The International Fragrance Association

RIFM®
RESEARCH INSTITUTE FOR FRAGRANCE MATERIALS

GUIDANCE FOR THE USE OF IFRA STANDARDS

June 30, 2023

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December 12, 2019: Notification of the IFRA 49th Amendment.

May 4, 2020: Update of implementation timeline of the IFRA 49th Amendment (consideration of 3 additional months as per the IFRA Board decision of March 30, 2020 – see IL1089).

June 30, 2023: Notification of IFRA 51st Amendment

Preamble

The International Fragrance Association (IFRA, www.ifrafragrance.org), founded in 1973, represents the interests and is the voice of the fragrance industry worldwide. It promotes the safety and benefits of the fragrance industry's products through stakeholder dialogue on a global basis.

Established in 1966, the Research Institute for Fragrance Materials (RIFM, https://rifm.org/) generates, analyzes, evaluates, and distributes data to provide a scientific basis for the safe use of fragrances. All of RIFM's findings are reviewed and approved by the Expert Panel for Fragrance Safety (http://FragranceSafetyPanel.org), an independent panel of academic experts with no ties to the fragrance industry. The Expert Panel for Fragrance Safety makes safety recommendations, including Maximum Acceptable Concentrations (MAC). Once the Expert Panel has approved a safety assessment, RIFM submits it to a reputable scientific journal for a thorough peer-review before publication, if accepted. All of RIFM's published research and safety assessments are made available to the public for free on the Fragrance Material Safety Resource Center (http://FragranceMaterialSafetyResource.elsevier.com).

When warranted by concerns regarding the safe use of a specific ingredient identified by the RIFM safety assessment program, IFRA will issue an IFRA Standard as part of an IFRA Amendment. IFRA Standards can either prohibit, restrict or set purity requirements for specific ingredients. The safety of ingredients, whether the subject of an IFRA Standard or not, remains the responsibility of IFRA members. Observance of the IFRA Standards is therefore necessary for compliance with the IFRA Code of Practice but may not be sufficient to ensure regulatory compliance and the safety of fragrance mixtures or ingredients.

The IFRA Standards and related documents are subject to regular changes as new information relevant to the safety of fragrance ingredients becomes available. All these changes are part of an IFRA Amendment, which is designed according to an inclusive procedure and is subject to a broad consultation of all relevant stakeholders before its Notification. The process for setting the Standards has been documented in detail and was broadly consulted with the membership. A summary of this process is provided in section 2.

Beginning with the 49th Amendment, IFRA Standards reflect the introduction of several improvements to the risk assessment methodology. These improvements specifically relate to the revised methodology of Quantitative Risk Assessment for fragrance ingredients for dermal sensitization (hereafter QRA2) and a new way to assess systemic toxicity based on an aggregate exposure model.

QRA2 is the result of the work undertaken by industry, academia, and other stakeholders under the IDEA (International Dialogue on the Evaluation of Allergens) multi-stakeholder forum to improve the original QRA methodology (hereafter QRA1) used prior to the 49th Amendment (Api et al., 2020). This included the review of the Safety Assessment Factors (SAFs) and the use of the RIFM/Creme model for aggregate exposure. For more details, please consult the QRA2 publications (http://fragrancematerialsafetyresource.elsevier.com/) as well as the DEA website (http://ideaproject.info/).

As a result, the following improvements were included as part of the 49th Amendment:

- The revision of the SAFs and the inclusion of aggregate exposure within QRA2 has led to different categories compared to QRA1. Thus, all the new and existing IFRA Standards for the dermal sensitization endpoint are based on QRA2 and include 12 QRA2 categories.
- The categories for Standards, based on systemic toxicity, have been reviewed according to the aggregate exposure. The IFRA categories for systemic toxicity have been harmonized with the IFRA categories for QRA2. Moreover, the upper concentration limits derived from QRA2 have been checked for the systemic toxicity endpoint. Thus, MAC levels reflected in the Standards are the lowest upper concentration limits between QRA2 and systemic toxicity.

It remains important that fragrance suppliers and users globally are fully informed about the above-mentioned changes, as those continue to be relevant for the 51st Amendment and its implementation. The main impact relates to the identification of acceptable levels of fragrance ingredients in different

product types and their management, on a practical basis, through grouping distinctive product types into product categories with specific limitations.

Compliance timelines for Amendments

The compliance timelines that will be applied to the Standards in the 51st Amendment are detailed in the respective Notification Letter. The timelines for the 51st Amendment are further specified in Table 1 and Figure 1.

The timelines provided in the Standards refer to mixtures of fragrance ingredients (formulas) and not to finished consumer product(s).

The date for compliance with the IFRA Amendments corresponds to the date of placement of fragrance mixtures on the market, meaning for them to leave a fragrance house. From a documentation point of view this should be considered to be the earliest of the following dates: the date of dispatch or the date of invoice.

"**New creations**" are defined as any fragrance mixture for which the brief[1] has been issued after the completion of the information exchange across the supply chain period (i.e., update of IT systems, bilateral information exchange between fragrance houses and information exchange between fragrance houses and customers as a total of 7 months – see also Figure 1).

In practice, this means that briefs received after the Notification can only be verified for compliance with the requirements of the new Amendment once companies are fully operational.

"**Existing creations**" are those fragrance mixtures that have already been placed on the market in consumer product(s) or are already in the development phase at the time the completion of information exchange comes to its end. This includes:

