IFRA RIFM QRA Information Booklet Version 4.1

Revised July 2009

The purpose of this booklet is to provide basic guidance to fragrance suppliers and users on the implementation of the new Quantitative Risk Assessment (QRA) approach for fragrance ingredients. The Information Booklet was first issued on May 12, 2006 to provide assistance in implementing the 40th Amendment to the IFRA Code of Practice.

This booklet is a dynamic document that will change and require periodic updating to reflect the most up-to-date Amendments to the IFRA Code of Practice. As such, it will be important to check the issue date (located at the bottom of each page) of this booklet. The current version of the booklet is the third update (Version 4.1, July 2009) and can be found on both the IFRA and RIFM websites (www.rifm.org/pub/publications.asp and www.ifraorg.org, Science and Regulatory / Risk-Assessment section)

This Booklet (Version 4.1, July 2009) includes important updated information on:

- **how new IFRA Standards will be set**
- **how existing IFRA Standards will be handled**
- **what should be expected in the 44th Amendment (Spring 2009) in terms of number of fragrance ingredients affected and the implementation time**
- **what will be considered for inclusion in future IFRA Amendments to the Code of Practice**
- **definition of the IFRA product categories**
- **Guidance on preparing IFRA Certificates (new part of this booklet)**
    - **Hair dyes have been re-categorized as rinse off products**
- **Changes in product categorization (this booklet does not contain changes)**

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 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 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 toxicology risk assessment. As such, it is a clear improvement over the risk management strategies formerly used by IFRA under which each specific fragrance ingredient identified as an allergen so far was limited to the same concentration across all skin contact product types (Api *et al*., 2008, Dermal sensitization Quantitative Risk Assessment (QRA) for fragrance ingredients. Regulatory Toxicology and Pharmacology,Volume 52, pages 3-23, 2008. The original technical dossier authored by the QRA Expert Group*, Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, Revised June 22, 2006, is also still available on the IFRA and RIFM websites (www.rifm.org/pub/publications.asp and www.ifraorg.org, Science and Regulatory / Risk-Assessment section).

In a brief overview, key steps of the QRA 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 Api *et al*., 2008 as referenced above and also the QRA Expert Group*, Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, Revised June 22, 2006, (www.rifm.org/pub/publications.asp and www.ifraorg.org, Science and Regulatory / Risk-Assessment section)

Based on RIFM's Expert Panel (REXPAN) recommendation, RIFM and IFRA formally adopted beginning with the 40th Amendment to the IFRA Code of Practice in May 2006 the QRA approach, refined for fragrance ingredients identified as dermal sensitizers, as the core strategy for primary prevention of dermal sensitization to these materials in consumer products. This methodology is now being used to determine global fragrance industry product management practices (IFRA Standards) for potentially sensitizing fragrance ingredients on an ongoing basis.

Given the impact of this major change, it is important that global fragrance suppliers and users are fully informed about the changes, the implementation of this new approach and how this will impact them. It mainly affects 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 with specific limitations.

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 began with the 40th Amendment to the IFRA Code of Practice (May 2006). There were major implications that included time for industry to become familiar with the changes and to update company computer systems. This all had to occur while maintaining the old system for existing IFRA Standards. Given this complexity, a staggered approach was chosen in which four materials were selected (citral, farnesol, phenylacetaldehyde and tea leaf absolute) for setting new IFRA Standards and the fragrance industry supplier compliance time was 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). This timing refers to the mixture of fragrance ingredients, the so-called fragrance compound (fragrance mixture or fragrance oil), not the finished consumer product.

42nd Amendment to the IFRA Code of Practice (Spring 2007)

In the 42nd Amendment to the IFRA Code of Practice (Spring 2007), the QRA approach was used to review and re-define all existing Standards set on the basis of dermal sensitization, for which adequate data exist (14 Standards, covering 25 materials which includes isomers of the 14). In addition 14 new IFRA Standards covering 26 materials (including isomers of the 14) are introduced. Some of these new IFRA Standards restrict fragrance ingredients that are present in other sources (e.g. essential oils). As such, some essential oils were impacted and Annex 1 to the IFRA Code of Practice, which provides guidance on the presence of IFRA restricted materials in other sources, was modified accordingly.

The timing for implementation of this Amendment in an existing fragrance mixture (i.e., fragrance compound or fragrance oil) was again extended to 25 months due to the extensive number of Standards that were revised. *Note:* the timing refers to the mixture of fragrance ingredients, the so-called fragrance compound (fragrance oil), and NOT to the finished consumer product.

43rd Amendment to the IFRA Code of Practice (July 2008)

In the 43rd Amendment to the IFRA Code of Practice (Spring 2008), the QRA approach was used to review and re-define existing Standards set on the basis of dermal sensitization, for which additional data were available (10 Standards). In addition 8 new IFRA Standards were introduced. Some of these new IFRA Standards restrict fragrance ingredients that are present in other sources (e.g. essential oils). As such, some essential oils were impacted and Annex 1 to the IFRA Code of Practice, which provides guidance on the presence of IFRA restricted materials in other sources, was modified accordingly.

The timing for implementation of this Amendment in an existing fragrance mixture (i.e., fragrance compound or fragrance oil) was again extended to 25 months due to the extensive number of Standards that were revised. *Note:* the timing refers to the mixture of fragrance ingredients, the so-called fragrance compound (fragrance oil), and NOT to the finished consumer product.

