

Letter to the Editor

A new IFRA Standard on the fragrance ingredient, hydroxyisohexyl 3-cyclohexene carboxaldehyde

To the Editor,

We read with interest the article by P. Braendstrup and J.D. Johansen on behalf of the Danish Contact Dermatitis Group which appeared in *Contact Dermatitis* 2008; 59: 187–188 and noted that IFRA Standards were referenced in the article. IFRA Standards have been in existence since the 1970s to ensure the safe use of fragrance ingredients. Member companies of IFRA account for approximately 90% of the marketed fragranced products (in volume) sold around the world. There are extremely efficient checks and balances for IFRA compliance within the fragrance industry suppliers and customer companies (e.g. for members of the European Cosmetics Association, COLIPA, IFRA compliance is a pre-requisite for the legally required safety assessment of cosmetic products). Further, it should be noted that IFRA Standards have been adopted either by reference or by inclusion in the legislation in a number of regions (the most recent one being China). In addition, beginning in 2006, IFRA initiated its compliance program, which focuses on the safety of fragranced consumer products by ensuring that the IFRA Code of Practice is fully adhered to and applied. It involves the analysis of a variety of consumer products for the presence of fragrance ingredients regulated by IFRA Standards. The product analysis is defined in specific procedures and is executed completely and independently by Eurofins Scientific, an international group of laboratories following strict internal procedures to ensure confidentiality and impartiality.

The purpose of the Standards based on dermal sensitization is to prevent primary induction. The authors were correct in stating that hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) (CAS 31906-04-4; 51414-26-6) was unrestricted before 24 April 2003, when the first IFRA Standard for this material was published. However, we want to use this opportunity to highlight the developments that happened just after the publication of the article, particularly in July 2008, when the IFRA Standard on this material was modified to restrict the use of this material further in consumer products. This Standard was again in July 2009 to restrict the material even

further to address concerns better regarding already sensitized consumers.

The initial IFRA Standard dictated that the level of HICC could not be more than 1.5% in fragrances created after the IFRA Standard became effective in finished consumer products with the potential for skin contact.

Since the promulgation of the initial IFRA Standard and based on the chemical, cellular, and molecular understanding of dermal sensitization, it has become possible to conduct an exposure-based Quantitative Risk Assessment (QRA) to determine safe use levels of fragrance ingredients in a variety of consumer product types. This new methodology is an improvement over former risk assessment practices because it specifically addresses the elements of exposure-based risk assessment that are unique to the induction of dermal sensitization, while being consistent with the principles of general toxicological risk assessment. As such, it is a clear improvement over the risk management strategies formerly used by IFRA (1). As a result, in July 2008, the IFRA Standard on HICC was converted to a QRA-based standard. All new fragrance creations had to follow this new IFRA Standard as soon as it was issued. Existing creations were to be modified within 24 months in order to be compliant with this update. The new QRA Standard for HICC further restricts its use in certain product categories. However, this QRA methodology, which represents a scientific advance over previous methods for ingredient use determinations, was not available in the late 1990s, when a significant number of patch test positive incidences to HICC were beginning to be reported in Europe.

HICC is one of three fragrance ingredients for which the frequency of sensitization in patients reporting to dermatology clinics with eczema is greater than 2% in Europe (2, 3). In published reports, this frequency is not observed in North America, Korea, or Iran where rates of 0.4%, 1.7%, and 0.8% of the patients, respectively, were observed (4–7).

The fragrance industry is very concerned about the reports of >2% frequency of sensitization to

Table 1. Restriction for HICC independent of the QRA

IFRA QRA CATEGORY	Product type that drives the category consumer exposure level	IFRA Standard 2003–2008	IFRA Standard July 2008	IFRA Standard July 2009
Category 1	Lip products	1.5%	0.11%	0.02%
Category 2	Deodorants/antiperspirants	1.5%	0.15%	0.02%
Category 3	Hydroalcohols for shaved skin	1.5%	0.60%	0.2%
Category 4	Hydroalcohols for unshaved skin	1.5%	1.5%	0.2%
Category 5	Hand cream	1.5%	1.0%	0.2%
Category 6	Mouthwash	1.5%	1.5%	Not applicable*
Category 7	Intimate wipes	1.5%	0.3%	0.02%
Category 8	Hair styling aids	1.5%	1.5%	0.2%
Category 9	Rinse-off hair conditioners	1.5%	1.5%	0.2%
Category 10	Hard surface cleaners	1.5%	1.5%	0.2%
Category 11	Incidental or non-skin contact	15%	Not restricted	Not restricted

HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; QRA, quantitative risk assessment.