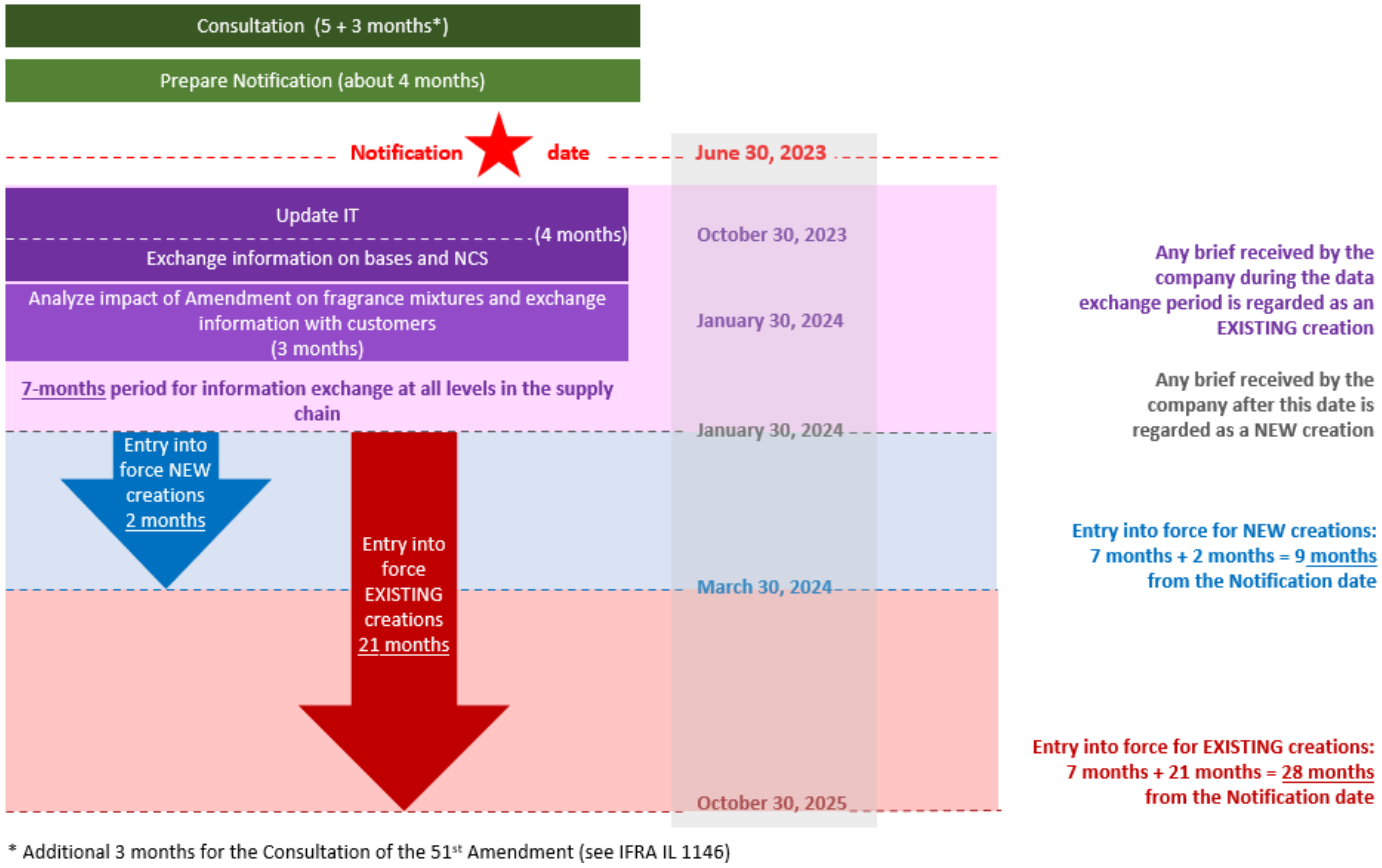
- fragrance mixtures for which a brief has been received prior to the date of the Notification of the Amendment;
- fragrance mixtures for which the brief has been received during the period of information exchange across the supply chain;
- fragrance mixtures that are already in development by the fragrance manufacturer or even in the hands of the consumer product manufacturer.

Table 1: Compliance timeline applicable for the 51st Amendment

IFRA Standards	Date for Standards entering into force for new creations	Date for Standards entering into force for existing creations
Standard prohibiting the use of ingredients	2 months after the date of the letter of Notification	13 months after the date of the letter of Notification
Standards restricting the use of ingredients or setting specifications	9 months after the date of the letter of Notification	28 months after the date of the letter of Notification

[1] 'Brief' refers to the request by a client – typically a consumer goods or a finished product manufacturer – for a fragrance mixture. The brief tells the fragrance house what the manufacturer would like to see from the fragrance mixture, the product concept, and other useful information that allows a perfumer to create a suitable fragrance mixture.

Figure 1: Representation of the timeline applicable for the restriction/specification Standards in the scope of 51st Amendment. A 7-months period is granted after the date of the Notification to ensure adequate information exchange across the supply chain.



* Additional 3 months for the Consultation of the 51st Amendment (see IFRA IL 1146)

1. Introduction to the IFRA Standards

The IFRA Standards form the basis for the globally accepted and recognized risk management system for the safe use of fragrance ingredients and are part of the IFRA Code of Practice. This is the self-regulating system of the industry, based on risk assessments carried out by the Expert Panel for Fragrance Safety. The Expert Panel for Fragrance Safety is an independent panel of experts that reviews the activities of RIFM. In addition, they determine the safety of use for fragrance ingredients through consideration of available information and active generation of additional data. If the Expert Panel for Fragrance Safety determines that a restriction of use is necessary for consumer and environmental protection, then an IFRA Standard will be published.

1.1 Definitions

Fragrance or Fragrance mixture: A mixture of fragrance ingredients and functional components formulated to impart an odor/flavor* or for its malodor coverage/taste* masking purposes.

**In the case of oral care and related products, please see respective explanations and requirements in Section 1.6.2 of this Guidance*

Existing creations: Fragrance mixtures that have already been placed on the market in consumer product(s) or are already in the development phase at the time the completion of information exchange comes to its end. This includes:

- fragrance mixtures for which a brief has been received prior to the date of the Notification of the Amendment;
- fragrance mixtures for which the brief has been received during the period of information exchange across the supply chain; and
- fragrance mixtures that are already in development by the fragrance manufacturer or even in the hands of the consumer product manufacturer.

Fragrance ingredient: Any basic substance (raw material) used for its odor properties or malodor coverage as a component of a fragrance mixture.

Fragrance functional component: Any basic substance necessary for the functionality and/or, stability of a fragrance ingredient or mixture (e.g., antioxidant, preservative, diluent, solvent, etc.).

Fragrance manufacturer: A company engaged in the production of a fragrance including processing, mixing, packaging and labelling.

Fragrance ingredient manufacturer: A company engaged in the production of any basic substance used as a fragrance ingredient for its odor properties or malodor coverage.

