 and ATP 5 of the CLP. ATP2 includes the new criteria for sensitization with sub-categorisation. The external consultation procedure for the draft Guidance managed by ECHA where member states and industry have taken part (Partner Expert Group, Risk Assessment Committee, Forum, CARACAL) is finalized. The conclusions of the CLH proposal on HICC has been compared to the most recent version, draft Guidance on the Application of the CLP Criteria (version 4.0) 2013, which could be found here:
http://echa.europa.eu/documents/10162/13562/draft_guidance_clp_health_caracal_en.pdf

Response to General comments

1 a) An extensive set of data on allergy to HICC and its widespread use support the need for action at Community level, as presented in Section 3 of the proposal.

In the draft Guidance on the Application of the CLP Criteria (version 4.0) 2013 extensive guidance on how to evaluate human data for classification and subcategorisation of sensitisers has been introduced. Human data mainly originate from diagnostic patch testing, thus guidance is provided on how to use these data for classification purposes.

The following guidance values are given for categorizing sensitisers in 1A, based on human diagnostic patch test data and exposure data. For comparison, in the third and fourth column, respectively, the actual values for HICC are given in italics.

Human diagnostic patch test data	**Frequency, guidance values for sub-cat. 1A**	***Frequency for HICC according to CLH proposal***
General population studies	≥ 0.2%	*0.28% (estimated by Schnuch et al (2009))*
Dermatitis patients (unselected, consecutive)	≥ 1.0%	*2-3% (compiled data)*
Selected dermatitis patients (aimed testing, usually special test series)	≥ 2.0%	*2.4% (Heisterberger et al (2010))*
Work place studies: 1) all or randomly selected workers 2) selected workers with known exposure or dermatitis	≥ 0.4% ≥ 1.0%	 *3.7% (Uter et al (2003))* *1% (Schüerer, Schwanitz (2004))*
Number of published cases	≥ 100 cases	*1500 cases (SCCS 2012)*

Exposure data	**Low exposure, score**	**High exposure, score**	***For HICC according to CLH***

			proposal
Concentration/ dose	< 1.0% < 500 µg/cm^2 (score 0)	≥1.0% ≥500 µg/cm^2 (score 2)	*1 – 6300 ppm/0.63% (score 0)*
Repeated exposure	< once daily (score 1)	≥once daily (score 2)	*anticipated score 1*
Number of exposures (irrespective of concentration of sensitizer)	< 100 exposures (score 0)	≥100 exposures (score 2)	*anticipated score 0*

An additive exposure index of 1-4 equates to low exposure. For HICC the exposure index would be 1 or a maximum of 4, thus low exposure.

Taken together HICC meets the guidance values for being a sub-category 1A sensitizer.

Patch testing measures an elicitation reaction, i.e. induction has taken place previously. Elicitation thresholds may not be a direct function of the induction potency, even if the elicitation usually occurs at lower concentrations than induction. Elicitation thresholds have been suggested to be less dependent on the potency of the substance but more on the degree of sensitization of the individual. For example, it may not be relevant to base safe limits on EC_3 values from LLNA which is a measure of potency of induction (Fischer *et al*, 2011). Following this it was also suggested that a general threshold for elicitation may be adequate for protection as it appeared that the magnitude of difference in elicitation thresholds was not so high between sensitisers. The SCCS (2012) noted that Quantitative Risk Assessment based on threshold values derived from predictive testing in animals or human volunteers have arrived in limits which have proven not to be safe for consumers. These methods have also not been validated. Their conclusion was that the only methods to identify safe levels of allergens in consumer products is to study clinical data and elicitation levels, as has been done with successful legislative measures for e.g. nickel. Thus, even if classification of sensitisers shall be based on induction it is necessary and relevant to study human clinical elicitation data, as has been done for HICC. Market surveys and recommendations from IFRA on safe levels in consumer products have been considered to deduce an SCL for HICC.

b, c) This CLH proposal is mainly based on human sensitization data, originating from diagnostic patch testing and summarized as population studies in Table 16. Nearly all studies are taken as key studies which means that the selection of individuals tested as well as the number of individuals tested is clarified in the study reports, the test substance is characterized and patch testing has been conducted according to international standards. International standards include application of patches, reading of reactions and interpretation of results. In the CLH proposal all data which are considered necessary for the evaluation are presented.

