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Implementation of the dermal sensitization Quantitative Risk Assessment (QRA) for fragrance ingredients

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ABSTRACT

Significant developments have recently been incorporated in the way dermal sensitization risk assessments are conducted for fragrance ingredients. Based on the RIFM Expert Panel's recommendation, RIFM and IFRA have formally adopted the QRA approach, refined for fragrance ingredients identified as contact allergens, as the core strategy for primary prevention of dermal sensitization to these materials in consumer products. This new methodology is a major improvement over the former approach 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 toxicological risk assessment. This methodology will be used to determine global fragrance industry product management practices (IFRA Standards) for potentially sensitizing fragrance ingredients, the first of which was implemented in May 2006 with the 40th Amendment to the IFRA Code of Practice. It contained the first four IFRA Standards based on the QRA, limiting the use of the materials for 11 individual product categories. One of the first four IFRA Standards based on the QRA was on the fragrance material citral. The basis for the acceptable exposure limits are presented in this paper.

1. Introduction

Significant developments have recently been incorporated in the way dermal sensitization risk assessments are conducted for fragrance ingredients. This, in turn, has had a significant impact on the way that IFRA ingredient use restrictions (IFRA Standards) based on dermal sensitization are implemented in the future. For more than a year an expert group, which included representatives from the fragrance and consumer products industries and RIFM, worked on refining this risk assessment methodology for fragrance ingredients. The details about the method for use with fragrance ingredients are explained in Api et al. (2008).

The previous approach for dermal sensitization used by IFRA was qualitative and not an exposure-based risk assessment. This QRA methodology is a major improvement over the former approach because (1) it is consistent with the principles of toxicological risk assessment; (2) can be applied to dermal sensitization since this is a threshold phenomenon and (3) addresses factors that are specific to dermal sensitization. The risk management strategies used in the past by IFRA for fragrance ingredients identified as an allergen limited the use of the fragrance ingredient to the same concentration across all product types that involved skin contact. In the new QRA approach there are 10 different product categories for skin contact products. Category 11 is designated for non-skin or incidental skin contact products. Since exposure is a key element of category determination, this enables maintenance of relevant exposure and therefore safety, while broadening the set of individual limitations and as a side effect also provides greater flexibility to the perfumer because the limit is no longer the same across all skin contact applications. This means that, in some product applications, a higher fragrance ingredient concentration will be possible, while in others, a lower level may be specified, compared to what has been used in the past.

In brief, the key steps of the dermal sensitization QRA process for fragrance ingredients are:

- determination of No Expected Sensitization Induction Level or NESIL;
- application of Sensitization Assessment Factors (SAF) and
- Calculation of Consumer Exposure (CEL) through product use.

Using these parameters, an Acceptable Exposure Level (AEL) can be calculated and compared with the Consumer Exposure Level (CEL). The ratio of the AEL to CEL must be favorable to support the safe use of the skin sensitizer. This ratio must be calculated for each fragrance ingredient identified as a potential skin sensitizer in each product type. For more details, see Api, 2006; Api et al., 2006, 2008; McNamee, 2006.

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2. Definition of IFRA QRA product categories

In the old approach all product types were categorized into two groups—skin contact and non-skin contact products. It is no longer considered sufficient to apply these two groups to the new QRA approach. In the new approach in excess of 50 product types were considered. Since this is such a large number, it is not practical or even desirable to set IFRA Standards based on dermal sensitization for every individual product type. A realistic application of the recommended QRA approach for fragrance ingredients is to use multiple product categories for the implementation of IFRA Standards. This is achieved by grouping consumer product types according to key parameters identified within the QRA approach. These parameters are SAFs and consumer product exposure, which when combined, lead to similar acceptable use levels of a fragrance ingredient. (For a detailed description of the SAFs and the rationale used to determine SAFs see Api et al., 2008) Table 1 provides an illustration of how similar SAFs and consumer product exposures were combined to create the IFRA QRA product categories, using categories 3, 4 and 5 as examples. Using these parameters, Table 2 outlines 11 different IFRA categories for dermal sensitization. For many categories it may appear that there is a wide diversity of product types. However, this is because the categories are based on scientific rationale (SAF and consumer product exposure), and not on the functional similarity of each product type. In cases, where a product is not currently categorized and where the likely consumer product exposure is clearly different or where the matrix may indicate a higher degree of potential penetration or irritation, then it is incumbent on the fragrance supplier to contact the IFRA secretariat (secretariat@ifraorg.org) for advice on appropriate product categorization. This would lead to a modification of the industry guidance available in form of a booklet on the RIFM as well the IFRA websites. In those cases the IFRA membership and stakeholders would be adequately informed about the change(s).