New creation: Any fragrance mixture for which the brief has been issued after the completion of the information exchange across the supply chain period (i.e., update of IT systems, bilateral information exchange between fragrance houses and information exchange between fragrance houses and customers).

Quality: Conformity of a fragrance ingredient with its olfactory, physical and chemical specifications and conformity of its production and control with the basic standards of Good Manufacturing Practice.

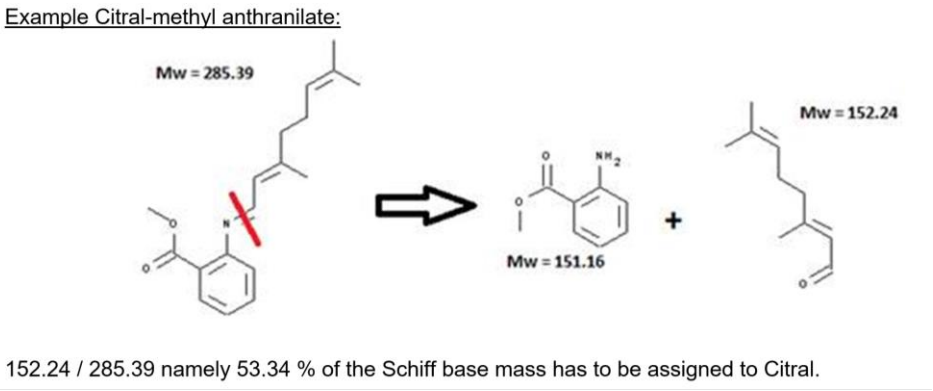
Toy: Toys under the scope of IFRA Standards follow the definition as contained in the EU Toy Directive (2009/48/EC) and the American National Standard ASTM F963, in its latest version.

Schiff Bases: Condensation products from aldehyde and (primary) amines, resulting in a (true) “Imine” with a C=N double bound. Due to the concern that this could affect some of the restricted ingredients by IFRA Standards present in fragrance mixtures/finished products and based on the available information e.g., on physicochemical properties information, these materials are considered under contributions from other sources in a precautionary approach. By default, the stoichiometric presence of the aldehydes of the Schiff bases is taken into account assuming 100% dissociation. An indicative list of Schiff bases incorporating aldehydes covered by an IFRA Standard of restriction is reported in the Annex on contributions from other sources to the IFRA Standards.

These Schiff bases must be considered for determination of the upper concentration limit of the respective aldehydes.

An example calculation for the Schiff bases used in the fragrance industry is listed therein (Figure 2) and in the Annex on contributions from other sources.

Figure 2: Example of calculation for the Schiff bases used in the fragrance industry as reported in the Annex on contributions from other sources to the IFRA Standards: Citral-methyl anthranilate.



Contributions of restricted aldehydes from all other Schiff bases should be calculated in the same way, as detailed in Figure 2. Please note that the hydrolysis rate of 100% might be replaced by a lower value if robust data on the specific Schiff base in the specific end product exist.

1.2 Scope of IFRA Standards

All fragranced consumer products are in the scope of the IFRA Standards with the exception of products not covered in the RIFM Safety Assessments, such as:

- medical devices,
- prescriptive drugs,
- aromatherapy applications,
- consumer products used in occupational settings (e.g., shampoos applied in hair salons, hand sanitizers applied in hospitals, etc.),
- sprays and scented stickers for facial masks,
- dental floss

Certain types of Over the Counter (OTC) products are also out of the scope of the IFRA Standards unless those products are regarded as cosmetic products under certain cosmetic product regulations worldwide. An example would be sun protection products, which are e.g., regarded as OTC in the United States or Australia but are considered as cosmetic products e.g., in Europe and are therefore in scope.

A detailed list of the products covered by the IFRA Standards is shown in Table 11. In case a final product application is not included therein, it remains under the responsibility of the final consumer product manufacturing company to adequately categorize this final product application in order to comply with the IFRA Standards requirements.

1.3 Types of IFRA Standards

The IFRA Standards can trigger:

- A restriction by a quantitative limit on the use of fragrance ingredients.

IFRA Standards that impose a quantitative limit on the use of fragrance ingredients are expressed as a Maximum Acceptable Concentration (MAC) of fragrance ingredients in the finished consumer

product, not in the fragrance mixture. This is based on the combined knowledge of the concentration of restricted fragrance ingredients in the mixture and the concentration of the mixture in the final consumer product. Fragrance suppliers are therefore required to inform manufacturers of consumer products, who use or intend to use a fragrance mixture, that due to the presence of a restricted ingredient, the mixture should only be used up to a specified maximum concentration. This can either be a maximum for several applications (driven by the most restrictive one) or in the form of an individual listing of maximum concentrations for well-defined applications, thereby complying with IFRA Standards.

Alternatively, a Certificate of Conformity of fragrance mixtures with IFRA Standards can be prepared with a reference to the actual end use and use level when known by the fragrance house. Unless otherwise specified, concentrations are expressed in weight-per-weight percent.

- A prohibition of the use of the fragrance ingredients in any final product application.

An IFRA Standard may ban the use of a substance when it is intended to be used as such in a fragrance mixture. The ban applies to all final product applications, including non-skin contact applications.

- A specification on the use of a fragrance ingredient, such as purity requirements.

Certain fragrance ingredients are considered safe for their use in final product application but only if they meet a defined maximum level of impurities (e.g., traces of solvents) or reaction products or defined procedures for extraction and/or production.

1.4 Contributions from other sources

The potential 'other sources' are depicted in the Annex on contributions from other sources to the IFRA Standards. This is a non-exhaustive, indicative list of 'other sources' of fragrance ingredients restricted or prohibited by IFRA Standards. It combines information from natural contributions (former Annex I) as well as Schiff bases (former Annex II) (see section 1.1 for definition) in two separate lists.

Restricted Substances

IFRA Standards establishing use restrictions for specific fragrance ingredients in final consumer products shall apply regardless of whether the restricted substance is added directly or indirectly to the fragrance mixture. Indirect contributions from other sources, e.g., the presence in Natural Complex Substances (NCS), must be considered in the calculations of the levels of the restricted substance.