44th Amendment to the IFRA Code of Practice (Spring 2009)

In the 44th Amendment to the IFRA Code of Practice (Spring 2009), the QRA approach will be used to review and re-define existing Standards set on the basis of dermal sensitization, for which additional data are now available (1 Standard). In addition 11 new IFRA Standards will be introduced. Some of these new IFRA Standards restrict fragrance ingredients that are present in other sources (e.g. essential oils). As such, some essential oils will be impacted and

Annex 1 to the IFRA Code of Practice, which provides guidance on the presence of IFRA restricted materials in other sources, will be modified accordingly.

The timing for implementation of these Standards in an existing fragrance mixture (i.e., fragrance compound or fragrance oil) will again be extended to 25 months due to the extensive number of Standards that are being revised. *Note:* the timing refers to the mixture of fragrance ingredients, the so-called fragrance compound (fragrance oil), and NOT to the finished consumer product.

45th Amendment to the IFRA Code of Practice (Spring 2010)

The 45th Amendment to the IFRA Code of Practice (Spring 2010) most probably will contain the revisions of the remaining existing IFRA Standards set on the basis of dermal sensitization, for which additional data are still needed. It may contain new IFRA Standards should the need occur.

Future Amendments to the IFRA Code of Practice (beyond 2010)

Beyond 2009, future Amendments to the IFRA Code of Practice will include new IFRA Standards (where none previously existed) on fragrance ingredients from the RIFM Database and will also include those existing IFRA Standards based on the QRA approach that are scheduled for their 5-year review or for which significant new data are available.

The prioritization for assessment will be based on criteria outlined in the RIFM human health criteria document (Ford *et al*., 2000, Regulatory Toxicology and Pharmacology, *31*, 166-181.) 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 for those materials with IFRA Standards that have not been updated.

Regular timing for Amendments:

Timing 42nd, 43rd and 44th Amendments:

*The timing refers to the mixture of fragrance ingredients, the so-called fragrance compound, not the finished consumer product.

"**New creations**" are defined as any fragrance compound (or fragrance oil) for which the brief has been issued after the publication date of the Amendment. This does not include fragrance compounds that were already in development or in the hands of either fragrance supplier or consumer product manufacturer, before the date of the Amendment (the latter are referred to as "pipeline fragrances" and are treated like 'existing creations').

"**Existing creations**" are those fragrance compounds (or fragrance oils) that have already been placed on the market in a consumer product or are already in the development pipeline.

QRA Implementation Workshop

RIFM and IFRA held a QRA Implementation Workshop for all (member and non-member) supplier and client companies on January 23, 2007 with a follow-up workshop held on Monday June 4, 2007**.** These workshops were designed to provide continued guidance to both the supplier and client industries. The workshops were open to all member and non-members and were conducted in person with concurrent use of webinar. Copies of the presentations made in all the workshops are available on the RIFM website (www.rifm.org).

Another Workshop for members and non-members was held on June 26, 2008 to coincide with the issuance of the 43rd Amendment to the Code of Practice. In the future, updates on the QRA will be conducted routinely through this booklet. Updates will also be available when RIFM holds its Information Exchanges. Webinars will also be held in the future.

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 consumer product exposure, which when combined, lead to similar acceptable use levels of a fragrance ingredient. Using these parameters, Table 2 outlines 11 different IFRA categories for dermal sensitization, which have been specified by the QRA Expert Group* and explained by Api and Vey, 2008 on "Implementation of the dermal sensitization Quantitative Risk Assessment (QRA) for fragrance ingredients" in Regulatory Toxicology and Pharmacology, Volume 52,

pages 53-61. Table 3 outlines the different IFRA categories by product type. 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.

Guidance for completion of IFRA Certificates

With the introduction of the first QRA Standards as part of the 40th Amendment to the IFRA Code of Practice, the preparation of the certificates to declare compliance with the IFRA Code of Practice and Standards that are part of this Code gained some additional complexity. Table 4 gives information to provide guidance intended to help you find your way through combining information about different types of Standards (QRA, systemic toxicity etc) in one certificate. Of great importance is the introduction of classes for reporting IFRA compliance and how they are set up. This table was established with the intention of covering the majority of possible cases of combinations but might not be absolutely comprehensive. This table will be updated with any additions or revisions, and will be included in this booklet.

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 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 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 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.
- In cases, where a product is not currently categorized and/or there are newly available data on consumer product exposure or surface area, then it is incumbent on the fragrance supplier to submit these data prior to October 1 each year. Data should be sent to either Dr. Matthias Vey, IFRA Scientific Director (mvey@ifraorg.org), the IFRA Secretariat (secretariat@ifraorg.org) or Dr. Anne Marie Api, Vice President Human Health Sciences (amapi@rifm.org). RIFM and IFRA have developed a form to providing all the necessary information. The form can be found at IFRA Information Letter 796 and also on the RIFM and IFRA websites (www.rifm.org/pub/publications.asp and www.ifraorg.org, Science and Regulatory / Risk-Assessment section). Supposed the provided information is sufficiently robust, this would lead to a modification of this information booklet and the IFRA membership and stakeholders would be adequately informed about the change(s).

- **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 limit is the one in the finished product.
  - **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.
- **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).
- **Animal sprays:** Animal sprays (or pet sprays), are categorized in IFRA QRA Category 11 (non-skin, incidental skin contact). For this specific type of product (where there is no direct application to humans) it is not necessary to differentiate between aerosol and pump applications.
- **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, 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.
- **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.