There are several key considerations regarding the product types and categories that must be noted:

- The QRA addresses the protection of human health and is specifically aimed at ideally eliminating the acquisition of dermal sensitization to fragrance ingredients under their conditions of use. The fragrance industry QRA approach defined for dermal sensitization should not be applied to other toxicological effects or usage patterns as it is specific for dermal sensitization.
- The products described are all retail consumer products.
- Product types are placed into IFRA product categories on the basis of grouping consumer product types according to key parameters identified within the QRA approach. These parameters are Sensitization Assessment Factors (SAFs) and consumer product exposure, which when combined, lead to similar acceptable use levels of a fragrance ingredient. It is not possible to list every conceivable type of product in the industry guidance document (booklet). Several product types have been placed in specific IFRA categories even in the absence of exposure data by taking into account how the product is used, what it contains and the extent of likely skin exposure. However, should consumer product exposure data become available; these product types may be re-categorized. Also, if additional relevant exposure data become available on any product type, this may also result in re-categorization of the product type. If you are aware of a product type that is not categorized, please contact the IFRA Secretariat (secretariat@ifraorg.org).
- **Aerosols:**
  - **Pressurized aerosols**: When calculating fragrance ingredient concentration in pressurized aerosols, to determine compliance with an IFRA Standard (determining the concentration reaching the skin), the propellant should be discounted because it flashes off very rapidly. The basis for the calculation should be the active solution or the mixture of the fragrance compound (fragrance mixture or fragrance oil) and other excipients (e.g. water, ethanol, active components).
  - **Aerosol skin contact**: Skin contact from aerosol products (e.g. aerosol air freshener) as defined in Category 9 relates to those aerosol products that are not intended for skin contact, but their use may result in skin contact. This excludes deodorant/antiperspirants, hair styling aids and sprays, which are part of other categories.
- **After sun creams and self-tanning Products**: After sun and sunless tanning products are not addressed separately, but are included in the major product types (e.g. facial cream, body cream) in line with other sun care products. Products used on mildly sunburned skin are also expected to fit into the major product categories without amendment to their QRA which is already sufficiently conservative. Use of products for severely sunburned skin could constitute a different exposure scenario, but since this borders on needing professional medical advice for treatment, this is considered to be outside the scope of this QRA activity.

Table 1
An example of constructing IFRA categories

Product types in IFRA product category	Inter-individual SAF	Matrix SAF	Use SAF	Overall SAF	Exposure[a] mg/cm^2/day	Citral (NESIL = 1400)
Category 3				300	2.2	0.2%
Hydroalcoholic products applied to recently shaved skin	10	3	10	300	(C& R)[b] 2.21	0.2%
Eye products of all types (eye shadow, mascara, eyeliner, eye make-up, etc.)	10	3	10	300	(CTFA, 2005a) 2.17	0.2%
Men's facial creams and balms	10	3	10	300	(EC, 1996) 2.06	0.2%
Tampons	10	1	20	200	(RIFM, 2006) 2.9	0.2%
Category 4				100	2.2	0.6%
Hydroalcoholic products applied to unshaved skin	10	3	3	100	(C& R)[b] 2.21	0.6%
Hair styling aids, hair sprays of all types (pumps, aerosol sprays, etc.)	10	3	3	100	(Loretz et al., 2006) 2.20	0.6%
Body creams	10	3	10	300	(Colipa, 2005) 0.6	0.8%
Category 5				100	4.2	0.3%
Women's facial creams/facial make-up	10	3	3	100	(CTFA, 2002) 3.17	0.5%
Hand cream	10	3	3	100	(Colipa, 2005) 4.2	0.3%

[a] (Source of exposure data).
[b] Cano and Rich (2001), Tozer et al. (2004), Cano (2006).