Regarding natural contributions, the Annex on contributions from other sources is a non-exhaustive indicative list of the typical natural presence of fragrance ingredients restricted by IFRA Standards.

This list is prepared with significant input from the IFRA Natural Complex Substances Task Force (NCS TF) and is intended to be used in the absence of the company's own or reliable supplier analytical data. If the analysis has shown that the level of the restricted ingredient in a NCS used by a company is different from what is indicated in this Annex on contributions from other sources, then the analytically determined level should be used instead of the indicative level.

Further, it should be noted that there are NCS that are not listed in this Annex, even though they might have known presence of an IFRA restricted ingredient as a constituent. These are the NCS for which the NCS TF cannot establish a typical composition (concentration profile) according to an established procedure currently followed and which are therefore considered out of the scope of the NCS TF activity.

The reason that no typical composition can be established is because of the variability in composition, either resulting from different starting materials (oil made of different types of citrus fruits for example) or because the NCS are derived from individual, non-standardized 'in house' processes that may vary from producer to producer or even a combination of both factors. For these NCS considered out of the scope of the NCS TF activity, users should rely on information from their supplier or own analytical data.

The indicative levels of restricted substances depicted in the Annex on contributions from other sources should be considered when determining the compliance of a fragrance mixture under its conditions of use as outlined above.

Fragrance manufacturers are invited to:

(a) Use, for calculation purposes, additional information they may have on levels of the restricted substances in any other essential oil, extract, etc. used as fragrance ingredients, but not already mentioned in the Annex on contributions from other sources to the IFRA Standards;

(b) Provide to IFRA (info@ifrafragrance.org) information on those substances and levels.

Prohibited Substances

An IFRA Standard may prohibit the use of a material when it is intended to be used as such in a fragrance mixture. However, this does not necessarily exclude the use of a NCS which contains the prohibited material as a constituent or impurity, or the use of a synthetic (chemically defined material) which contains the prohibited material as an impurity (i.e., added indirectly). This is subject to the condition that in the judgment of the Expert Panel for Fragrance Safety, there is sufficient data supporting the safe use of the fragrance ingredient and that it is not being used to provide an alternative, indirect source of the prohibited material.

It is important to recognize that, due to scientific advancements and the evolution of analytical methods, previously undetectable levels of unwanted impurities in raw materials may now be detectable. Even with state-of-the-art sourcing and best manufacturing practices, these unwanted prohibited substances may appear at trace levels in finished consumer products. The concept of acceptable traces of prohibited substances is addressed in several regulatory frameworks e.g., the section on impurities within the Guidance Document for the preparation of Safety Assessments under the Cosmetics Regulation (see EUR-Lex - 32013D0674 - EN - EUR-Lex (europa.eu)) require that the presence of traces of prohibited substances should be kept as low as reasonably achievable (ALARA) under good manufacturing practices.

However, even though the concept of “traces of technically unavoidable substances in finished product” is mentioned in several regulations across the globe as a parameter that must be addressed in the safety assessment, this concept does not benefit from any internationally recognized common interpretation and therefore remains the responsibility of the producer of raw materials and mixtures in co-operation with the finished product manufacturer.

One source of prohibited substances may be small amounts of organic solvents that could be carried over into a synthetic fragrance ingredient or an NCS during the manufacturing process. There are specific steps within a manufacturing process designed to remove minor amounts of solvents, but these steps may not always be completely successful and therefore result in extremely low, technically unavoidable traces of substances in the finished product.

In general, fragrance ingredients that are synthetic materials or NCS (in any form) should be analyzed to identify components or impurities (especially those that are prohibited) at levels that allow a meaningful safety assessment.

Every IFRA member becoming aware of the presence of IFRA prohibited materials in fragrance ingredients, not already addressed by the respective IFRA Standard (or Annex on contributions from other sources to the Standards), shall inform IFRA so that an adequate assessment by the Expert Panel for Fragrance Safety can be carried out.

If the Expert Panel for Fragrance Safety finds that the presence of a prohibited substance in other fragrance ingredients (either a synthetic chemical or NCS) cannot be supported based on a risk assessment, the chemical or NCS will itself be prohibited from use.

However, there may be situations in which an IFRA Standard could be established by setting a limit level for a prohibited substance as an impurity in a synthetic material or as a component in an NCS based on an assessment by RIFM and validated by the Expert Panel for Fragrance Safety.

If a safe limit level for a prohibited material is not established by RIFM and the Expert Panel for Fragrance Safety, as expressed in an IFRA Standard, it remains the responsibility of the fragrance house in co-ordination with the consumer product manufacturer, to ensure that the material is not present as an impurity at a level posing a safety concern for the use of the consumer product. Such an assessment should be based on generally accepted principles of toxicology and risk assessment and can, as one element, refer to assessments of the material in question made by a recognized authoritative body.

1.5 IFRA Standards for environmental protection

IFRA establishes IFRA Environmental Standards of fragrance ingredients based on the following principles:

- Evaluation for aquatic risk following the RIFM Framework (Salvito, Senna, and Federle; 2002)
- Ingredient identification with properties for Persistence, Bioaccumulation and (eco)Toxicity (PBT or vPvB).

The criteria and approaches described within the RIFM Framework are used to assess that all relevant consumer uses of fragrance ingredients associated with perfumery are safe for the environment. Following this RIFM Framework and using the periodic IFRA Volume of Use (VoU) survey to estimate exposure, the industry may need to implement risk management measures by issuing an IFRA Standard.

For PBT and vPvB identification, the screening assessment is based on current criteria defined in the EU REACH legislation (Annex XIII). Materials identified by IFRA as PBT or vPvB shall be banned and an IFRA Standard issued.

1.6 Important information for the application of IFRA Restriction Standards

1.6.1 Phototoxic ingredients

The IFRA Standards on phototoxic ingredients have been set based on:

- The phototoxicity potential of the fragrance ingredient itself (Table 2). Additional details are provided in Section 1.6.1.1.
- The phototoxicity potential of furocoumarins present in certain essential oils (Table 3). No changes are introduced with the 51st Amendment on the IFRA policy on furocoumarins. Additional details on this policy are provided in Section 1.6.1.2.

Table 2: List of IFRA Standards on phototoxic ingredients based on the phototoxicity potential of the fragrance ingredient itself.