2 a, b) The CLH proposal for HICC is based on the provisions of the CLP Regulation and a classification of HICC should therefore be based on its inherent properties. HICC has a widespread use in cosmetics and household products, therefore the encounter with HICC could occur from different sources. Human evidence is relevant for evaluation of its inherent properties whether they originate from HICC in cosmetic products or other chemical products. A classification of HICC will have legal implications for chemical products under the CLP regulation.

c) In the draft Guidance on the Application of the CLP Criteria (version 4.0) 2013, para 3.4.2.2.5, it is exemplified how SCLs can be set based on animal studies. However it doesn't exclude that human data can be used for this purpose. In fact, the draft guidance contains new extensive passages on how human data can be used to evaluate the sensitizing properties of substances, including sub-categorisation. An example of an SCL that is mainly

derived from human data is the SCL set for MCI/MI (Kathon).

See also response to comment number 7 from the Netherlands on the SCL for HICC.

d) Correct. Table 16 c in the proposal is not a support for the CLH proposal, but is rather provided as information.

Response to Specific comments

1) There is an extensive set of human data demonstrating the sensitizing properties of HICC. These data meet the criteria for sub-categori 1A in table 3.4.2 of Annex I of CLP, which are further elaborated in the draft Guidance to CLP, section 3.4.2.2.3.1. Regarding conflicting data, such as animal versus human data, see also 3.4.2.2.4.2 in Annex I of CLP and 3.4.2.2.3.3 of the draft guidance to CLP.

IFF refers to a human provocation study, HRIPT, where a dose of 8000µg/cm^2 did not cause sensitization in 109 human volunteers. The value of the negative HRIPT is limited due to the possible large interindividual differences, insufficient number of test subjects to detect an effect, no controls used, reduced dose due to evaporation of the substance and few applications.

Even though the LLNA had an EC_3 value which indicates sub-category 1B, this cannot neglect the extensive human data presented in the CLH proposal. There are other cases where sensitization shows different patterns in human and animals, nickel being a well-known example.

2) See response to Specific comment no 1) above.

Human evidence in the CLP explicitly includes data from diagnostic patch testing in a defined population and in relation to exposure, see 3.4.2.2.2.1 b) in Annex I of CLP. Most of the studies referred to in the CLH proposal are diagnostic patch test studies in defined populations; this is the common way for dermatological clinics to compile patch test data, whereby prevalences and trends of contact allergy in differently selected groups at the clinic can be followed. These studies are 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, the test substance is characterized and patch testing has been conducted according to international standards. International standards include application of patches, reading of reactions and interpretation of results. Therefore these results are very relevant for evaluation of sensitizing properties of different allergens. HICC has a wide distribution in consumer products and from market surveys the size of exposure can be derived. Applied recommendations on limit values in products can also considered. Comparing patch test data and data on exposure with the guidance values as presented in the draft guidance for CLP, leads to the conclusions on classification in sub-category 1A in 4.6.1.4 of the CLH proposal. For the comparison, please see response to General comment no 1a).

The prevalence of positive diagnostic patch test response as reported by dermatological clinics is not equivalent to potency, as commented by IFF. Potency is related to dose and effect. HICC may be called a potent allergen in the sense that it induces contact allergy on repeated exposure even at relatively low concentrations.

3) The guideline study with LLNA is reported with necessary information for evaluation.

4) Patch testing is a sensitive and specific tool for diagnosis of contact allergy to a particular

substance. The concentration of a sensitizer in the standard patch has been screened out to be the optimal concentration to diagnose sensitization to a particular substance while not inducing sensitization to the same substance when patch testing. The patch test concentrations used are optimal also in the sense that eventual skin irritation properties should not interfere with the reading of the patch test. Thus the patch test concentration is not a threshold for elicitation, which may be much lower. Induction and elicitation reactions usually evolve from repeated exposure during a long time in contrast to a diagnostic patch test reaction which follows after a single exposure. A relationship between patch test concentrations and concentrations used in Repeated Open Application Test has been suggested by Fischer LA, *et al* (2009)*. In ROAT, with repeated daily applications, the dose in µg/cm^2 per application was lower (approximately a factor of 30) than the single patch test dose in µg/cm^2 for a given response. It's an indication that repeated exposure to low doses of an allergen is supporting the development of contact allergy.