Table 2
SAF and product type consumer exposure levels that drive the IFRA QRA Category

IFRA QRA Category	SAF	Category consumer exposure[a] mg/cm^2/day	Product type that drives the category consumer exposure level	Maximum Pragmatic Level
Category 1	300	11.7	Lip products	Acceptable Exposure Level derived from QRA
Category 2	300	9.0	Deodorants/Antiperspirants	Acceptable Exposure Level derived from QRA
Category 3	300	2.2	Hydroalcoholics for unshaved skin	Acceptable Exposure Level derived from QRA
Category 4	100	2.2	Hydroalcoholics for shaved skin	Acceptable Exposure Level derived from QRA
Category 5	100	4.2	Hand cream	Acceptable Exposure Level derived from QRA
Category 6	100	1.4	Mouthwash	Acceptable Exposure Level derived from QRA
Category 7	300	4.4	Intimate wipes	Acceptable Exposure Level derived from QRA
Category 8	100	1.0	Hair styling aids	2% The maximum concentration will not exceed 2% and may be lower if determined by the QRA
Category 9	100	0.2	Rinse-off hair conditioners	5% The maximum concentration will not exceed 5% and may be lower if determined by the QRA
Category 10	100	0.1	Hard surface cleaners	2.5% The maximum concentration will not exceed 2.5% and may be lower if determined by the QRA
Category 11	10	0.00033	Candles	These products result in negligible skin contact. The approach for a pragmatic concentration of fragrance ingredient in this category is explained in the notes section and below in the Frequently Asked Questions section

[a] The category consumer exposure Level (mg/cm^2/day) is driven by the product type in that category with the combined highest consumer exposure level and highest Sensitization Assessment Factor (SAF). In order to identify the product type consumer exposure that drives the category consumer exposure please refer to the Technical Dossier, Table 9.

- **Baby products**: The categorization of baby shampoos and washes includes the assumption that the dose/unit area is similar to this value for adults (i.e. for babies, less product used over a smaller surface area). Should specific exposure and surface area data for babies become available, these product types may be re-categorized.
- **Children's toys**: This product type has been placed in Category 1 based on the absence of exposure data. Should exposure data become available, these product types may be re-categorized.

Due to the possibility of ingestion of small amounts of fragrance ingredients (if oral exposure is foreseeable), materials present in the fragrance compound for use in this toy category must be approved for use in food, meaning that all ingredients should be listed as having "no safety concern", for example by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and/or as Generally Recognized As Safe (GRAS) in accordance with the US Federal Food, Drug and Cosmetic Act.

- **Dental Products**
  - **Toothpaste and mouthwash products**: With the implementation of the QRA approach, the IFRA Standards will include oral care products. Mouthwash and toothpastes are the principal oral care products currently identified in IFRA Category 6. Exposure limits for these products are established to reduce the risk of peri-oral dermal sensitization and as such, are not related to considerations of safe levels for ingestion. The safety of flavor/fragrance ingredients present in products intended to be orally ingested is outside the scope of IFRA's risk assessment process. In the latter cases, salivary dilution and short/variable contact time in the oral cavity would suggest a different risk assessment approach for ingested flavor/fragrance substances. The aspect of safety through ingestion is managed by the International Organization of Flavor Industries (IOFI, see its Code of Practice).
    Due to the possibility of ingestion of small amounts of fragrance ingredients, materials present in the fragrance compound for use in this category must be approved for use in food, meaning that all ingredients should be listed as having "no safety concern", for example by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and/or as Generally Recognized As Safe (GRAS) in accordance with the US Federal Food, Drug and Cosmetic Act.
    Existing IFRA Standards (not based on the QRA) will not be applied to these oral care product types in IFRA Category 6. As the QRA approach for fragrance ingredient dermal sensitizers is implemented, then maximum use levels of these ingredients in toothpaste and mouthwash products will be introduced through definition of new or revised IFRA Standards.
  - **Denture adhesives and tooth whiteners**: These are regulated globally as medical devices. Since medical device regulations include separate safety assessment guidelines, these product types are not included in the IFRA categorization based on the QRA approach.