CAS number	IFRA Standard
15323-35-0	5-Acetyl-1,1,2,3,3,6-Hexamethyl indan (AHMI)
85-91-6	Methyl-N-methyl anthranilate
93-08-3	Methyl β-naphthyl ketone
91772-29-1 8016-84-0 91770-75-1 90131-43-4	Tagetes oil and absolute
41270-80-8	Methyl 2-(formylamino)benzoate

Table 3: List of IFRA Standards on phototoxic ingredients based on the phototoxicity potential of furocoumarins present in certain NCS.

CAS number	IFRA Standard
8015-64-3	Angelica root oil
908007-75-8	Bergamot oil expressed
68916-04-1 72968-50-4	Bitter orange peel oil expressed
Not available	Citrus oils and other furocoumarins containing essential oils
8014-13-9	Cumin oil
8016-20-4	Grapefruit oil expressed
8008-56-8	Lemon oil cold expressed
8008-26-2	Lime oil expressed
8014-29-7	Rue oil

1.6.1.1 Progressive implementation of the revised policy on phototoxicity

The scope of application of restrictions based on phototoxic effects includes any product that is applied to body areas reasonably expected to be exposed to sunlight. For non-skin contact consumer products (i.e., Category 12), phototoxicity considerations do not apply and therefore IFRA Standards do not set a restriction on them.

Following up on changes introduced for Tagetes oil and absolute in the IFRA 49th Amendment, the new policy as described below is progressively implemented to materials having an IFRA Standard due to phototoxicity as they are reviewed by RIFM.

For the 51st Amendment the policy is now applied to Methyl-N-methyl anthranilate:

- Introducing a restriction level to rinse-off products in the Standard of Methyl-N Methyl anthranilate.
- Subcategorization of Category 7 in A and B to consider the presence of rinse-off and leave-on products included in this category.
- Consideration of potential phototoxicity for all product types included in Category 8 (even if there is no expected exposure to sunlight).
- Subcategorization of Category 11 in A and B to consider the presence of rinse-off and leave-on products included in this category.

This is explained in more detail in the following sections.

a) Introducing a restriction level to rinse-off products

Traditionally, phototoxicity considerations for rinse-off products were not applied and this was reflected by an absence of restriction in the respective IFRA Standards. With the 49th Amendment, a restriction limit for rinse-off products has been introduced for the first time in the Standard of Tagetes oil and absolute, and now with the 51st Amendment is also applied for Methyl-N-methyl anthranilate.

This leads to a significant change in the rationale to attribute phototoxicity considerations to finished consumer products. In order to take into account, the fact that some Standards include a restriction limit for rinse-off products, the rationale included in Table 11 has been adapted as shown in Table 4.

Table 4: Change of the rationale applied for phototoxicity considerations introduced with the 49th Amendment and comparison with the rationale used in previous IFRA Amendments.

	Rationale in previous Amendments	Rationale introduced with the 49th Amendment
Leave-on products	Applicable	Applicable
Rinse-off products	Not applicable	Applicable
Leave-on products without UV exposure	Not applicable	Not applicable
Non-skin contact products	Not applicable	Not applicable

As part of the Consultation of the 51st Amendment clarification was asked about the rationale for the approach of having phototoxicity leave-on considerations applicable for Category 6. Indeed, this approach was very conservative in nature, since the lip exposure is “incidental”, the primary area of application being the oral cavity not that much exposed to sunlight. IFRA therefore consulted the Expert Panel for Fragrance Safety for advice. The Panel feels that for the average person toothpaste and mouth wash is a rinse-off but there are other types like breath spray, where it might have some leave-on aspects. Whether more potential remedies from the application on lips and adjacent skin area justifies leave-on phototoxicity considerations is doubtful and from a clinical perspective there is no indication of patients with phototoxicity effects due to e.g. use of mouthwash. The Expert Panel for Fragrance Safety therefore concluded that the products in Category 6 can be considered rinse-off with regard to phototoxicity. Consequently, the rationale for phototoxicity considerations in IFRA standards has been updated accordingly as basis for future IFRA Standards (new or revised).

b) Subcategorization of Category 7 in A and B to consider the presence of rinse-off and leave-on products included in this category.

Category 7 contains leave-on and rinse-off products for which phototoxicity considerations are applicable.

In line with the goal to harmonize the IFRA Categories with the former IFRA Classes used in the Certificates, Category 7 is therefore divided into Categories 7A (rinse-off products) and 7B (leave-on products).

c) Consideration of potential phototoxicity for all product types included in Category 8 (even if there is no expected exposure to sunlight).

Potential phototoxic effects are taken into consideration for Category 8 (Products with significant anogenital exposure), for reasons of conservativism to consider some uses of the products that could include UV exposure (e.g., baby wipes).

d) Subcategorization of Category 11 in A and B to consider the presence of rinse-off and leave-on products included in this category.

Category 11 contains leave-on products for which phototoxicity considerations are either applicable or not, depending on the likeliness of UV exposure.

In line with the goal to harmonize the IFRA Categories with the former IFRA Classes used in the Certificates, Category 11 is now divided into Categories 11A (Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate without UV exposure) and 11B (Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate with potential UV exposure).

Moreover, Category 11A contains products that are applicable to the skin but without UV exposure. Consequently, the applicability of phototoxicity considerations becomes irrelevant for the products of Category 11A. This is translated in IFRA Standards by an absence of restriction for the products included in this subcategory.

A summary of the restrictions applicable to Standards based on phototoxicity considerations is presented in Table 5.

Table 5: Outline of the revised rationale on phototoxicity considerations introduced with the 49th Amendment and its application to the Standard of Methyl N-methyl anthranilate comparing the former Standard with the revised version introduced with the 51st Amendment.