Regarding severity of reaction, please see response to Additional comment no 6) below.

Regarding human data originating from cosmetics, please see response to General comment no 2a,b) above.

Regarding frequency and the number of people being tested, please see response to General comment no 1b,c) above.

*Fischer LA, *et al* (2009) The dose-response relationship between the patch test and ROAT and the potential use for regulatory purposes. *Contact Dermatitis 61: 201-208.*

5) Concerning the patch test concentration in relation to the lower concentrations which consumers are exposed to in products, please see response to Specific comment number 4).

6) Regarding the use of human data to set an SCL, please see the response to General comment no 2c) above and also the response to Comment no 7 from the Netherlands.

Regarding time lines - after the IFRA recommendation in 2009 to limit the HICC concentration in products to 200 ppm a decline in positive patch test frequencies would have been expected. It's reasonable to believe that patch test frequencies also include new cases of contact allergy; not only cases of sensitization which were acquired many years ago. Therefore the observation that patch test frequencies have not declined since 2009 is a sign that 200 ppm is not sufficient to protect from sensitization (Heisterberg *et al* (2012), Schnuch *et al* (2012)).

Response to Additional comments

1) Classification in 1A has been justified in the CLH proposal.

2) A registration dossier was not available by the time the CLH proposal was submitted to ECHA.

3) In Annex I of CLP, 3.4.2.2.2.1, it is stated that human evidence that can be used for classification in sub-category 1A can include diagnostic patch test data and other epidemiological evidence. This is further elaborated in the draft guidance to CLP.

Clinical patch testing is conducted according to international standards which include

how to apply the patch, read the reaction and to interpret the results. This is the available tool and an adequate way to follow the status of contact allergy to a specific substance in different populations and to see trends.

4) It is very likely that most positive patch test data originate from contact allergy to consumer products as HICC has a widespread use in such products; for a large number of people the possibility to be exposed is therefore high.

The human evidence presented in the CLH proposal in combination with the low concentrations of HICC in consumer products meet the criteria for classification in sub-category 1A as worded in 3.4.2.2.2.1 (b) and (c) in Annex I of CLP.

5) Please see response to General Comment no 2ab) above regarding HICC in cosmetics versus household products. Market surveys of HICC in consumer products also include non-cosmetics. Please see Part A, section 3 of the CLH proposal.

6) Potency is related to dose and effect. HICC may be called a potent allergen in the sense that it induces contact allergy on repeated exposure even at relatively low concentrations.

Please see response to Specific Comment no 4) above regarding patch test concentrations.

Regarding severity of reaction, please see the draft Guidance to CLP, section 3.4.2.2.2. Severity refers to hospitalization, chronic dermatitis and systemic dermatitis; normally not to the strength of the patch test reaction.

Bonefeld et al (2011) found that mixtures of allergens may enhance the induction and elicitation of contact allergy. This is a finding which may not have implications on classification of sensitisers at the moment.

7) Noted.

8) Thanks. Noted that complete physico-chemcal properties are presented in the registration dossier.

9) Thanks for information on marketed volumes of HICC in Europe.

10) No toxicokinetic studies on HICC were found. Therefore similarities in structure, partition coefficient and molecular weight were presented for HICC and citral which is a very fast skin penetrant. From these similarities it was assumed that also HICC has skin penetrating properties. Read across to the contact allergen citral is not applied for classification of HICC.

11) Correct.

12) Please, see response to General Comment no 1) b).

13) The test concentrations were based on literature data and were adequate. However, it can not be completely excluded that the increase in ear thickness in the mixed dosing was due to irritation; in such a case indicating an enhanced irritation response in the mixture. The result of this study does not have implications on the CLH proposal.

14) SAR information is not used for the proposed assignment of HICC to sub-category 1A.