- **Diapers, feminine hygiene pads, liners and tampons**: As with all other product types, levels of fragrance ingredients in diapers and feminine hygiene products are being based on the final product. For clarification, the final products here are the diaper, feminine hygiene pad or liner or tampon. It is recognized that products such as these involve special considerations because the fragrance mixture or compound is included in the final product based on weight rather than percent concentration. A re-categorization of these product types may be necessary as additional understanding of these special considerations as they relate to the expression of IFRA Standards is further developed.
- **Non-skin contact or incidental skin contact products**: Most of the non-skin contact or incidental skin contact products (as defined in the Code of Practice) are included in Category 11. Due to the expected insignificant skin exposure from such products the risk of induction of dermal sensitization through the normal formulation and use of such products is considered to be negligible. As such, the concentration of fragrance ingredient should not exceed the concentration of the fragrance compound that is stipulated in the fragrance brief for the finished product. For example, if the concentration of the fragrance compound in the final product is at 20%, then any individual fragrance ingredient within the compound would not exceed 20% of the final product. An example of the is given later in the context of the practical example (citral).
  The differentiation as defined in the Code of Practice between non-skin contact products and skin contact products will remain until all existing sensitization Standards are transferred into Standards based on the QRA.

Table 3
IFRA Categories for dermal sensitization, QRA approach, arranged by category

Product type	Maximum Pragmatic Level	Comments
Category 1	Acceptable Exposure Level derived from QRA	
Lip products of all types (solid and liquid lipsticks, balms, clear or colored, etc.)		Products that contain sunscreen or sun-block are not listed separately and are included in the major product type (e.g. lip creams containing sunscreen are included in the lip products category). Due to the possibility of ingestion of small amounts of fragrance ingredients, materials present in the fragrance compound for use in this category must be approved for use in food, meaning that all ingredients should be listed as having "no safety concern", for example by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and/or as Generally Recognized As Safe (GRAS) in accordance with the US Federal Food, Drug and Cosmetic Act.
Toys		This product type has been placed in Category 1 based on the absence of exposure data. Should exposure data become available, these product types may be re-categorized. Due to the possibility of ingestion of small amounts of fragrance ingredients (if oral exposure is foreseeable), materials present in the fragrance compound for use in this toy category must be approved for use in food, meaning that all ingredients should be listed as having "no safety concern", for example by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and/or as Generally Recognized As Safe (GRAS) in accordance with the US Federal Food, Drug and Cosmetic Act.
Category 2	Acceptable Exposure Level derived from QRA	
Deodorant and antiperspirant products of all types (spray, stick, roll-on, under-arm and body, etc.)		
Category 3	Acceptable Exposure Level derived from QRA	
Hydroalcoholic products applied to recently shaved skin		
Eye products of all types (eye shadow, mascara, eyeliner, eye make-up, etc.)		
Men's facial creams, balms		
Tampons		
Category 4	Acceptable Exposure Level derived from QRA	
Hydroalcoholic products applied to unshaved skin		
Hair styling aids, hair sprays of all types (pumps, aerosol sprays, etc.)		
Body creams, oils, lotions, fragrancing creams of all types (including baby creams, lotions, oils)		Products that contain sunscreen or sun-block are not listed separately and are included in the major product type (e.g. lip creams containing sunscreen are included in the lip products category).
Ingredients of perfume kits		
Fragrance compounds for cosmetic kits		
Scent strips for Hydroalcoholic products, "scratch and sniff" samples, other paper products not mentioned elsewhere for which skin exposure is only incidental (e.g. spectacle cleaning tissues)		These product types have been placed in Category 4 based on the absence of exposure data, but it is recognized that these products have similarities to hydroalcoholic products applied to unshaved skin. Should exposure data become available, these product types may be re-categorized.
Foot care products		This product type has been placed in Category 4 based on the absence of exposure data, but it is recognized that this product is similar to body creams, lotions. Should exposure data become available, this product type may be re-categorized.
Hair deodorant		This product type has been placed in Category 4 based on the absence of exposure data, but it is recognized that this product is similar to hair styling aids and hair sprays. Should exposure data become available, this product type may be re-categorized.
Category 5	Acceptable Exposure Level derived from QRA	
Women's facial creams/Facial make-up		
Hand cream		
Facial masks		
Wipes or refreshing tissues for face, neck, hands, body		These product types have been placed in Category 5 based on the absence of exposure data, but it is recognized that these products are generic to males and females and have similarities with the product types in this category. Should exposure data become available, these product types may be re-categorized.
Category 6		Acceptable Exposure Level derived from QRA