Category	Product type	Phototoxicity considerations	Restriction for Methyl N-methyl anthranilate (old)	Restriction for Methyl N-methyl anthranilate (51st Amendment)[1]
1	Products applied to the lips	Applicable (leave-on)	0.10%	0.10%
2	Products applied to the axillae	Applicable (leave-on)	0.10%	0.10%
3	Products applied to the face/body using fingertips	Applicable (leave-on)	0.10%	0.10%
4	Products related to fine fragrance	Applicable (leave-on)	0.10%	0.10%
5	Products applied to the face and body using the hands (palms), primarily leave-on:			
5A	Body lotion products applied to the body using the hands (palms), primarily leave on	Applicable (leave-on)	0.10%	0.10%
5B	Face moisturizer products applied to the face using the hands (palms), primarily leave on	Applicable (leave-on)	0.10%	0.10%
5C	Hand cream products applied to the hands using the hands (palms), primarily leave on	Applicable (leave-on)	0.10%	0.10%
5D	Baby creams, baby oils and baby talc	Applicable (leave-on)	0.10%	0.10%
6	Products with oral and lip exposure	Applicable (rinse-off)	0.10%[2]	0.50%
7	Products applied to the hair with some hand contact			
7A	Rinse-off products applied to the hair with some hand contact	Applicable (rinse-off)	No restriction	0.50%
7B	Leave-on products applied to the hair with some hand contact	Applicable (leave-on)	0.10%	0.10%

Category	Product type	Phototoxicity considerations	Restriction for Methyl N-methyl anthranilate (old)	Restriction for Methyl N-methyl anthranilate (51st Amendment)[1]
8	Products with significant anogenital exposure	Applicable (leave-on)[3]	0.10%	0.10%
9	Products with body and hand exposure, primarily rinse off	Applicable (rinse-off)	No restriction	0.50%
10	Household care products with mostly hand contact:			
10A	Household care products with mostly hand contact	Applicable (rinse-off)[4]	No restriction	0.50%
10B	Household care products with mostly hand contact, including aerosol/spray products (with potential leave-on skin contact)	Applicable (leave-on)	0.10%	0.10%
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate			
11A	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate without UV exposure	Not applicable (leave-on without UV exposure)[5]	No Restriction	No Restriction
11B	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate with potential UV exposure	Applicable (leave-on)	0.10%	0.10%
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not applicable (non-skin contact)	No Restriction	No Restriction

[1] The MAC level allowed by the revised IFRA Standard for Methyl N-methyl anthranilate is 0.10% in leave-on products and 0.50% in rinse-off products.

[2] In the 49th Amendment Category 6 was considered leave-on, therefore the respective MAC is found here.

[3] Potential phototoxic effects are taken into consideration for Category 8 (Products with significant anogenital exposure), for reasons of conservativism to consider some uses of the products that could include UV exposure (e.g., baby wipes).

[4] Category 10A includes rinse-off products and products with limited skin contact. All the products included in Category 10A are treated as rinse-off products for phototoxicity considerations.

[5] Category 11A contains products which are applicable to the skin but without UV exposure. Therefore, the applicability of phototoxicity considerations becomes irrelevant for the products of Category 11A.

1.6.1.2 IFRA policy on Furocoumarins

The IFRA policy on Furocoumarins remains unchanged until ongoing work has been completed. An update of the policy is foreseen for the 52nd Amendment.

Combination effects of phototoxic ingredients are only taken into consideration for furocoumarin containing fragrance ingredients (NCS).

If combinations of furocoumarin-containing phototoxic fragrance ingredients (NCS) are used, the use levels must be reduced accordingly. The sum of the concentrations of all furocoumarin-containing phototoxic fragrance ingredients (NCS), expressed in % of their recommended upper concentration limit in the consumer product shall not exceed 100.

If the level of furocoumarins is unknown, the restriction level specified in the respective IFRA Standards for the specific NCS as listed in the Standard of Citrus oils and other furocoumarins containing NCS applies (see the list of NCS in Table 3).

1.6.2 Oral Care Products and other products with the potential of ingestion

1.6.2.1 Products with the potential of ingestion in the scope of the IFRA Standards

In general, IFRA Standards are applicable for fragrance mixtures used in non-food products.

Depending on the regulatory framework, ingredients used in oral care and similar products could either be regarded as fragrance or flavor applications. For the purpose of the IFRA Code of Practice, when referring to single ingredients and mixtures we talk about fragrance ingredients and fragrance mixtures (perfume) respectively, even if the ingredients and mixtures, in the end, are fulfilling flavor requirements and are in fact produced as flavor mixtures and could thus be legitimately termed “flavor”. Therefore, all oral care products that carry a fragrance, like any other fragranced product, must follow the IFRA Standards and general guidelines as contained in the IFRA Code of Practice.

Mouthwash and toothpaste are the principal oral care products currently identified in the respective category. Other oral care products like toothpowder, strips, and mouthwash tablets are also in scope. The introduction of aggregate exposure with the 49th Amendment implies that simultaneous usage of e.g., a toothpaste and a mouthwash (two products from the same category) is assessed, but not the concomitant use as a flavor ingredient in food.

Exposure limits for oral care products resulting from the QRA process are established to reduce the risk of peri-oral skin sensitization.

Besides oral care products there are certain other products containing fragrance ingredients that are not intended for ingestion, but have the possibility of ingestion of minute amounts of the fragrance ingredients, like lip products of all types (solid and liquid lipsticks, balms, etc.), or specific types of toys. Due to the possibility of ingestion of small amounts of fragrance ingredients from the use of the aforementioned allowable product categories (such as oral care, lip products or certain types of toys), materials present in the fragrance mixture must comply not only with IFRA Standards, but must also have an approved flavor material status as defined by the IOFI Code of Practice (http://www.iofi.org/). Such materials are those that meet one or more of the following requirements:

- Accepted by the authoritative body the Joint FAO/WHO Expert Committee on Food Additives (JECFA) as acceptable flavoring materials that “pose no safety concerns at current levels of intake”;
- Have been evaluated and found, using the same or similar methodology as used by JECFA, to present “no safety concern under conditions of intended use” by authoritative bodies such as the European Food Safety Authority (EFSA) or the Japanese Food Safety Authority (FSC);
- Deemed to be Generally Recognized As Safe (GRAS) or approved food additives by the US Food and Drug Administration (FDA) including GRAS determinations published by the independent Expert Panel of the Flavor and Extract Manufacturers Association of the United States (FEMA);
- Are compliant with appropriate national/regional regulations covering the use of flavorings ‘for local use’ and respective product uses as outlined above.

