QUANTITATIVE RISK ASSESSMENT (QRA) for FRAGRANCE INGREDIENTS

Although some substances in common use today may have the potential to cause dermal sensitization, they can be formulated into consumer products at safe levels. This is also the case for fragrance ingredients. Based on the chemical, cellular and molecular understanding of dermal sensitization, it is 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.

Significant developments have recently been incorporated in the way dermal sensitization risk assessments are conducted for fragrance ingredients. This new methodology is a major improvement over current 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 toxicology risk assessment. As such, it is a clear improvement over the risk management strategies currently used by IFRA under which each specific fragrance ingredient identified as an allergen is currently limited to the same concentration across all skin contact product types (QRA Expert Group*, Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.)

In brief, overview key steps of the quantitative risk assessment process are determination of benchmarks (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 the skin sensitizer in each product type. For more details, see the QRA Expert Group*, Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

Based on REXPAN's recommendation, RIFM and IFRA have formally agreed to adopt 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 methodology will be used to determine global fragrance industry product management practices (IFRA Standards) for potentially sensitizing fragrance ingredients, the first of which will be implemented in April 2006.

Given the impact of this major change, it is important that global fragrance suppliers and users are fully informed about the changes and the implementation of this new approach. It will affect them in terms of the identification of acceptable levels of fragrance ingredients in different product types and how this will be managed on a practical basis through grouping of certain product types into product categories.

The purpose of this booklet is to provide basic guidance on the implementation of this new approach to fragrance suppliers and users. It will specifically provide information on:

- **how new IFRA Standards will be set**
- **how existing IFRA Standards will be handled**
- **what should be expected in the 41st (2007) and future IFRA Amendments to the Code of Practice**
- **definition of the IFRA categories**
- **relevant product types included in each category**

This booklet is a dynamic document that will change and require periodic updating. As such it will be important to check the issue date (located at the bottom of each page) of this booklet.

40th Amendment to the IFRA Code of Practice (May 2006).

The QRA methodology can be used both to set IFRA Standards for fragrance ingredients identified as dermal sensitizers where none previously existed as well as for review of current IFRA Standards. The use of QRA to set IFRA Standards begins with the 40th Amendment to the IFRA Code of Practice (May 2006). There will be major implications that include time for industry to become familiar with the changes and to update company computer systems. This needs to occur while maintaining the old system for existing IFRA Standards. Given this complexity, a staggered approach has been chosen in which four materials have been selected (citral, farnesol, phenylacetaldehyde and tea leaf absolute) for setting new IFRA Standards and the compliance time has been extended (13 months after the date of the letter of notification for new creations; 25 months after the date of the letter of notification for existing fragrance compounds).

41st and Future Amendments to the IFRA Code of Practice (Spring 2007 & beyond)

The next phase for implementation of the QRA approach will occur with the 41st Amendment to the IFRA Code of Practice (Spring 2007). In that Amendment, the QRA approach will be used to review and re-define all existing Standards set on the basis of dermal sensitization, for which adequate data exist. For those materials identified as lacking sufficient data, additional studies will be considered for future QRA review and incorporation into revised IFRA Standards. Also included in the 41st and future Amendments to the IFRA Code of Practice will be a number of new IFRA Standards (where none previously existed) on fragrance ingredients from the RIFM Database. The prioritization for assessment will be based on criteria such as volume of use, dermal exposure and structural alerts for dermal sensitization. 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 that are used at greater than 1 metric ton per year on a worldwide basis.

Existing IFRA Standards

It is important to note that until all existing IFRA Standards have been revised according to the QRA approach, the old approach with two product categories (skin contact and non-skin contact products) will be maintained in simultaneous use alongside the new QRA approach.

Definition of IFRA Categories

While the old approach of two product categories (skin contact and non-skin contact products), is no longer considered sufficient for application to the new QRA approach, it is also not desirable or practical 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 Sensitization Assessment Factors (SAFs) and exposure, which when combined, lead to similar acceptable use levels of a fragrance ingredient. Using these parameters, Table 1 outlines 11 different IFRA categories for dermal sensitization, which have been specified by the QRA Expert Group*. It may appear that, for many categories, there is a wide diversity of product types. However, this is because the categories are based on scientific rationale (SAF and exposure), and not on the functional similarity of each product type. In cases, where a product is not currently categorized and where the likely exposure is clearly different or where the matrix may indicate a higher degree of potentiation of 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 may lead to a modification of this information booklet and an IFRA Information Letter to advise the whole industry.