*Not applicable because HICC is not approved for flavour use.

HICC in eczema patients in Europe. The frequency of sensitization in Europe has neither increased nor decreased significantly. It is believed that, had the QRA been available and implemented in the 1990s, the level of HICC sensitization in patients in Europe might not be as high as it is today. The industry firmly believes and continues to support thresholds based on induction rather than elicitation. However, given the exceptional situation in Europe, the fragrance industry elected to take further restrictive action on this material.

Dermatological reports in Europe show that antiperspirant or deodorant products are more problematic with respect to HICC sensitization than any other product types (8). Therefore, an additional restriction on HICC has recently been implemented to lower its use to a level which would be expected effectively to reduce the frequency of sensitization observed in patients in Europe. This new lower limit has also been implemented for products in QRA Categories 1 (lip products) and 7 (intimate hygiene products). Use in all other categories has also been further restricted to ensure additional consumer safety (except non-skin).

These significant additional restrictions are independent of the QRA methodology and were selected only to promote a decrease in the frequency of sensitization observed in eczema patients in Europe. The new restrictions have been included in the latest IFRA Standard on HICC, issued in July 2009 and are detailed in Table 1. The new restrictions have been broadly communicated to the fragrance and its customer industry and will also be made available in the IFRA website (www.ifraorg.org).

Anne Marie Api¹ and Matthias Vey²

¹Research Institute for Fragrance Materials, Inc.,
Woodcliff Lake
New Jersey, USA
Tel: +1 201 689 8089
Fax: +1 201 689 8090
e-mail: amapi@rifm.org

²International Fragrance Association,
Brussels, Belgium

References

1. Api A M, Basketter D A, Cadby P A et al. Dermal sensitization Quantitative Risk Assessment (QRA) for fragrance ingredients. *Regul. Toxicol Pharmacol* 2008; 52: 3–23.
2. Schnuch A, Uter W, Geier J, Lessmann H, Frosch P J. Sensitization to 26 fragrances to be labelled according to current European regulation. *Contact Dermatitis* 2007; 57(1): 1–10.
3. Frosch P J, Rastogi S C, Pirker C et al. Patch testing with a new fragrance mix - reactivity to the individual constituents and chemical detection in relevant cosmetic products. *Contact Dermatitis* 2005; 52(4): 216–225.
4. Belsito D V, Fowler J F Jr, Sasseville D, Marks J G Jr, De Leo V A, Storrs F J. Delayed-type hypersensitivity to fragrance materials in a select North American population. *Dermatitis (Formerly American Journal Contact Dermatitis)* 2006; 17(1): 23–28.
5. An S, Lee A Y, Lee C H, et al. Fragrance contact dermatitis in Korea: a joint study. *Contact Dermatitis* 2005; 53(6): 320–323.
6. Eun H C, An S, Lee H et al., 2004. Safety of various fragrances: Allergy and phototoxicity, joint study in Korea. *Contact Dermatitis*, 2004; 50(3): 174–175.
7. Kashani M N, Gorouhi F, Behnia F, Nazemi M J, Dowlati Y, Firooz A. Allergic contact dermatitis in Iran. *Contact Dermatitis* 2005; 52(3): 154–158.
8. Jorgensen P H, Jensen C D, Rastogi S, Andersen K E, Johansen J D. Experimental elicitation with hydroxyisohexyl-3-cyclohexene carboxaldehyde-containing deodorants. *Contact Dermatitis* 2007; 56(3): 146–150.