Materials without an approved flavor status according to the criteria above are not permitted in products where incidental oral ingestion may occur.

The above-mentioned products (e.g., oral care or lipsticks), which are under the scope of the IFRA Standards, are not designed and therefore not intended to be ingested, even so, accidental ingestion can occur.

1.6.2.2 Multiple uses products including exposure to lips

Some additional clarification appears necessary related to product types that can have some use on the lips, for which the exposure scenario concerning their potential for ingestion is significantly different from the one for products targeted in Category 1. In the latter group their exposure scenario leads to the additional requirements for the flavor status of the materials used.

IFRA together with RIFM concluded that Category 1 is for those products typically applied to the lips several times a day and to remain there for a longer time period (leave-on, like lipstick) as a designed function of the products, which therefore have a potential for ingestion. There are other products for which the exposure of fragrance ingredients to the lips is minimal due to the products being wiped or rinsed off. For such cases where there may be minimal exposure to the lips, we consider the potential for ingestion to be negligible.

If a product is designed and clearly marketed for lips as well as for other application(s), then the product must follow the requirements of Category 1 regarding its potential for ingestion. This is only the case where, in addition, the resulting exposure conditions are similar to the products targeted in Category 1. Therefore, for example, a makeup remover also suitable for lips is still considered similar to a make-up remover marketed for ‘face’, which includes the lip area anyhow. Those products are not considered to have exposure conditions e.g., comparable to lipsticks and therefore do not automatically fall under the requirements as described in section 1.6.2 of the Guidance. However, products designed and clearly marketed for leave-on use on lips as well as for other application(s), such as Lip & Cheek Blush or Tints, should follow the requirements of Category 1.

1.6.2.3 Products with the potential of ingestion outside the scope of the IFRA Standards

The safety of (fragrance) ingredients or mixtures present in products intended for ingestion (like ‘ingestible perfumes or deodorants, fragrances for odorizing potable water, cleaning products intended for food contact’) is outside the scope of RIFM’s and IFRA’s current risk assessment and management process.

It is the responsibility of the companies to assess the safe use of these products based on the specific use conditions and the legal requirements applicable in the respective country/region. Therefore, this safety assessment is key for decision and is prevailing above any other type of consideration like material status (e.g., approved flavor material food grade status). In conclusion, IFRA cannot incorporate them in the IFRA products categorization.

1.6.3 Use of fragrance ingredients in toys (or other children’s products)

Toys under the scope of IFRA Standards follow the definition as contained in the EU Toy Directive (2009/48/EC)[2] and the American National Standard ASTM F963[3] in its latest version.

1.6.3.1 Prohibition of use of fragrance ingredients in toys or other children’s products where there is the likelihood of mouth contact (independently of whether exposure data is available or not)

[2] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32009L0048
[3] https://www.astm.org/toys.html

IFRA prohibits the use of fragrance ingredients and mixtures in toys or other children's products where there is a likelihood of mouth contact. Following the criteria established by the toy industry, these include:

1) toys for children less than 3 years of age;
2) any toy designed and intended to go into the mouth; and/or
3) those toys for which mouth contact is reasonably foreseeable.

1.6.3.2 Restriction of use of fragrance ingredients in toys or other children's products where there is no likelihood of mouth contact and for which there is no exposure data available

IFRA restricts the use of fragrance ingredients and mixtures in toys or other children's products where there is no likelihood of mouth contact. Following the criteria established by the toy industry, these include:

1) toys for children older than 3 years of age;
2) any toy not designed and not intended to go into the mouth; and/or
3) those toys for which mouth contact is not reasonably foreseeable.

Although there is an absence of exposure data, these toys have been placed in Category 1 (leave-on products generally applied to the lips) due to the potential of ingestion of minute amounts of fragrance ingredients. Should exposure data become available, these product types may be re-categorized.

1.6.3.3 Toys for which there is no foreseeable exposure

Considering feedback received during the Consultation of the 49th Amendment, the product type of "Olfactive Board Games" has been assessed by the QRA Expert Group. Due to non-foreseeable exposure, Olfactive Board Games have been categorized in Category 12.

2. IFRA Standards setting process

The IFRA Standards are the basis of the globally recognized risk management system for the safe use of fragrance ingredients as outlined in the IFRA Code of Practice. This document summarizes the process followed for setting and reviewing the IFRA Standards. A more detailed and specific description of the process is available from IFRA (info@ifrafragrance.org).

2.1 IFRA Commitment to safety

The **International Fragrance Association (IFRA)** and its members are committed to providing fragrances that are safe to use in consumer products.

The **IFRA Code of Practice** requires that member companies are responsible to ensure safety and regulatory compliance for the use of fragrance ingredients and mixtures. This includes the requirement to follow the IFRA Standards.

The **IFRA Standards** are set to protect consumers and the environment from potential adverse effects when fragrances are present in consumer products.

2.2 Key principles of the IFRA Standards

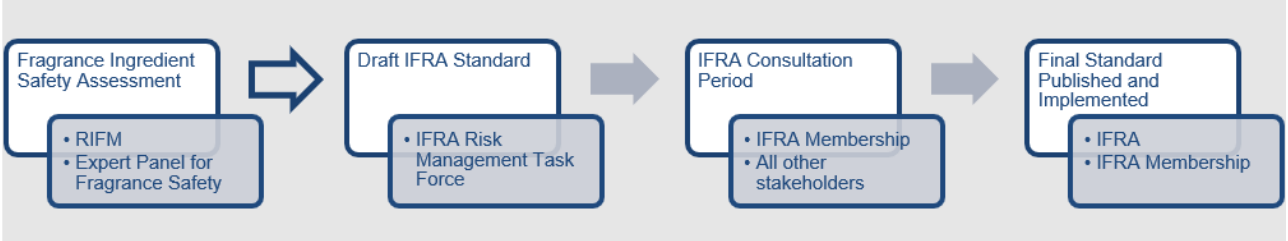
- Where there are concerns over the safe use of a fragrance ingredient, IFRA will issue an IFRA Standard.
- Consequently, not all fragrance ingredients are subject to an IFRA Standard.
- IFRA Standards may prohibit, restrict or set purity requirements for specific ingredients.
- Each member company is ultimately responsible for ensuring the fragrance ingredients or mixtures they supply are compliant with applicable laws and are safe for intended uses.