Important Information Relevant To the Product Types Included In Each Category

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 contact allergies 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 contact allergy.
- 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 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 this document. 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 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).
- **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 safety 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. The safety by oral ingestion of fragrance ingredients that are also flavor ingredients will continue to be managed by the International Organization of Flavor Industries (IOFI, see its Code of Practice or www.iofi.org). 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.

  Existing IFRA Standards will not be applied to these oral care product types in IFRA Category 6. As the QRA approach to fragrance ingredient dermal sensitizers is implemented, with the establishment of new or existing IFRA Standards, then maximum use levels of these ingredients in toothpaste and mouthwash products will be introduced.
- **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.
- **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).
- **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 risk assessment 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.

- **Children's toys**: Due to the tendency of small children to place objects in their mouths, the use of fragrance in a toy is considered to be a skin contact application. Such toys include dolls, teething rings, pliable modeling compounds, and other related products. It is essential to consider the intentional use and other foreseeable uses of such toys. Further, there is the possibility of ingestion of minute amounts of fragrance ingredients should such toys be placed in the mouth. Therefore, fragrance materials used in the fragrance compound for use in toys must be approved for use in food, meaning that all ingredients should be listed as having "no safety concern" by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and/or as Generally Recognized As Safe (GRAS) in accordance with the US Code of Federal Regulations (21CFR§170.30).
- **Pressurized aerosols**: When calculating fragrance ingredient concentration in pressurized aerosols, to determine compliance with an IFRA Standard, the propellant should not be taken into account.
- **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.
- **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.
- **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.
- **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 will be defined as that "not exceeding the usual concentration of the fragrance compound in the finished product". In Table 1 these levels are indicated in the column identified as "Maximum Pragmatic Level". 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.
- **Non-skin contact or incidental skin contact products**: All non-skin contact or incidental skin contact products are included in Category 11. Due to the expected neglible 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. Additional examples are given later in the booklet in the context of the practical example (citral).

Table 1 gives the 11 IFRA categories for dermal sensitization based on the QRA approach. It also gives detailed comments for specific product types.

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Table 1: IFRA CATEGORIES FOR DERMAL SENSITIZATION, QRA APPROACH

Product Type	Maximum Pragmatic Level	Comments
Category 1	Not Necessary 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).
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 tendency of small children to place objects in their mouths, the use of fragrance in a toy is considered to be a skin contact application. Such toys include dolls, teething rings, pliable modeling compounds, and other related products. It is essential to consider the intentional use and other foreseeable uses of such toys. Further, there is the possibility of ingestion of minute amounts of fragrance ingredients should such toys be placed in the mouth. Therefore, fragrance materials used in the fragrance compound for use in toys must be approved for use in food, meaning that all ingredients should be listed as having "no safety concern" by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and/or as Generally Recognized As Safe (GRAS) in accordance with the US Code of Federal Regulations (21CFR§170.30)
Insect Repellent intended to be applied to the skin		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.
Category 2	Not Necessary Acceptable Exposure Level derived from QRA	
Deodorant and Antiperspirant Products of all types (spray, stick, roll-on, under-arm and body, etc.)		

Product Type	Maximum Pragmatic Level	Comments
Category 3	Not Necessary	
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, Wipes, Refreshing Tissues		
Tampons		
Category 4	Not Necessary 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	Not Necessary Acceptable Exposure Level derived from QRA	
Women's Facial Creams/Facial Make-up/Facial Wipes		
Hand Cream		
Facial Masks		

Product Type	Maximum Pragmatic Level	Comments
Category 6	Not Necessary	
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 safety 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. The safety by oral ingestion of fragrance ingredients that are also flavor ingredients will continue to be managed by the International Organization of Flavor Industries (IOFI, see its Code of Practice or www.iofi.org). 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. Existing IFRA Standards will not be applied to these oral care product types in IFRA Category 6. As the QRA approach to fragrance ingredient dermal sensitizers is implemented, with the establishment of new or existing IFRA Standards, then maximum use levels of these ingredients in toothpaste and mouthwash products will be introduced.
Toothpaste		
Category 7	Not Necessary Acceptable Exposure Level derived from QRA	
Intimate Wipes		
Baby Wipes		

Product Type	Maximum Pragmatic Level	Comments
Category 8	2%	
Make-up Removers of all types (not including face cleansers)	The maximum concentration will not exceed 2% and may be lower if determined by the QRA.	
Hair Styling Aids Non-Spray of all types (mousse, gels, leave-in conditioners, etc.)		
Nail Care		
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	5%	
Conditioner (Rinse-Off)	5% The maximum concentration will not exceed 5% and may be lower if determined by the QRA.	
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)[5] 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)		