Table 3 (*continued*)

Product type	Maximum Pragmatic Level	Comments
Mouthwash		Toothpaste and mouthwash products: With the implementation of the QRA approach, the IFRA Standards will include oral care products. Mouthwash and toothpastes are the principal oral care products currently identified in IFRA Category 6. Exposure limits for these products are established to reduce the risk of peri-oral skin sensitization and as such, are not related to considerations of safe levels for ingestion. The safety of flavor/fragrance ingredients present in products intended to be orally ingested is outside the scope of IFRA's risk assessment process. In the latter cases, salivary dilution and short/'variable contact time in the oral cavity would suggest a different risk assessment approach for ingested flavor/fragrance substances. The aspect of safety through ingestion is managed by the International Organization of Flavor Industries (IOFI, see its Code of Practice).
Toothpaste		Due to the possibility of ingestion of small amounts of fragrance ingredients, materials present in the fragrance compound for use in this category must be approved for use in food, meaning that all ingredients should be listed as having ''no safety concern'', for example by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and/or as Generally Recognized As Safe (GRAS) in accordance with the US Federal Food, Drug and Cosmetic Act. Existing IFRA Standards will not be applied to these oral care product types in IFRA Category 6. As the QRA approach for fragrance ingredient dermal sensitizers is implemented, then maximum use levels of these ingredients in toothpaste and mouthwash products will be introduced through definition of new or revised IFRA Standards.
Category 7 Intimate wipes Baby wipes Insect repellent (intended to be applied to the skin)	Acceptable Exposure Level derived from QRA	
Category 8 Make-up removers of all types (not including face cleansers) Hair styling aids non-spray of all types (mousse, gels, leave-in conditioners, etc.) Nail care	2% The maximum concentration will not exceed 2% and may be lower if determined by the QRA.	
All powders and talcs (including baby powders and talcs)		These product types have been placed in Category 8 based on the absence of exposure data, but it is recognized that the exposure would be similar to body creams, lotions. Although the exposure is expected to be similar to body creams, lotions, the overall SAF for powders and talcs is, however, lower and so these products are placed into a different category compared to body creams, lotions. Should exposure data become available, these product types may be re-categorized.
Category 9 Conditioner (rinse-off) Liquid soap Shampoos of all types (including baby shampoos) Face cleansers of all types (washes, gels, scrubs, etc.) Shaving creams of all types (stick, gels, foams, etc.) Depilatory Body washes of all types (including baby washes) and Shower Gels of all types Bar soap (Toilet soap) Feminine hygiene—-pads Feminine hygiene—liners Bath gels, foams, mousses, salts, oils and other products added to Bathwater Other aerosols (including air fresheners sprays but not including deodorant/antiperspirants, hair styling aids spray)	5% 5% The maximum concentration will not exceed 5% and may be lower if determined by the QRA.	
Category 10	2.5%	

(*continued on next page*)

Table 3 (*continued*)