- **Hydroalcoholics for Shaved Skin**: Men's aftershaves, colognes and toilet waters are all likely to be applied to recently shaved skin and hence all of these types of products fall under IFRA QRA category 3.

- **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”. 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**: 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 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.

  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.

- **Scent pads and foil packs:** Scent pads and foil packs are two types of fragrance sampling technology that contain the hydroalcoholic product for unshaved skin on a pad or in a foil pack. As such these product types are categorized in IFRA QRA Category 4.

- **Scent Strips:** The concentration of the fragrance compound or fragrance oil that is used for IFRA compliance review of a fragrance to be used in a scent strip product (a sampling technology that potentially gets rubbed on the skin) should be the same concentration that is used for the related fragrance oil or fragrance mixture or compound in the consumer product for which the scent strip is meant to be a sampled. For example, if the consumer product is a hydroalcoholic product for unshaved skin containing 15% fragrance compound or fragrance oil, then the concentration of the fragrance compound or fragrance oil to be used in the scent strip should be 15% for review in IFRA QRA Category 4.
- **Tissues:** Tissues or facial tissues are soft (dry) tissues (IFRA QRA Category 9) that are usually contained in boxes. Wipes or refreshing tissues (IFRA QRA Category 5) are moist towels and are usually contained in (re)sealable plastic packages.

Table 1 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 2 gives the 11 IFRA QRA categories for dermal sensitization based on the QRA approach. It also gives detailed comments for specific product types. Table 3 is an alphabetical list of product types and their corresponding IFRA QRA Category.

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Table 1: SAF and Product Type Consumer Exposure Levels that Drive the IFRA QRA Category.

IFRA QRA Category	SAF	Category Consumer Exposure[1] mg/cm^2/day	Product Type That Drives the Category Consumer Exposure Level	Maximum Pragmatic Level
Category 1	300	11.7	Lip Products	Not Necessary Acceptable Exposure Level derived from QRA
Category 2	300	9.1	Deodorants/Antiperspirants	Not Necessary Acceptable Exposure Level derived from QRA
Category 3	300	2.2	Hydroalcoholics for Shaved Skin	Not Necessary Acceptable Exposure Level derived from QRA
Category 4	100	2.2	Hydroalcoholics for Unshaved Skin	Not Necessary Acceptable Exposure Level derived from QRA
Category 5	100	4.2	Hand Cream	Not Necessary Acceptable Exposure Level derived from QRA
Category 6	100	1.4	Mouthwash	Not Necessary Acceptable Exposure Level derived from QRA
Category 7	300	4.4	Intimate Wipes	Not Necessary 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	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.

[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.

Table 2: IFRA Categories For Dermal Sensitization, QRA Approach, Arranged By Category.

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). 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	Not Necessary Acceptable Exposure Level derived from QRA	
Deodorant and Antiperspirant Products of all types (spray, stick, roll-on, under-arm and body, etc.)		
Category 3	Not Necessary 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, eye masks, eye pillows, etc.)		
Men's Facial Creams, Balms		
Tampons		
Baby Creams, Lotions, Oils		

Product Type	Maximum Pragmatic Level	Comments
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 (except baby creams and lotions)		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 Pads, Foil Packs		
Scent Strips for Hydroalcoholic Products		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		
Hand Cream		
Facial Masks		
Baby Powder and Talc		
Hair Permanent and Other Hair Chemical Treatments (e.g. relaxers) but not hair dyes		Fragrance ingredients in hair permanent and other hair chemical treatments have been placed in Category 5. There are no exposure data on these product types. It is recognized that these product types involve repeated low frequency exposure. In order to define a per diem exposure, a conservative surrogate product has been chosen, which is leave-on conditioners. Should exposure data become available, these product types may be re-categorized.
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.

Product Type	Maximum Pragmatic Level	Comments
Category 6	Not Necessary Acceptable Exposure Level derived from QRA	
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). 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.
Toothpaste		
Category 7	Not Necessary Acceptable Exposure Level derived from QRA	
Intimate Wipes		
Baby Wipes		
Insect Repellent (intended to be applied to the skin)		

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 (except 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.
Hair Dyes		Fragrance ingredients in hair dyes have been placed in Category 8. In the SCCP Notes of Guidance, 2003, the daily exposure to hair dyes was not calculated due to the low frequency of exposure. Since there are no daily exposure data to hair dyes and exposure in this QRA for fragrance ingredient approach is expressed as per diem, a similar product type is identified as a surrogate to define per diem exposure. The product type chosen as this surrogate is leave-on conditioners. However, it is recognized that this is a very simplistic and very conservative approach since the actual exposure to hair dyes is not per diem, but a repeated low frequency exposure. Should exposure data become available, this product type may be re-categorized.
Category 9	**5%**	
Bar Soap (Toilet Soap)	5% The maximum concentration will not exceed 5% and may be lower if determined by the QRA.	
Bath Gels, Foams, Mousses, Salts, Oils and Other Products Added To Bathwater		
Body Washes of all types (including baby washes) and Shower Gels of all types		
Conditioner (Rinse-Off)		
Depilatory		
Face Cleansers of all types (washes, gels, scrubs, etc.)		
Facial Tissues		
Feminine Hygiene – Pads		
Feminine Hygiene – Liners		
Liquid Soap		
Napkins		
Paper Towels		
Shampoos of all types (including baby shampoos)		
Shaving Creams of all types (stick, gels, foams, etc.)		
Toilet Paper		
Other Aerosols (including air fresheners sprays but not including deodorant/antiperspirants, hair styling aids spray)		

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,)		
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		
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	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.	
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 Fragranced lamp ring 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) Reed diffusers Scratch and sniff Scent pack Shoe Polishes Toilet Blocks Treated Textiles (e.g. starch sprays, fabric treated with fragrances after wash, deodorizers for textiles or fabrics, tights with moisturizers)		

Table 3: IFRA Categories for Dermal Sensitization, QRA Approach, Arranged Alphabetically By Product Type.