RAC's response

RAC's response to section A (summary) and B (rationale for Classification) in registrant´s/SIEF´s comments:
RAC agrees with DS that the available human data is sufficient for classification in Skin Sens. 1A, even if the animal data fulfils the criteria for classification in category 1B based on the EC3 value. Human diagnostic patch test data may be used for classifying a substance in sub-category 1A, as described in CLP, 2nd ATP, Table 3.4.2 and CLP Guidance Tables 3.4.2-b, -c, and –d. Also other human data support this sub-category.

SCLs should be set when there is adequate and reliable scientific information available showing that the specific hazard is evident below the GCL for classification. SCLs may be based on human studies (as mentioned in CLP Guidance, page 365), e.g. work place studies, however data on concentration of HICC associated with induction of sensitisation in humans is limited. Therefore RAC concludes that no SCLs can be assigned to HICC. RAC agrees with the DS that the two unpublished HRIPT studies submitted in the REACH registration add little to the weight of evidence analysis of HICC. The two studies have been summarized in the Background document under "Additional key elements".

RAC's response to General comments (section C. a. in registrant´s/SIEF´s comments):
RAC considers all incoming proposals and leaves the legal question of justification for action at community level for other hazard classes than CMR and respiratory sensitisers up to ECHA and COM. However RAC sees a concern for this very potent sensitiser in the presented data. The presented proposal contains enough information for RAC to conclude on the proposed classification. RAC considers that the relevance of the *in vitro* studies of the phototoxic properties of HICC is low for classification.

RAC's response to Specific comments (section C. b. in registrant´s/SIEF´s comments):
RAC agrees with the DS that the extensive human data cannot be neglected, and support the DS view on the comments from IND, apart from the DS´ assumption that an effect from the IFRA recommendation from 2009 to limit the content of HICC in products to 200 ppm could already be seen in the studies submitted. RAC considers the timeline to be too short for that.

RAC's response to Additional comments (section C. c. in registrant´s/SIEF´s comments):
RAC has included the data from the REACH registration in the Background Document, see "Additional Key Elements".

Date	Country	Organisation	Type of Organisation	Comment number

14.08.2013	United Kingdom		National Authority	3
Comment received				
The SCCS has already proposed the addition of HICC to Annex II to Regulation (EC) no 1223/2009 and therefore this proposal is appropriate.				
Dossier Submitter's Response				
Thanks for your support!				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2013	Belgium	A.I.S.E. AISBL	Industry or trade association	4
Comment received				
A.I.S.E and his member companies FULLY SUPPORT the IFRA general comments related to the CLH REPORT for HYDROXYISOHEXYL 3-CYCLOHEXENE CARBOXALDEHYDE (HICC) Summary: IFRA's comments are related to the use of the opinion on fragrance allergens in consumer products; adopted by the SCCS at its 15th plenary meeting of 26-27 June 2012 (SCCS/1459/11) as basis for deriving conclusions under the EU Regulation (EC) No 1272/2008 (CLP), to which IFRA strongly disagrees. *ECHA note: Attachment provided as a separate document*				
Dossier Submitter's Response				
Please see response to comments by IFRA; comment number 5.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.08.2013	Belgium	International Fragrance Association (IFRA)	Industry or trade association	5
Comment received				
Summary: IFRA's comments are related to the use of the opinion on fragrance allergens in consumer products, adopted by the SCCS at its 15th plenary meeting of 26-27 June 2012 (SCCS/1459/11) as basis for deriving conclusions under the EU Regulation (EC) No 1272/2008 (CLP), to which IFRA strongly disagrees. Rationale: The aim of the CLP Regulation is to ensure that the hazards presented by chemicals are clearly communicated to workers and consumers in the European Union through classification and labelling of chemicals. The hazardous chemicals also have to be labelled according to a standardized system so that workers and consumers know about their effects before they handle them. The Swedish CLH dossier on HICC mainly uses the SCCS opinion 1459/11 as basis to support its conclusion that HICC is a very potent sensitizer and should be classified SS1A and also to derive a specific concentration limit.				

The SCCS provides opinions on health and safety risks (chemical, biological, mechanical and other physical risks) of non-food consumer products.
The opinion 1459/11 does focus on risk assessment of fragrance exposure via cosmetic products. Cosmetic products are following its own regulation 1223/2009 and are therefore exempted from the CLP regulation. Further, the CLP is clearly focusing on hazard.