Product type	Maximum Pragmatic Level	Comments
Handwash laundry detergents of all types Fabric Softeners of all types including fabric softener sheets Other household cleaning products (fabric cleaners, soft surface cleaners, carpet cleaners,) Machine wash laundry detergents (liquids, powders, tablets, etc.) including laundry bleaches Hand dishwashing detergent Hard surface cleaners of all types (bathroom and kitchen cleansers, furniture polish) Diapers	The maximum concentration will not exceed 2.5% and may be lower if determined by the QRA.	
Shampoos for pets		It was assumed that the exposure to humans from shampoos for pets could be expected to be similar to hand dishwashing liquids.
Dry cleaning kits		This product type has been placed in Category 10 based on the absence of exposure data, but it is recognized that this product is similar to fabric softener sheets. Should exposure data become available, this product type may be re-categorized.
Toilet seat wipes		This product type has been placed in Category 10 based on the absence of exposure data, but it is recognized that this product is similar to hard surface cleaner. Should exposure data become available, this product type may be re-categorized.
Category 11 All non-skin contact or incidental skin contact. Including: Air fresheners and fragrancing of all types (plug-ins, solid substrate, membrane delivery, electrical, pot pourri, powders, fragrancing sachets, incense, liquid refills) Animal sprays Candles Cat litter Deodorizers/Maskers not intended for skin contact (e.g. fabric drying machine deodorizers, carpet powders) Floor wax Fuels Insecticides (e.g. mosquito coil, paper, electrical, for clothing) Joss sticks or incense sticks Machine dishwash detergent and deodorizers Machine only laundry detergent (e.g. liquitabs) Odored distilled water (that can be added to steam irons) Paints Plastic articles (excluding toys) Shoe polishes Toilet blocks Treated textiles (e.g. starch sprays, fabric treated with fragrances after wash, deodorizers for textiles or fabrics, tights with moisturizers)	Due to the expected negligible skin exposure from such products the risk of induction of dermal sensitization through the normal formulation and use of such products is considered to be negligible. As such, the concentration of fragrance ingredient is not restricted in the finished product.	

- **Sunscreens**: Products that contain sunscreen or sun-block are not listed separately but are included in the major product type (e.g. lip creams containing sunscreen are included in the lip products category).
- Table 2 provides the SAF and product type consumer exposure levels that drive the IFRA QRA category. These data are used with the NESIL to calculate the acceptable exposure levels to individual fragrance ingredients. Table 3 gives the 11 IFRA QRA categories for dermal sensitization based on the QRA approach. It also gives detailed comments for specific product types. It should be noted that both Tables 2 and 3 contain a column which defines a "**Maximum Pragmatic Level**". Practical considerations require setting a default maximum level of the fragrance ingredients identified as dermal sensitizers for some product types. This pragmatic level is defined as that "not exceeding the usual concentration of the fragrance compound in the finished product". If the Acceptable Exposure Level (AEL) derived from the QRA for a fragrance ingredient in a specific product type is less than the concentration identified as the "Maximum Pragmatic Level", the AEL will take precedence and be applied. IFRA and RIFM will determine whether the AEL or the "Maximum Pragmatic Level" should be applied. The appropriate value will be given in the IFRA Standard.

3. Practical application of the QRA approach for fragrance ingredients: Citral

Citral (Fig. 1) has been chosen as an example to demonstrate the practical application of the principles of QRA. This material is one of the four fragrance ingredients that were part of the 40th Amendment to the IFRA Code of Practice for which Standards have been set based on the QRA approach. The dermal sensitization data on citral include the availability of robust animal sensitization data,

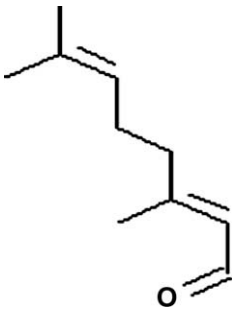

Fig. 1. Citral.

confirmatory human sensitization data as well as diagnostic patch test studies. Table 4 provides a summary of the data used to generate the Weight of Evidence (WoE) No Expected Sensitization Induction Level (NESIL). The summary table is based on the detailed data provided in Lalko and Api (2008) and is presented here for convenience of the reader. The LLNA EC3 value is given as a weighted mean value. The weighted mean EC3 value is the average of the mean EC3 values from studies performed in the same vehicle.

Table 5 provides all the summary data used in the risk characterization of citral in two arbitrarily chosen product types. This table demonstrates how the data are used to determine acceptable levels of use in the two product types, a hydroalcoholic product for unshaved skin and a solid antiperspirant. The first product type is one that defines IFRA Product Category 4 and the second defines IFRA Product Category 2. Using these two product types, this table provides a step-by-step illustration of how the acceptable exposure is calculated.