Product Type	IFRA QRA Category
Aerosols (including air fresheners sprays but not including deodorant/antiperspirants, hair styling aids spray)	Category 9
Air Fresheners and Fragrancing of all types (plug-ins, solid substrate, membrane delivery, electrical, pot pourri, powders, fragrancing sachets, incense, liquid refills)	Category 11
Animal Sprays	Category 11
Baby Lotion, Cream and Oil	Category 3
Baby Powder and Talc	Category 5
Baby Wipes	Category 7
Bar Soap (Toilet Soap)	Category 9
Bath Gels, Foams, Mousses, Salts, Oils and Other Products Added To Bathwater	Category 9
Body Creams, Oils, Lotions, Fragrancing Creams of all types (except baby creams and lotions)	Category 4
Body Washes of all types (including baby washes) and Shower Gels of all types	Category 9
Candles	Category 11
Cat litter	Category 11
Conditioner (Rinse-Off)	Category 9
Cosmetic Kits - Fragrance Compounds	Category 4
Deodorant and Antiperspirant Products of all types (spray, stick, roll-on, under-arm and body, etc.)	Category 2
Deodorizers/Maskers Not Intended For Skin Contact (e.g. fabric drying machine deodorizers, carpet powders)	Category 11
Depilatory	Category 9
Diapers	Category 10
Dry Cleaning Kits	Category 10
Eye Products of all types (eye shadow, mascara, eyeliner, eye make-up, eye masks, eye pillows, etc.)	Category 3
Fabric Softeners of all types including fabric softener sheets	Category 10
Face Cleansers of all types (washes, gels, scrubs, etc.)	Category 9
Facial Masks	Category 5
Feminine Hygiene – Liners	Category 9
Feminine Hygiene – Pads	Category 9
Floor wax	Category 11
Foot Care Products	Category 4
Fuels	Category 11
Facial Tissue	Category 9
Fragranced Lamp Ring	Category 11
Hair Deodorant	Category 4
Hair Dyes	Category 8
Hair Permanent and Other Hair Chemical Treatments (e.g. relaxers)	Category 5
Hair Styling Aids Non-Spray of all types (mousse, gels, leave-in conditioners, etc.)	Category 8
Hair Styling Aids, Hair Sprays of all types (pumps, aerosol sprays, etc.)	Category 4
Hand Cream	Category 5
Hand Dishwashing Detergent	Category 10
Handwash Laundry Detergents of all types	Category 10
Hard Surface Cleaners of all types (bathroom and kitchen cleansers, furniture polish)	Category 10
Household Cleaning Products, Other Types (fabric cleaners, soft surface cleaners, carpet cleaners,)	Category 10
Hydroalcoholic Products Applied To Recently Shaved Skin	Category 3
Hydroalcoholic Products Applied To Unshaved Skin	Category 4
Insect Repellent (intended to be applied to the skin)	Category 7
Insecticides (e.g. mosquito coil, paper, electrical, for clothing)	Category 11

Product Type	IFRA QRA Category
Intimate Wipes	Category 7
Joss Sticks or Incense Sticks	Category 11
Lip Products of all types (solid and liquid lipsticks, balms, clear or colored, etc.)	Category 1
Liquid Soap	Category 9
Machine Dishwash Detergent and Deodorizers	Category 11
Machine Only Laundry Detergent (e.g. liquitabs)	Category 11
Machine Wash Laundry Detergents (liquids, powders, tablets, etc.) including laundry bleaches	Category 10
Make-up Removers of all types (not including face cleansers)	Category 8
Men's Facial Creams, Balms	Category 3
Mouthwash	Category 6
Nail Care	Category 8
Napkins	Category 9
Odored Distilled Water (that can be added to steam irons)	Category 11
Paints	Category 11
Paper Towels	Category 9
Perfume Kit Fragrance Ingredients	Category 4
Powders and talcs, all types (except baby powders and talcs)	Category 8
Plastic articles (excluding toys)	Category 11
Reed Diffusers	Category 11
Scent Pad and Foil Pack	Category 4
Scent Strips for Hydroalcoholic Products	Category 4
Shampoos for Pets	Category 10
Scratch and Sniff	Category 11
Scent Pack	Category 11
Shampoos of all types (including baby shampoos)	Category 9
Shaving Creams of all types (stick, gels, foams, etc.)	Category 9
Shoe Polishes	Category 11
Tampons	Category 3
Toilet Blocks	Category 11
Toilet Paper	Category 9
Toilet Seat Wipes	Category 10
Toothpaste	Category 6
Toys	Category 1
Treated Textiles (e.g. starch sprays, fabric treated with fragrances after wash, deodorizers for textiles or fabrics, tights with moisturizers)	Category 11
Wipes or Refreshing Tissues for Face, Neck, Hands, Body	Category 5
Women's Facial Creams/Facial Make-up	Category 5

Table 4: Guidance for preparing IFRA Certificates.