For those reasons, risk related conclusions derived in the SCCS opinion do not qualify as basis for justifying conclusions under the CLP.

The SCCS opinion is exactly that, an opinion. It serves as basis for the respective unit within DG Sanco to derive risk management measures.
The opinion does heavily focus on a subset of the population that has already been sensitized (+/- 2%) and bases its risk assessment conclusions mainly on this subset, not the general population.

The SCCS opinion further mainly uses patch test data as basis for the criteria to differentiate 'sensitizers' and 'sensitizers of special concern'. Those criteria have not been broadly discussed and accepted by the scientific community and were challenged during the public consultation of the opinion. In general, the prevalence of patch testing does not necessarily equate to the potency of an allergen.

IFRA, with support of the European Commission (DG Sanco), has set up a work plan to address questions raised by the SCCS opinion in a broad multi-stakeholder dialogue, including representation from the SCCS and academia. One central element of the work plan is the topic of definition of sensitizers and those of special concern. A very important element here will be the discussion of clinical relevance, meaning that a positive patch test does not necessarily imply that the consumer has an issue under normal product use conditions – which means assessing the risk under realistic exposure. A series of workshops is planned, the first one of this specific topic taking place in August. The outcome of the workshops should be awaited before using the SCCS opinion as reference other than for the Cosmetic Regulation.

Further, consumer exposure related information (labelling) under the scope of the CLP Regulation does exclude cosmetic products, which are solely covered by the Cosmetic Regulation but this is the exposure which 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.

Further, when deriving the specific concentration limit, the CLH dossier refers to the IFRA Standard on HICC. While in general IFRA Standards are based on induction and the levels adequate to prevent consumers to become sensitized (induction), the HICC Standard includes elements of elicitation and is therefore inadequate to make conclusions on specific concentration limits to prevent induction (CLH dossier page 32). Further, according to the CLP guidance (ECHA 2012, 3.4.2.5), SCL should normally be based on animal studies.

ECHA note: Attachment provided as a separate document

Dossier Submitter's Response

Response to IFRA comments

The Guidance to the CLP criteria is currently subject to an update due to the ATP 2 and ATP

5 of the CLP. ATP2 includes the new criteria for sensitization with sub-categorisation. The external consultation procedure for the draft Guidance managed by ECHA where member states and industry have taken part (Partner Expert Group, Risk Assessment Committee, Forum, CARACAL) is finalized. The conclusions of the CLH proposal on HICC has been compared to the most recent version, draft Guidance on the Application of the CLP Criteria (version 4.0) 2013, which could be found here: http://echa.europa.eu/documents/10162/13562/draft_guidance_clp_health_caracal_en.pdf

The SCCS (2012) opinion relates to the use of fragrances in cosmetics with focus on risk assessment. The opinion may serve as a basis for review of the provisions for safe use of cosmetics under the Cosmetic Products Regulation. However, the opinion is also a very valuable document as an expert review of current state of knowledge of sensitization and the inherent properties of sensitisers, not only in cosmetics but also for other applications of sensitisers. Therefore reference has been made to the opinion.

Classification under the CLP is based on the inherent properties of substances, not on risk. The criteria for skin sensitisers are found in Annex I of CLP section 3.4.2.2. For evaluation of the inherent properties the source of data is not necessarily important, e.g. sensitization caused by use of cosmetics is valuable data which could be used to elucidate the inherent properties of an ingredient. Data presented in the CLH proposal originate from exposure to household products as well as cosmetic products. See also article 1.5(c) in the CLP which states that the CLP should not be applied on cosmetics in the finished state, intended for the final user. However the ingredients of cosmetics are not excluded.

The specific criteria in the CLP are spelled out in Table 3.4.2 of Annex I. Further on it is explained what kind of human evidence could be used; explicitly diagnostic patch test data in a defined population and other epidemiological evidence in relation to exposure are mentioned. No reference to specific product types is mentioned.

Therefore human diagnostic patch test data as well as exposure data originating from use of different product types, including cosmetics, are adequate as a basis for classification of HICC.