Product Type	Maximum Pragmatic Level	Comments
Category 10	2.5%	
Handwash Laundry Detergents of all types	The maximum concentration will not exceed 2.5% and may be lower if determined by the QRA.	
Fabric Softeners of all types including fabric softener sheets		
Other Household Cleaning Products (fabric cleaners, soft surface cleaners, carpet cleaners, etc.)		
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, etc.)		
Diapers		
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.
Category 11	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.	
All non-skin contact or incidental skin contact. Including: Candles Air Fresheners and Fragrancing of all types (plug-ins, solid substrate, membrane delivery, ambient, electrical, pot pourri, powders, fragrancing sachets, incense, liquid refills etc.) Shoe Polishes Deodorizers/Maskers Not Intended For Skin Contact (e.g. . fabric drying machine deodorizers, carpet powders) Insecticides (mosquito coil, paper, electrical, etc.) Toilet Blocks Joss Sticks Machine Dishwash Detergent and Deodorizers Machine Only Laundry Detergent (e.g. liquitabs) Plastic articles (excluding toys[3]) Fuels Paints Cat litter Animal Sprays Treated Textiles (e.g. starch sprays, fabric treated with fragrances after wash) Odored Distilled Water (that can be added to steam irons)		

Example: Citral

Citral has been chosen as an example to demonstrate the practical application of the principles of quantitative risk assessment. This material is one of the four fragrance ingredients that are part of the 40th Amendment to the IFRA Code of Practice for which Standards have been set based on the QRA approach. The sensitization data on citral include the availability of robust animal sensitization data, confirmatory human sensitization data as well as diagnostic patch test studies.

Table 2 shows the practical application of the recommended risk assessment approach for fragrance ingredients, in the 11 IFRA categories, when implementing the QRA for dermal sensitization. It lists the acceptable levels for citral in each IFRA category. Following Table 2 some frequently asked questions about the implementation and designation of IFRA categories are given.

Table 2: Acceptable levels of citral in each of the 11 IFRA categories based on QRA.

IFRA Category	SAF	Category Consumer Exposure[1] mg/cm^2/day	IFRA Standard Limit for Citral[2]	Maximum Pragmatic Level
Category 1	300	11.7	**0.04%**	Not Necessary Acceptable Exposure Level derived from QRA
Category 2	300	8.5	**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%**	2% The maximum concentration will not exceed 2% and may be lower if determined by the QRA.
Category 9	100	0.2	7.0%	**5%** The maximum concentration will not exceed 5% and may be lower if determined by the QRA.
Category 10	100	0.1	11.7%	**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**	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

[1]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.

[2]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.

Frequently Asked Questions

How does IFRA/RIFM calculate the AEL that defines a product category?

The table listed below demonstrates how all the data are used to determine acceptable levels of use as an example for citral in IFRA Category 4. It also demonstrates how important consumer exposure levels are to a risk assessment. The exposures and SAFs listed in Table 2 provide the information that is used to calculate the Acceptable Exposure Level (in the "Citral" column) for each product category. Although there are AELs defined for different product types, the maximum product type AEL is used to define the AEL for a specific IFRA product category. For a detailed description of exposure levels and SAFs for each product type, please refer to the Technical Dossier (QRA Expert Group*, Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp

Citral	Calculation of Acceptable Level for IFRA Category 4
WoE NESIL (from Table 2)	1400 ug/cm^2
SAF (from Technical Dossier)	100 (10 X 3 X 3)
AEL	14.0 ug/cm^2
Category 4 Consumer Exposure Level (CEL)	2.2 mg/cm^2/day[1]
AEL/CEL	AEL/CEL (14.0 ug/cm^2 X 0.001 mg/µg) ÷ 2.2 mg/cm^2/day = 0.0064
Concentration of citral in the product based on **AEL ≥ CEL**	≤ 0.64%
Risk Assessment	Acceptable if citral level is less than 0.64%

WoE NESIL = Weight of Evidence No Expected Sensitization Induction Level
Sensitization Assessment Factor
AEL = Acceptable Exposure Level
CEL = Consumer Exposure Level

Why do some product categories have a "Maximum Pragmatic Level"?