Product Type (QRA)	Category for skin sensitization up to IFRA 39	Category for systemic toxicity	max use level for methyleugenol	Phototoxicity	Food use approval	Class for IFRA Certificate
Category 1						
Lip Products of all types (solid and liquid lipsticks, balms, clear or colored, etc.)	leave-on	leave-on	4 ppm	Applicable	YES*	**Class 1***
Toys	leave-on	leave-on	4 ppm	Applicable	YES	**Class 1**
Category 2						
Deodorant and Antiperspirant Products of all types (pump spray, aerosol spray, stick, roll-on, under-arm and body, etc.)	leave-on	leave-on	4 ppm	Applicable		**Class 2**
Category 3						
Hydroalcoholic Products applied to recently shaved skin	leave-on	EDT	80 ppm	Applicable		**Class 3.A**
	leave-on	Fine Fragrance	200 ppm	Applicable		**Class 3.B**
Eye Products of all types (eye shadow, mascara, eyeliner, eye make-up, etc.)including eye care	leave-on	leave-on	4 ppm	Applicable		**Class 3.C**
Men's Facial Creams and Balms	leave-on	leave-on	4 ppm	Applicable		**Class 3.C**
Tampons	leave-on	leave-on	4 ppm	Not applicable		**Class 3.D**
Baby Creams, Lotions, Oils	leave-on	leave-on	4 ppm	Applicable		**Class 3.C**
Category 4						
Hydroalcoholic Products applied to unshaved skin	leave-on	EDT	80 ppm	Applicable		**Class 4.A**
	leave-on	Fine Fragrance	200 ppm	Applicable		**Class 4.B**
Hair Styling Aids Sprays of all types (pumps, aerosol sprays, etc.)	leave-on	leave-on	4 ppm	Applicable		**Class 4.C**
Body Creams, Oils, Lotions of all types (except baby creams, lotions, oils)	leave-on	leave-on	4 ppm	Applicable		**Class 4.C**
Fragrancing cream	leave-on	Fragrancing cream	40 ppm	Applicable		**Class 4.D**
Ingredients of Perfume Kits	leave-on	EdT	80 ppm	Applicable		**Class 4.A**
Fragrance Compounds for Cosmetic Kits	leave-on	leave-on	4 ppm	Applicable		**Class 4.C**
Scent Pads, Foil packs	leave-on	EDT	80 ppm	Applicable		**Class 4.A**
Scent Strips for hydroalcoholic products	leave-on	EDT	80 ppm	Applicable		**Class 4.A**
Foot Care Products	leave-on	leave-on	4 ppm	Applicable		**Class 4.C**
Hair deodorant	leave-on	leave-on	4 ppm	Applicable		**Class 4.C**

Product Type (QRA)	Category for skin sensitization up to IFRA 39	Category for systemic toxicity	max use level for methyleugenol	Phototoxicity	Food use approval	Class for IFRA Certificate
Category 5						
Women's Facial Creams/Facial Make-up	leave-on	leave-on	4 ppm	Applicable		**Class 5**
Hand Cream	leave-on	leave-on	4 ppm	Apliccable		**Class 5**
Facial Masks	leave-on	leave-on	4 ppm	Applicable		**Class 5****
Baby Powder and Talc	leave-on	leave-on	4 ppm	Applicable		**Class 5**
Hair permanent and other hair chemical treatments (e.g. relaxers) but not hair dyes	leave-on	leave-on	4 ppm	Applicable		**Class 5**
Wipes or Refreshing Tissues for Face, Neck, Hands, Body	leave-on	leave-on	4 ppm	Applicable		**Class 5**
Category 6						
Mouthwash	rinse off	rinse off	10 ppm	Not applicable	YES*	**Class 6**
Toothpaste	rinse off	rinse off	10 ppm	Not applicable	YES*	**Class 6**
Category 7						
Intimate Wipes	leave-on	leave-on	4 ppm	Not applicable		**Class 7.A**
Baby Wipes	leave-on	leave-on	4 ppm	Not applicable		**Class 7.A**
Insect Repellent (intended to be applied to the skin)	leave-on	leave-on	4 ppm	Applicable		**Class 7.B**
Category 8						
Make-up Removers of all types (not including face cleansers)	leave-on	leave-on	4 ppm	Applicable		**Class 8.A**
Hair Styling Aids Non-Spray of all types (mousse, gels, leave-in conditioners, etc.)	leave-on	leave-on	4 ppm	Applicable		**Class 8.A**
Nail Care	leave-on	leave-on	4 ppm	Applicable		**Class 8.A**
*Powders and talcs (**not** including baby powders and talcs)*	leave-on	leave-on	4 ppm	Applicable		**Class 8.A**
Hair Dyes	rinse-off	rinse-off	10 ppm	Not applicable		**Class 8.B**