See also response to General comment no 1a) and 2a, b) from IFF.

Regarding the setting of SCLs, it is not a requirement that they should be based on animal data, see article 10 of CLP. In the draft Guidance on the Application of the CLP Criteria (version 4.0) 2013 it is shown how animal data could be used for setting SCLs; however human data are not excluded. The SCL for MCI/MI is an example where the SCL is mainly based on human data.

See also response to comment no 7 from the Netherlands.

RAC's response
See the response to comment number 2, above.

Date	Country	Organisation	Type of Organisation	Comment number
13.08.2013	Netherlands		MemberState	6
Comment received				

p12. Wijnhoven et al. (2008) is cited in the text but is not included in the reference list.
p12. The report The presence of fragrance allergens in scented consumer products, RIVM, Ezendam, J. et al. (2009) (http://www.rivm.nl/bibliotheek/rapporten/340301002.pdf)also gives some figures on the presence of HICC in scented consumer products.
p21. To further strengthen the case of HICC as human sensitizer, the CESES project reports an 8% positive response to HICC patch tested in 327 patients at dermatological centers in the time period 2009-2012 in the Netherlands.
Cosmetovigilance in The Netherlands Trend report 2011 – 2012, RIVM, de Wit-Bos, L. et al. (2012) (http://www.rivm.nl/bibliotheek/rapporten/320113005.pdf)

ECHA note: Attachment provided as a separate document

Dossier Submitter's Response

The following reference is missing in section "7 References" of the CLH dossier:
Wijnhoven S.W.P. *et al* (2008), Allergens in Consumer Products, RIVM Report 320025001/2008.

Thanks for additional data to support the proposal:

According to the NVIC (Dutch National Poison Control Centre) database 17.7% of 113 scented products on the Dutch market contains HICC. A manufacturer of scented products declared on its website that 16.3% of their 49 scented products contains HICC.
Ezendam J *et al* (2009), The presence of fragrance allergens in scented consumer products, RIVM Report 340301002/2009.

The CESES project reports an 8% positive response to HICC patch tested in 327 patients at dermatological centers in the time period 2009-2012 in the Netherlands.
de Wit-Bos, L. *et al* (2012), Cosmetovigilance in The Netherlands, Trend report 2011 – 2012, RIVM Report 320113005/2012,
http://www.rivm.nl/bibliotheek/rapporten/320113005.pdf).

RAC's response

Noted.

OTHER HAZARDS AND ENDPOINTS – Skin Senzitation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
13.08.2013	Netherlands		MemberState	7

Comment received

The Netherlands does agree with the classification of HICC as Skin Sensitizer 1A.

The criteria for inclusion of a skin sensitizer in category 1 is:
Substances shall be classified as skin sensitisers (Category 1) where data are not sufficient for sub- categorisation in accordance with the following criteria: (a) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons; or (b) if there are positive results from an appropriate animal test

And subsequent criteria for classification in subclass A:
Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered. Human evidence for sub-category 1A can include:

(a) positive responses at ≤ 500 µg/cm 2 (HRIPT, HMT — induction threshold);
(b) 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;
(c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

The draft Guidance on the application of CLP criteria (third draft to generate version 4.0) further stipulates a sub classification decision table providing criteria for relatively high incidence and relatively low exposure of human data. For the frequency of occurrence of skin sensitisation the following criteria are given:

Comparing the human studies (table 16a (i and ii)) presented in the CLH report for HICC with these criteria is can be noted that in more than half of (14/25) the patch test studies with selected dermatitis patients the frequency is >2.0%. For unselected, consecutive patients almost all patch test studies (9/11) have a frequency of >1.0%. The total number of published cases is well above 100. Considering the data above, it can be concluded that there is a high frequency of occurrence of HICC skin sensitization.

For the relative exposure the following criteria are given:

The CLP report for HICC states that average concentrations found in consumer products are between 0.0036 and 0.63%. However, higher concentrations are found of 3.8% and even 6.2%. Given the data presented it can be anticipated that these high percentages are outliners and average percentage of HICC as fragrance in consumer products is <1.0%. As consumer products containing HICC are abundant (10-80% of the products analyzed contained HICC) it is anticipated that the repeated exposure would be >1 once/daily with >100 exposures in total.
Considering the data above, it can be concluded that the cumulative exposure score is 4. This score lists the exposure as relative low.