For some IFRA Categories, the calculated acceptable concentrations may be unrealistically high because the calculated consumer exposure levels in (see Table 2) for certain product types are very low. Practical reasons dictate setting a default maximum level of the fragrance ingredients identified as dermal sensitizers for these product types. This pragmatic level will be defined as that "not exceeding the concentration of the fragrance compound that has been stipulated in the fragrance brief for the finished product". In Tables 1 and 2 these levels are indicated in the column identified as "Maximum Pragmatic Level". If the 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 must take precedence and be applied.

How do I determine the "Maximum Pragmatic Level" for products in Category 11 (non-skin/ incidental skin contact)?

Due to the expected very low skin exposure from the products in Category 11 the risk of induction of dermal sensitization through the normal formulation and use of such products is considered negligible.

Atypical use of an ingredient in a category 11 product would need to be the subject of a separate risk assessment.

Example 1: You are asked to submit a fragrance for a candle brief that will contain 10% fragrance compound. The maximum level of citral in the final product (the candle) cannot exceed 10% in the final product.

Example 2: You are asked to make a fragrance compound for a room air freshener that will contain 16% fragrance compound. The maximum level of citral in the room air freshener cannot exceed 16% in the final product.

Example 3: You are asked to submit a fragrance for a toilet block that will contain 8% fragrance compound. The maximum level of citral in the toilet block cannot exceed 8% in the final product.

Why should levels of citral be limited?

The patch test database survey from the Contact Allergy Unit, University Hospital Leuven, Belgium indicates, at least for toilet water/perfume products that a limit for citral should be established. 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 6 reacted to citral in hydroalcoholic products.

IFRA reported in 2001 that the average maximum concentration of citral in hydroalcoholic products was 1.76% or 37.4 μg/cm^2 /day. Figure 1 shows how the average maximum concentration reported in 2001 is unacceptable (i.e. the Acceptable Exposure Level or AEL is less than the customer exposure level or CEL). The figure also demonstrates how the current IFRA limit for this product type (Category 4, hydroalcoholic product for unshaved skin) is acceptable (i.e. the AEL is greater than the CEL).

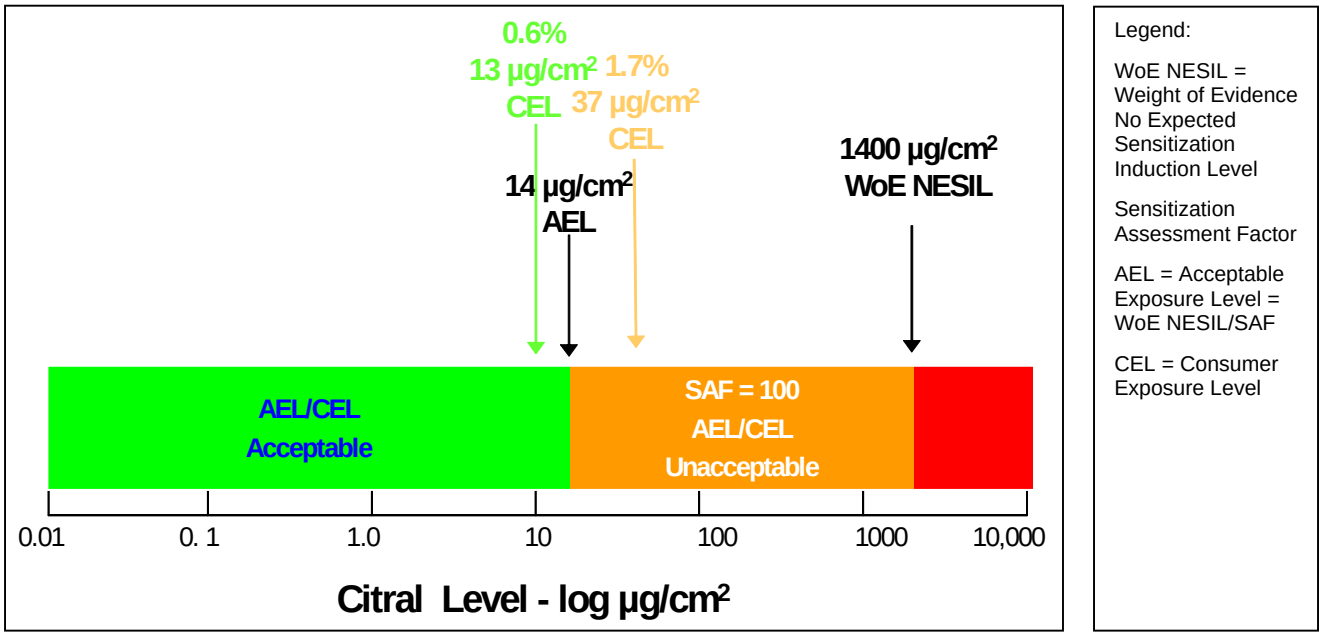

Figure 1: Illustration of AEL/CEL ratio for the current average maximum dermal use level for citral (1.7%; IFRA, 2001) in a hydroalcoholic product for unshaved skin.