Product Type (QRA)	Category for skin sensitization up to IFRA 39	Category for systemic toxicity	max use level for methyleugenol	Phototoxicity	Food use approval	Class for IFRA Certificate
Category 9						
Conditioner (Rinse-Off)	rinse- off	rinse off	10 ppm	Not applicable		**Class 9.A**
Liquid Soap	rinse- off	rinse off	10 ppm	Not applicable		**Class 9.A**
Shampoos of all types (including baby shampoos)	rinse- off	rinse off	10 ppm	Not applicable		**Class 9.A**
Face Cleansers of all types (washes, gels, scrubs, etc.)	rinse- off	rinse off	10 ppm	Not applicable		**Class 9.A**
Shaving Creams of all types (stick, gels, foams, etc.)	rinse- off	rinse off	10 ppm	Not applicable		**Class 9.A**
Depilatory	rinse- off	rinse off	10 ppm	Not applicable		**Class 9.A**
Body Washes of all types (including baby washes) and Shower Gels of all types	rinse- off	rinse off	10 ppm	Not applicable		**Class 9.A**
Bar Soap (Toilet Soap)	rinse- off	rinse off	10 ppm	Not applicable		**Class 9.A**
Feminine hygiene - pads, liners	leave-on	other non cosmetic	10 ppm	Not applicable		**Class 9.B**
Bath Gels, Foams, Mousses, Salts, Oils and Other Products added to bathwater	rinse- off	rinse off	10 ppm	Not applicable		**Class 9.A**
Facial tissues	leave-on	other non cosmetic	10 ppm	Applicable		**Class 9.C**
Napkins	leave-on	other non cosmetic	10 ppm	Applicable		**Class 9.C**
Paper towels	leave-on	other non cosmetic	10 ppm	Applicable		**Class 9.C**
Toilet paper	leave-on	other non-cosmetic	10 ppm	Not applicable		**Class 9.B**
Other' Aerosols (incl. air freshener sprays but not deodorants / antiperspirants, hair styling aids spray and animal sprays)	leave-on	other non-cosmetic	10 ppm	Applicable		**Class 9.C**

Product Type (QRA)	Category for skin sensitization up to IFRA 39	Category for systemic toxicity	max use level for methyleugenol	Phototoxicity	Food use approval	Class for IFRA Certificate
Category 10			-			
Handwash Laundry Detergents of all types	rinse- off	Other non cosmetic	10 ppm	Not applicable		**Class 10.A**
Fabric Softeners of all types including fabric softener sheets	rinse- off	Other non cosmetic	10 ppm	Not applicable		**Class 10.A**
Other Household Cleaning Products (fabric cleaners, soft surface cleaners, carpet cleaners, etc.)	rinse- off	Other non cosmetic	10 ppm	Not applicable		**Class 10.A**
Machine Wash Laundry Detergents (liquids, powders, tablets, etc.) including laundry bleaches	rinse- off	Other non cosmetic	10 ppm	Not applicable		**Class 10.A**
Hand Dishwashing Detergent	rinse- off	Other non cosmetic	10 ppm	Not applicable		**Class 10.A**
Hard Surface Cleaners of all types (bathroom and kitchen cleansers, furniture polish, etc.)	rinse- off	Other non cosmetic	10 ppm	Not applicable		**Class 10.A**
Diapers	leave-on	other leave-on	4 ppm	Not applicable		**Class 10.B**
Shampoo for pets	rinse- off	Other non cosmetic	10 ppm	Not applicable		**Class 10.A**
Dry cleaning kits	rinse- off	Other non cosmetic	10 ppm	Not applicable		**Class 10.A**
Toilet seat wipes	leave-on	other leave-on	4 ppm	Not applicable		**Class 10.B**
Category 11						
All non-skin contact	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**
or incidental skin contact ***Including:***	leave on	other non-cosmetic****	10 ppm****	not applicable		**Class 11.B**
Candles	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**
Air Fresheners and Fragrancing of all types (plug-ins, solid substrate, membrane delivery, ambient, electrical..) excluding aerosol products	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**
Pot pourri, fragrancing sachets, liquid refills for air fresheners (non-cartridge systems), Reed diffusers	leave-on	other non cosmetic	10 ppm	not applicable		**Class 11.B**
Liquid refills for airfresheners (cartridge systems)	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**

Product Type (QRA)	Category for skin sensitization up to IFRA 39	Category for systemic toxicity	max use level for methyleugenol	Phototoxicity	Food use approval	Class for IFRA Certificate
Shoe Polishes	leave-on	other non cosmetic	10 ppm	not applicable		**Class 11.B**
Deodorizers/Maskers not intended for skin contact (e.g. fabric drying machine deodorizers, carpet powders)	leave-on	other non-cosmetic	10 ppm	not applicable		**Class 11.B**
Insecticides (mosquito coil, paper, electrical, for clothing etc.) excluding aerosols	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**
Toilet Blocks	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**
Joss Sticks, Incense	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**
Mashine dishwash detergent and deodorizers	leave-on	other non cosmetic	10 ppm	not applicable		**Class 11.B**
*Machine only Laundry detergent (e.g. liquitabs)****	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**
Plastic articles (excluding toys)	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**
Fuels	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**
Fragranced lamp ring	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**
Scratch and Sniff (sampling technology)	leave-on	other non cosmetic	10 ppm	not applicable		**Class 11.B**
Scent pack	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**

Product Type (QRA)	Category for skin sensitization up to IFRA 39	Category for systemic toxicity	max use level for methyleugenol	Phototoxicity	Food use approval	Class for IFRA Certificate
Paints	non-skin	non-skin	200 ppm / in frag. compound	not applicable		**Class 11.A**
Cat litter	leave-on	other non cosmetic	10 ppm	not applicable		**Class 11.B**
Animal sprays (all types)	leave-on	other non cosmetic	10 ppm	not applicable		**Class 11.B**
Treated Textiles (e.g. starch sprays, fabric treated with fragrances after wash, deodorizers for textiles or fabrics, tights with moisturizers)	leave-on	other non cosmetic	10 ppm	not applicable		**Class 11.B**
Floor wax	non-skin	non-skin	200 ppm / infragrance compound	not applicable		**Class 11.A**
Odored distilled water (that can be added to steam irons)	leave-on	other non cosmetic	10 ppm	not applicable		**Class 11.B**

Comments

* With IL 764 revised it has been recommended that companies apply comparable rules to lipsticks and oral care products as they do to children's toys when it comes to the potential risk of ingestion of minute amounts of the fragrance. This will be included in the Code of Practice with its next revision.