Table 6 shows the practical application of the dermal sensitization QRA approach for fragrance ingredients in the 11 IFRA QRA categories. It lists the acceptable levels for citral in each IFRA QRA category.

In the context of the QRA activity, RIFM sponsored a survey of the patch test database at the Contact Allergy Unit, University Hospital Leuven, Belgium. The survey commissioned for the QRA activity for fragrance ingredients focused on two areas: (1) identification of the product types that contained specific fragrance ingredients; and (2) the number of positive clinical patch test reactions to these fragrance ingredients in the different product types covering the period 2000–2005.

A total of 3323 subjects were investigated by the Contact Allergy Unit. 9.1% of these patients were found to have a positive patch test reaction to the fragrance-mix; 6.7% to balsam of Peru; 4.8% to colophony. Some of these patients showed positive reactions to multiple fragrance ingredients. Of the patients who reacted positively to the fragrance-mix, 133 exhibited positive patch tests to their own cosmetic products. Of these 133 patients, 66 involved fragrance-related contact-allergic reactions and served as the basis for the results. The only reactions observed with citral were six reactions to toilet water/perfume products.

At this time it is difficult to fully interpret these patch test database survey results in the context of the QRA since the IFRA Standard was implemented in 2006, but the final compliance for existing products will not be completed until May 2008. Translation of this to meaningful changes in elicitation trends observed in the clinic may take some time. However, it is reasonable to make some preliminary conclusions for citral.

The results indicate products which were reported to cause elicitation of skin sensitization. It must be noted that it is difficult to relate to the product that caused the induction of skin sensitization. Therefore use of such surveys is of limited use regarding induction of skin sensitization, but do identify fragrance ingredients for which there may be an incidence of patch test positive patients in the dermatology clinics.

Prior to the IFRA Standard on citral the reported average maximum concentration of citral in hydroalcoholic products was 1.7%. The IFRA Standard based on the QRA approach limits the use in this product type to 0.6%. The data from the patch test database at the Contact Allergy Unit, University Hospital Leuven, Belgium on citral supports that citral was being used at a level that exceeded the acceptable exposure concentration for hydroalcoholics since the only reactions observed were to toilet water/perfume products. It is interesting to note that reactions to other product types, such as deodorants/antiperspirants were not observed in this database.

Table 4
Citral: Sensitization potency estimation based on weight of evidence

Fragrance material	CAS No.	LLNA weighted mean EC3 values (μg/cm^2) [no. studies]	Potency classification based on animal data[a]	Human Data			WoE NESIL[c] (μg/cm^2)
				NOEL-HRIPT (induction) (μg/cm^2)	NOEL–MAX (induction) (μg/cm^2)	LOEL[b] (induction) (μg/cm^2)	
Citral	5392-40-5	1414[11]	Weak	1400	NA	3876	1400

NOEL, No observed effect level; HRIPT, Human Repeat Insult Patch Test; MAX, Human Maximization Test; LOEL, lowest observed effect level.
[a] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[b] Data derived from HRIPT or HMT.
[c] WoE NESIL limited to three significant figures.

Table 5
Example: Application of QRA to use of citral in hydroalcoholic products for unshaved skin and in solid antiperspirant product types

Citral	Hydroalcoholic product for unshaved skin	solid antiperspirant
WoE NESIL (from Table 4)	1400 μg/cm^2	1400 μg/cm^2
Sensitization Assessment Factor (SAF)	100 (10 × 3 × 3)	300 (10 × 3 × 10)
Acceptable Exposure Level (AEL)	14.0 μg/cm^2	4.7 μg/cm^2
Consumer Exposure Level (CEL) Product	2.2 mg/cm^2/day[a]	9.1 mg/cm^2/day[b]
AEL/CEL	AEL/CEL (14.0 μg/cm^2 × 0.001 mg/μg) ÷ 2.2 mg/cm^2/day = 0.0064	AEL/CEL (4.7 ug/cm^2 × 0.001 mg/μg) ÷ 9.1 mg/cm^2/(day) = 0.0005
Concentration of citral in the product giving AEL ⩾ CEL	⩽0.64%	⩽0.05%
Risk assessment	Acceptable if citral level is less than 0.6%	Acceptable if citral level is less than 0.05%

[a] Cano and Rich (2001) and Tozer et al. (2004), 95th percentile Tozer et al. (2004), 95th percentile.
[b] Cowan-Ellsberry et al., 2008.