Do I apply the QRA to existing Standards?

No. Existing Standards based on sensitization effects were established using the NOEL data and two product categories (skin contact in which the NOEL/10 was used and non-skin contact in which the NOEL was used). It is not possible to translate existing Standards into the QRA approach since different data (e.g. NESILS rather than NOELs) are used to address for many more product categories. As such, the old Standards are not comparable to those produced from the QRA approach.

With the 41st Amendment to the IFRA Code of Practice (Spring 2007), the QRA approach will be used to review and re-define all existing Standards set on the basis of dermal sensitization, for which adequate data exist.

Do I apply the QRA for mouthwash and toothpaste products for existing Standards?

No. Existing IFRA Standards will not be applied to mouthwash and toothpaste products. As the QRA approach to fragrance ingredient dermal sensitizers is implemented, with the establishment of new or existing IFRA Standards, then maximum use levels of these ingredients in toothpaste and mouthwash products will be introduced when Standards are reviewed and re-defined.

Are any other oral care products included?

No. Other oral care products (tooth whiteners and denture adhesives) were considered, but were specifically excluded from the QRA approach. This is because these products are regulated globally as medical devices and regulations covering such products include specific safety assessment guidelines.

For perspective, 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 safety 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. The safety by oral ingestion of fragrance ingredients that are also flavor ingredients will continue to be managed by the International Organization of Flavor Industries (IOFI, see its Code of Practice). 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/fraqgrnce substances.

Do I have to calculate the NESIL and AELs?

No. NESILs and AELs will be determined by RIFM and approved by the RIFM Expert Panel and will be the basis for the IFRA Standards.

What happens if I have a product that is not in a category?

You should contact the IFRA Secretariat (secretariat@ifraorg.org). When the QRA approach was established, as many products as possible were identified and placed into IFRA categories. However, there will be infrequent instances where a product type will be identified as not included in the IFRA categories. In these cases, that product type will be incorporated into the IFRA categories. IFRA/RIFM has established a QRA subcommittee to address this type of situation. The IFRA Secretariat will request this subcommittee to define the IFRA category in

which the product belongs. You will be informed via an IFRA Information Letter and any additions or changes will appear in updates of the QRA Information booklet.

Why was the QRA developed? What was wrong with the old method?

The QRA approach was defined to address limitations in the historical methodology that related to the qualitative nature of the risk assessments and the definition of only two product categories (skin contact and non-skin contact). This new methodology is a major improvement over current risk assessment practices because it is quantitative in nature and 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 toxicology risk assessment.

What are the implementation times for the new Standards (40th Amendment)?

The use of QRA to set IFRA Standards begins with the 40th Amendment to the IFRA Code of Practice (May 2006). There will be major implications that include time for industry to become familiar with the changes and to update company computer systems. This needs to occur while maintaining the old system for existing IFRA Standards. Given this complexity, a staggered approach has been chosen in which four materials have been selected (citral, farnesol, phenylacetaldehyde and tea leaf absolute) for setting new IFRA Standards and the compliance time has been extended (13 months after the date of the letter of notification for new creations; 25 months after the date of the letter of notification for existing fragrance compounds).

Where can I get help in understanding the QRA approach and making the appropriate procedural changes?

This booklet is the first interface for global fragrance suppliers and users. For more in-depth understanding of the QRA approach it is important to read the Technical Dossier that is published on the RIFM website (QRA Expert Group*, Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp). The QRA Expert Group is currently working a series of publications on this methodology in peer-reviewed scientific journals.

Will the NESILS and AELs ever change requiring reformulation as a result of a revised QRA?

While highly improbable it is not impossible that a fragrance ingredient NESIL once defined would be changed. However, the additional data would need to provide significant additional perspective for such a change to be necessary. It is more likely that the AEL would change on the basis of additional relevant exposure data becoming available. Such changes would be incorporated into future IFRA Amendments and updated versions of this information booklet.

Glossary

AEL – Acceptable Exposure Level
CEL – Consumer Exposure Level
SAF – Sensitization Assessment Factor
NESIL – No Expected Sensitization Induction Level
QRA – Quantitative Risk Assessment
WoE – Weight of Evidence