****** Class 5, Facial masks: There are several types of masks: peel off (similar to rinse-off, rinse-off and leave-on (you only remove the excess with a Kleenex®). To ease the split the most restrictive, i.e. leave-on is applied for all.

*** Liquitabs corresponds to a dose of liquids wrapped in a film: no contact with hands is expected under normal conditions of use

****The definition and treatment of non-skin contact products is changing with the introduction of the Standards for skin sensitization based on QRA. The resulting distinction linked to the Methyleugenol Standard currently contained will therefore disappear in the future with the publication of revised versions of existing Standards up to the 39th Amendment

The table was prepared with the intention to cover the vast majority of the products, however it may not cover some specific applications. In this case other classes may be attributed based on a specific risk assessment.

Example: Citral

Citral 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, confirmatory human sensitization data as well as diagnostic patch test studies.

Table 5 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.

Following Table 5 some frequently asked questions (FAQ) about the implementation and designation of IFRA categories are given.

Table 5: 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	9.1	**0.05%**	Not Necessary Acceptable Exposure Level derived from QRA
Category 3	300	2.2	**0.20%**	Not Necessary Acceptable Exposure Level derived from QRA
Category 4	100	2.2	**0.60%**	Not Necessary Acceptable Exposure Level derived from QRA
Category 5	100	4.2	**0.30%**	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	**0.10%**	Not Necessary Acceptable Exposure Level derived from QRA
Category 8	100	1.0	**1.40%**	Not Applicable[3]
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.

[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.

[3] 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).

Frequently Asked Questions (FAQs)

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 level of use for citral in IFRA QRA 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. For a detailed description of exposure levels and SAFs for each product type, please refer to Api *et al*., 2008, Dermal sensitization Quantitative Risk Assessment (QRA) for fragrance ingredients. Regulatory Toxicology and Pharmacology,Volume 52, pages 3-23, 2008 or the Technical Dossier (QRA Expert Group*, Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, Revised June 22, 2006, http://www.rifm.org/pub/publications.asp and also on the IFRA websites (www.ifraorg.org on Science and Regulatory/Risk-Assessment part or)

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 QRA Categories, the calculated acceptable concentrations of fragrance ingredients in the final product may be unrealistically high because the calculated consumer exposure levels 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 is 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.

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 dermal 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.

From the 42nd Amendment to the IFRA Code of Practice (Spring 2007) on, 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 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.

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 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).

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 (REXPAN) and will be the basis for the QRA derived IFRA Standards.

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

In cases, where a product is not currently categorized and/or there are newly available data on consumer product exposure or surface area, then it is incumbent on the fragrance supplier to submit these data prior to October 1 each year. Data should be sent to either Dr. Matthias Vey, IFRA Scientific Director (mvey@ifraorg.org), the IFRA Secretariat (secretariat@ifraorg.org) or Dr. Anne Marie Api, Vice President Human Health Sciences (amapi@rifm.org). RIFM and IFRA have developed a form to providing all the necessary information. The form can be found at IFRA Information Letter 796 and also on the RIFM and IFRA websites (www.ifraorg.org on Science and Regulatory/Risk-Assessment part or www.rifm.org/pub/publications.asp.) Supposed the provided information is sufficiently robust, this would lead to a modification of this information booklet and the IFRA membership and stakeholders would be adequately informed about the change(s).

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 more qualitative nature of the dermal sensitization risk assessments and the definition of only two product categories (skin contact and non-skin contact). This new methodology is a major improvement over former 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. Since exposure is a key element of category determination, this enables maintenance of relevant exposure and therefore safety, while providing greater flexibility to the perfumer because the limit is no longer the same across all skin contact applications. This means that compared to what has been used in the past, in some product applications, a higher fragrance ingredient concentration will be possible, while in others, a lower level may be specified, .

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

The use of QRA to set IFRA Standards began with the 40th Amendment to the IFRA Code of Practice (May 2006). There were major implications that included time for industry to become familiar with the changes and to update company computer systems. This all had to occur while maintaining the old system for existing IFRA Standards. Given this complexity, a staggered approach was chosen in which four materials were selected (citral, farnesol, phenylacetaldehyde and tea leaf absolute) for setting new QRA based IFRA Standards and the fragrance industry supplier compliance time was 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). This timing refers to the mixture of fragrance ingredients, the so-called fragrance compound (or fragrance mixture or fragrance oil), not the finished consumer product.

What are the implementation times for the new Standards in the 42nd Amendment to the IFRA Code of Practice (Spring 2007)?