According to the sub-categorisation decision table stated in the guidance, the combination of a relative low exposure and a relative high frequency of occurrence of skin sensitization to HICC justifies the classification of HICC as Skin Sens. 1A.

The Netherlands does not agree with the specific concentration limit (SCL) of 0.01%

According to art. 10 of the CLP regulation:
Specific concentration limits shall be set [….] where adequate and reliable scientific information shows that the hazard of a substance is evident when the substance is present at a level below the concentrations set for any hazard class in Part 2 of Annex I or below the generic concentration limits set for any hazard class in Parts 3, 4 and 5 of Annex I.

The information stated in the CLH report for HICC does not show adequate and reliable scientific information that the hazard (the induction of skin sensitization by HICC) is evident when HICC is present at a level below 0.1% (the generic concentration limit).
The current support provided in the CLH report consists of the reference to two risk assessment models (Johansen, et al. 2003 and Gerberick, et al. 2001) on induction thresholds to determine a sensitization reference dose. The risk assessment model proposed by Gerberick, et al.2001 is based on a generic hypothesized NOEL for sensitization combined with subjective uncertainty factors. No experimental data on HICC is provided regarding its induction potential in this risk assessment. The reference to Johansen et al.

2003 provided only elicitation data in already sensitized individuals. A second argument is that the IFRA recommendation from 2009 to limit exposure to 200 ppm has not resulted in a decrease of cases of skin sensitization. However, the available information does not show that the current exposure concentration is below 200 ppm as the stated range was 100 to 6300 ppm. Although ethical sound, specific data on HICC effect concentrations is only available for the elicitation phase. We kindly invite the Swedish CA to provide more adequate and reliable scientific information supporting the claim that induction by HICC is evident below 0.1%.

ECHA note: Attachment provided as a separate document. The comment was originally entered under respiratory sensitisation.

Dossier Submitter's Response

The need for an SCL for HICC is based on the evidence that sensitisation to HICC has not gone down since recommendations to restrict its use to a maximum of 200 ppm in consumer products were given by SCCNFP in 2003 and by IFRA in 2009. This has been demonstrated by Heisterberg *et al* (2012), Schnuch *et al* (2012) and Thyssen *et al* (2012).

Market surveys between 1999 and 2008 have shown levels of HICC from few ppm up to some thousands of ppm. More recent surveys, after 2009, have not been available. Despite an anticipated maximum HICC content of 200 ppm in consumer products following the IFRA recommendation in 2009 the positive patch test frequencies have not gone down. Thus the 200 ppm (0.02%) level is not sufficient to protect from induction of sensitisation and the classification level of 0.1% is inadequate. It should be noted that even if single products contain HICC above 200 ppm, induction of sensitisation may have occurred at lower concentrations.

Identification of threshold values for induction of sensitisation is a complex issue as, for example, not only the dose (per unit area) is relevant but also the accumulated dose. Thus it's problematic to use human or animal experimental induction data to derive safe levels for consumers. With the application of safety factors the resulting levels have not proven safe for consumers. In the report of SCCS 2012 it is concluded that clinical data and elicitation data have proven to be the most reliable sources to derive safe use levels for consumers. The SCCS also derived a general threshold value for safe use of fragrances in consumer products; this was due to the commonly absence of substance specific data. The general threshold was based on ED10-values, i.e. the patch test concentration where 10% of sensitized individuals elicit reactions. Statistical analyses of available data in scientific literature was performed on 20 studies with eight allergens, including two fragrances. The identified general threshold was 0.8µg/cm^2, which corresponds to 0.01% in products, based on deodorants. It was also noted that safe use thresholds which are based on elicitation data also reduces the risk for induction. Examples of that are restrictions on nickel and chromium. As regards HICC, the ED10 identified in three studies were very close to the derived general threshold: 0.9µg/cm^2 (Johansen *et al*, 2003), 1.17µg/cm^2 (Jörgensen *et al*, 2007) and 0.662µg/cm^2 (Fischer *et al*, 2009).