Table 6
Acceptable levels of citral in each of the 11 IFRA categories Based On QRA

IFRA Category	SAF	Category consumer exposure[a] mg/cm^2/day	IFRA Standard limit for citral[b]	Maximum Pragmatic Level
Category 1	300	11.7	0.04%	Not necessary Acceptable Exposure Level derived from QRA
Category 2	300	9.0	0.05%	Not necessary Acceptable Exposure Level derived from QRA
Category 3	300	2.2	0.2%	Not necessary Acceptable Exposure Level derived from QRA
Category 4	100	2.2	0.6%	Not necessary Acceptable Exposure Level derived from QRA
Category 5	100	4.2	0.3%	Not necessary Acceptable Exposure Level derived from QRA
Category 6	100	1.4	1.0%	Not necessary Acceptable Exposure Level derived from QRA
Category 7	300	4.4	0.1%	Not necessary Acceptable Exposure Level derived from QRA
Category 8	100	1.0	1.4%	Not Applicable[c]
Category 9	100	0.2	Maximum Pragmatic Level Used	5% The maximum concentration will not exceed 5% and may be lower if determined by the QRA.
Category 10	100	0.1	Maximum Pragmatic Level Used	2.5% The maximum concentration will not exceed 2.5% and may be lower if determined by the QRA.
Category 11	10	0.00033	NA	Due to the expected negligible skin exposure from such products the risk of induction of dermal sensitization through the normal formulation and use of such products is considered to be negligible. As such, the concentration of fragrance ingredient is not restricted in the finished product

[a] The category Consumer Exposure Level (mg/cm^2/day) is driven by the product type in that category with the combined highest consumer exposure level and highest Sensitization Assessment Factor (SAF). In order to identify the product type consumer exposure that drives the category consumer exposure please refer to the Technical Dossier, Table 9.

[b] *Note*: It is important to note that although the WoE NESIL (Weight of Evidence No Expected Sensitization Induction Level) is not included in the table above it is essential to the determination of the IFRA Standard since the Acceptable Exposure Level (AEL) is derived from the WoE NESIL divided by the Sensitization Assessment Factor (SAF) and multiplied by the consumer exposure level. The WoE NESIL for citral is 1400 μg/cm^2.

[c] The maximum pragmatic level of 2% was not invoked for Category 8 because the acceptable exposure level derived from the QRA is less than 2% (the Maximum Pragmatic Level).

The IFRA survey showed that the use of citral in these product types was at or below the acceptable exposure level determined by the QRA.

4. Concluding remarks

In the future, the dermal sensitization QRA for fragrance ingredients will be used to establish new IFRA Standards for all fragrance ingredients that are potential dermal sensitizers. The prioritization for assessment will be based on criteria outlined in the RIFM human health criteria document (Ford et al., 2000) such as volume of use, dermal exposure and structural alerts for dermal sensitization. There is still a small group of materials that have existing IFRA Standards based on dermal sensitization, which are still using the previous two category approach. Additional data are being obtained on these materials and the implementation of the QRA in the IFRA Standards for these materials will occur in the near future.

As part of the overall objective of IFRA and RIFM to minimize fragrance allergy in the general population, a key goal is to review by 2011 all chemically defined fragrance ingredients that have structural alerts for dermal sensitization and used at greater than 1 metric ton per year on a worldwide basis. In addition, refinement of the method will continue. Updating the categorization of product types including new product types, improved exposure data and the inclusion of cosmetic products used in an occupational/professional environment are important refinements to be considered.

It is important that dermal sensitization QRA for fragrance ingredients will be used in combination with the clinical results from the dermatology community and company post-market surveillance data to confirm the effectiveness of fragrance ingredient use limits.

Conflict of Interest

Anne Marie Api is an employee of the Research Institute for Fragrance Materials, an independent research institute supported by the manufacturers of fragrances and consumer products containing fragrances.

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