In the 42nd Amendment to the IFRA Code of Practice (Spring 2007), the QRA approach was used to review and re-define all existing Standards set on the basis of dermal sensitization, for which adequate data exist (14 Standards, covering 25 materials which includes isomers of the 14). In addition 14 new IFRA Standards covering 26 materials (including isomers of the 14) are introduced. Some of these new IFRA Standards restrict fragrance ingredients that are present in other sources (e.g. essential oils). As such, some essential oils were impacted and Annex 1 to the IFRA Code of Practice, which provides guidance on the presence of IFRA restricted materials in other sources, was modified accordingly.

The timing for implementation of this Amendment in an existing fragrance mixture (i.e., fragrance compound or fragrance oil) was again extended to 25 months due to the extensive number of Standards that are being revised. *Note:* the timing refers to the mixture of fragrance ingredients, the so-called fragrance compound (fragrance oil), and NOT to the finished consumer product.

What are the implementation times for the new Standards in the 43rd Amendment to the IFRA Code of Practice (July 2008)?

In the 43rd Amendment to the IFRA Code of Practice (July 2008), the QRA approach was used to review and re-define existing Standards set on the basis of dermal sensitization, for which additional data were available (10 Standards). In addition 8 new IFRA Standards were introduced. Some of these new IFRA Standards restrict fragrance ingredients that are present in other sources (e.g. essential oils). As such, some essential oils were impacted and Annex 1 to the IFRA Code of Practice, which provides guidance on the presence of IFRA restricted materials in other sources, were modified accordingly.

The timing for implementation of this Amendment in an existing fragrance mixture (i.e., fragrance compound or fragrance oil) was again extended to 25 months due to the extensive number of Standards that were revised. *Note:* the timing refers to the mixture of fragrance ingredients, the so-called fragrance compound (fragrance oil), and NOT to the finished consumer product.

What are the implementation times for the new Standards in the 44th Amendment to the IFRA Code of Practice (Spring 2009)?

In the 44th Amendment to the IFRA Code of Practice (Spring 2009), the QRA approach will be used to review and re-define existing Standards set on the basis of dermal sensitization, for which additional data are now available (1 Standard). In addition 11 new IFRA Standards are being introduced. Some of these new IFRA Standards restrict fragrance ingredients that are present in other sources (e.g. essential oils). As such, some essential oils will be impacted and Annex 1 to the IFRA Code of Practice, which provides guidance on the presence of IFRA restricted materials in other sources, will be modified accordingly.

The timing for implementation of this Amendment in an existing fragrance mixture (i.e., fragrance compound or fragrance oil) will again be extended to 25 months due to the extensive number of Standards that are being revised. Note: the timing refers to the mixture of fragrance ingredients, the so-called fragrance compound (fragrance oil), and NOT to the finished consumer product.

Why is “capping” implemented on some Standards?

In some cases, due to the more exact science of the QRA approach, and especially because it is an exposure based risk assessment and specific to various product applications, the QRA

methodology would suggest that a higher use level could be established for certain materials which have an existing IFRA Standard. This is particularly true for rinse-off product types. This would result in raising the maximum use level of materials known to have some capacity for inducing contact allergy for a number of specific product applications.

Raising the limit for fragrance ingredients on the basis of the QRA methodology is not expected to result in new inductions. However, increased exposure due to elevated use levels presents the theoretical possibility that certain pre-sensitized individuals might experience an allergic contact dermatitis where previously they had not. Should this occur, it would be impossible for the dermatologists to distinguish whether such an effect is the result of elicitation of an existing allergy or the result of a new induction. The scientific tools are not available today to allow for this distinction to be made.

Therefore, for materials that already have an IFRA Standard, IFRA and its members have decided, as a precautionary measure to "cap" at the level of the previous IFRA Standard on a temporary basis until the end of a 5 year monitoring phase. At the end of those 5 years, the position will be re-evaluated. This excludes category 11 (non-skin contact products) as well as oral care products, which had no IFRA restriction before the introduction of the QRA. Therefore, for oral care products the limits as determined by the QRA will remain in place even if they are higher than the limits in the original Standards.

The QRA methodology is being used prospectively (creation of new Standards for formerly non-restricted materials) as well as retrospectively (creation of revised Standards for materials that already had a restriction based on sensitization). Its prospective use will continue to result in the establishment of IFRA Standards where none currently exist. Based on our discussions with key dermatologists, this community supports this prospective use of the QRA methodology. For all prospective uses (new IFRA Standards), restrictions will be established by the QRA methodology (for example, Citral, where the QRA Standard was introduced with the 40th Amendment in 2006). There will be no changes to the acceptable exposure levels established by the QRA methodology for all prospective uses of the QRA method.

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 Api *et al*., 2008, Dermal sensitization Quantitative Risk Assessment (QRA) for fragrance ingredients. Regulatory Toxicology and Pharmacology, Volume 52, pages 3-23, 2008. The original technical dossier authored by the QRA Expert Group*, Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, Revised June 22, 2006, is also still available on the IFRA and RIFM websites (http://www.rifm.org/pub/publications.asp and http://www.ifraorg.org/Home/Science+Regulatory/Risk-Assessment/Quantitative-Risk-Assessment-QRA-/page.aspx/114.)

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 could 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
FAQ – Frequently Asked Question
IOFI - International Organization of Flavor Industries
SAF – Sensitization Assessment Factor
NESIL – No Expected Sensitization Induction Level
NOEL – No Effect Level
QRA – Quantitative Risk Assessment
REXPAN – RIFM Expert Panel
WoE – Weight of Evidence