Taken together it is clear from available human data that 0.1% is not an adequate classification limit. 200 ppm (0.02%) appears to be insufficient to protect against sensitization. In the light of this and in the absence of more specific induction data on HICC a reduction of the GCL with a factor of 10 is considered to be proportionate, i.e. 0.01%. This is also supported by the general safe limit, 0.01%, as identified by SCCS.

RAC's response

RAC agrees with The Netherlands that a specific concentration limit (SCL) of 0.01% is not justified.

Date	Country	Organisation	Type of Organisation	Comment number
13.08.2013	France		MemberState	8
Comment received				
FR supports the proposal classification in category 1A for skin sensitization for HICC, based on the high frequency of sensitization occurrence in humans with a broad use at low concentration. Moreover, the toxicokinetic evaluation from chemical, structural and mechanistic considerations on known strong skin sensitizers comforts the classification in category 1A.				
Dossier Submitter's Response				
Thanks for your support!				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
09.08.2013	Germany		MemberState	9
Comment received				
Based on the extensive human evidence (high frequencies of positives with a mean of 2-3% and up to 17%) in patch tests and case studies at presumed low exposure concentrations in consumer products, classification in the sub-category 1A is justified. Specific data on the LLNA test are missing in the CLH report, however this test is not the trigger for classification in 1A. Nevertheless, the discrepancy between the moderate potency in the LLNA (EC3=17.1%; endpoint induction) and the broad recognition of HICC as a major human allergen is quite remarkable. Since the patch test detects already sensitized individuals (an elicitation threshold as low as 25 ppm has been found in 10% of the patients), it would be of interest if the relatively low current levels of HICC are responsible for induction of the immune response, or past exposures to much higher doses cannot be completely excluded. In addition, the time since introduction of the latest concentration limit of 200 ppm in 2009 might be too short to significantly influence the incidence of HICC sensitization because a potential positive effect might have been masked by a backlog from prior exposures. If indeed a concentration limit of 200 ppm (0.02%) was not sufficiently protective to insure prevention of new cases of HICC sensitization, than lowering the SCL by factor of only 2 (i.e., 0.01%) as currently proposed might not be sufficient as well. In this case, application of lower SCL should be discussed or briefly explained why a concentration limit of 0.001 % (w/v) due to "extreme potency" is not justified.				
Dossier Submitter's Response				
Please find response to comment under Comment number 7 from the Netherlands.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.08.2013	Finland		MemberState	10
Comment received				
We support the proposed classification as Skin Sens. 1A; H317 for HICC. There is a special concern caused by HICC to human health due to its high frequency of sensitisation in humans despite the low concentrations in products and its wide use in many consumer				

products in Europe. However we wonder the justification for the proposed SCL 0.01% based entirely on human data about the frequencies of positive human patch tests to HICC in European clinics after IFRA`s recommendation to lower the maximum concentration of HICC in final products to 200 ppm in 2009. Is the information provided adequate and reliable scientific data which could be used for setting the SCL? Based on evidence and compared to the IFRA`s recommendation we understand that GCL 0.1% for the mixtures would not probably be safe enough.
Dossier Submitter's Response
Please find response to comment under Comment number 7 from the Netherlands.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
15.08.2013	United States	International Flavors & Fragrances Inc.	Company-Manufacturer	11
Comment received				
See uploaded attachment and general comments.				
Dossier Submitter's Response				
Please see response to comment number 2 from IFF.				
RAC's response				
Noted.				

Attachments:

1. IFF Lead registrant's comments, on behalf of the SIEF, on the CLH REPORT FOR HYDROXYISOHEXYL 3-CYCLOHEXENE CARBOXALDEHYDE (HICC), provided by International Flavors & Fragrances Inc., USA.
2. IFRA General Comments related to the CLH REPORT FOR HYDROXYISOHEXYL 3-CYCLOHEXENE CARBOXALDEHYDE (HICC) provided by AISE and IFRA, Belgium.
3. Comments on the proposed classification of HICC (Lyral) (Hydroxyisohexyl 3-cyclohexene carboxaldehyde) provided by NL MSCA