2.3 The IFRA Standards setting process

The IFRA Standards aim to ensure effective risk management of fragrance ingredients. As explained further below, the IFRA Standards are set based on safety assessments resulting from the RIFM safety assessment program. IFRA then introduces risk management measures through an inclusive process (described below), which involves a consultation open to all relevant stakeholders to ensure all comments and data are considered. A robust summary of the final safety assessment forming the basis of the Standard is published by RIFM.

The four key steps in this process and the stakeholders involved at each stage are illustrated in the Figure 3 and summarized in the next sections.

Figure 3: Illustration of the procedure for setting IFRA Standards.



2.3.1 Identification of an ingredient to be considered for a Standard

A risk for a potential adverse effect may be identified during the safety assessment of a fragrance ingredient. A draft safety assessment is prepared by the Research Institute for Fragrance Materials following a published set of criteria (RIFM Criteria Document II). This assessment reviews nine toxicological endpoints as well as the environmental safety of the ingredient.

The draft safety assessment undergoes independent review by the Expert Panel for Fragrance Safety prior to finalization. Robust summaries of the finalized safety assessments are published and available through the open-access Food and Chemical Toxicology Fragrance Material Safety Assessment Center (http://fragrancematerialsafetyresource.elsevier.com/). The published safety assessments will contain MAC if warranted by concerns regarding safe use.

2.3.2 Proposed Risk Management Measures (Draft IFRA Standard)

Once an ingredient is identified as a potential concern under the current use conditions, a draft Standard is prepared by IFRA through the IFRA Risk Management Task Force (hereafter RMTF). This is based on the safety assessment conclusions of the Expert Panel for Fragrance Safety.

The RMTF consists of Industry regulatory and safety experts and the IFRA Secretariat. This group may consult other IFRA expert groups where necessary in drafting the Standard. For example, to determine the presence of materials in natural extracts, confirmation of CAS numbers or any specific uses of ingredients in the market.

The draft Standard, once completed, are shared with RIFM, who are part of the RMTF.

2.3.3 Stakeholder Consultation

Draft IFRA Standards are circulated and open for comments to the IFRA membership and stakeholders fora commenting period that typically lasts 3-6 months. Stakeholders include the IFRA and RIFM membership (including national association members), trade association partners, regulatory bodies, downstream users, and other interested stakeholders.

All comments are reviewed and may result in a revised draft or, in the case of new data, may be referred back to RIFM and the Expert Panel for Fragrance Safety for review.

If elements of this process leading to relevant data (e.g., collection of new exposure information) require more time, the RMTF can decide to move a Standard into the next Amendment, considering the potential risk in the marketplace of deferring the Standard. The RMTF can consult with the IFRA Executive Technical Committee (ETC) or the IFRA Board on the final decision.

It should be noted that deferral of a Standard related to new incoming data will only be considered if there is no test data for that endpoint yet (i.e., read-across or modeling was used). Further, the new test data must have a reasonable likelihood of changing the SA outcome and scheduled to be completed no later than six months after the proposed date of notification of the Standard. The rationale for deferring a Standard will be documented and communicated to RIFM.

Following Consultation, an ‘End of Consultation Letter’ is provided to all Stakeholders explaining how comments were considered and any impact on the Standard.

2.3.4 Adoption of the IFRA Standard and Publication

Following the Consultation process, the final standards are adopted and are published by IFRA on the public website (https://ifrafragrance.org/). All Stakeholders are informed through a ‘Letter of Notification’ which includes the timelines for the implementation of the Standard.

2.3.5 Off-cycle Amendments

There might be circumstances where scientific findings do not allow the completion of a RIFM SA and the Panel will declare that no safe use can be determined for a given fragrance ingredient.

In such a case, a summary of the relevant toxicological data is provided by the Panel to IFRA and the RMTF to conclude on the risk management measures required and their timing.

In case the resulting Standard cannot be integrated timely in a regularly scheduled "Normal cycle" Amendment, IFRA has the option of taking immediate risk management measures by issuing a so-called 'off-cycle' Amendment.

For such immediate risk management measures, the following schedule would normally apply, (1) a Consultation period of 4 weeks is considered adequate and with regard to implementation time, (2) 4 weeks will normally be allowed for an exchange of information on the bases; (3) Another 4 weeks will be allowed to bring new submissions in line with the new Standard and after an additional 11 months, existing fragrance mixtures will need to comply to the new Standard. This would result in a total time of 13 months from the Notification date to the final date of compliance for existing mixtures. The timelines above are only indicative and IFRA may decide to adjust these on a case-by-case basis where needed, e.g. to account for holiday periods or in case of widespread use.

2.3.6 Reviewing Existing Standards

RIFM safety assessments are reviewed every five years or if significant new toxicological and/or exposure data becomes available. Exposure information is also surveyed on a regular basis. RIFM conducts exposure surveys every five years. These surveys are open to all stakeholders. This may lead to the need for updating or setting a new IFRA Standard.

2.3.7 Participation in the IFRA Standard-Setting Process

The IFRA Standard setting process is intended to be open and transparent. It has been reviewed from an antitrust perspective and designed to be as inclusive as possible. IFRA members (directly or via national associations) may apply to participate in the IFRA Task Forces engaged in the process and all Stakeholders may participate in the exposure surveys, provision of data to RIFM and commenting during the Consultation period. Any interest to participate should be addressed directly to IFRA (info@ifrafragrance.org) or a member association.

2.3.8 Additional information

International Fragrance Association (IFRA): https://ifrafragrance.org/

IFRA Code of Practice: https://ifrafragrance.org/self-regulation/ifra-code-of-practice

IFRA Standards: https://ifrafragrance.org/self-regulation/introduction

RIFM: www.rifm.org

RIFM Criteria Document II:
http://fragrancematerialsafetyresource.elsevier.com/sites/default/files/Criteria_Document_Final.pdf

RIFM NCS Criteria Document:
http://fragrancematerialsafetyresource.elsevier.com/sites/default/files/Natural%20Complex%20Substances%20Article.pdf

Expert Panel for Fragrance Safety: http://fragrancesafetypanel.org/

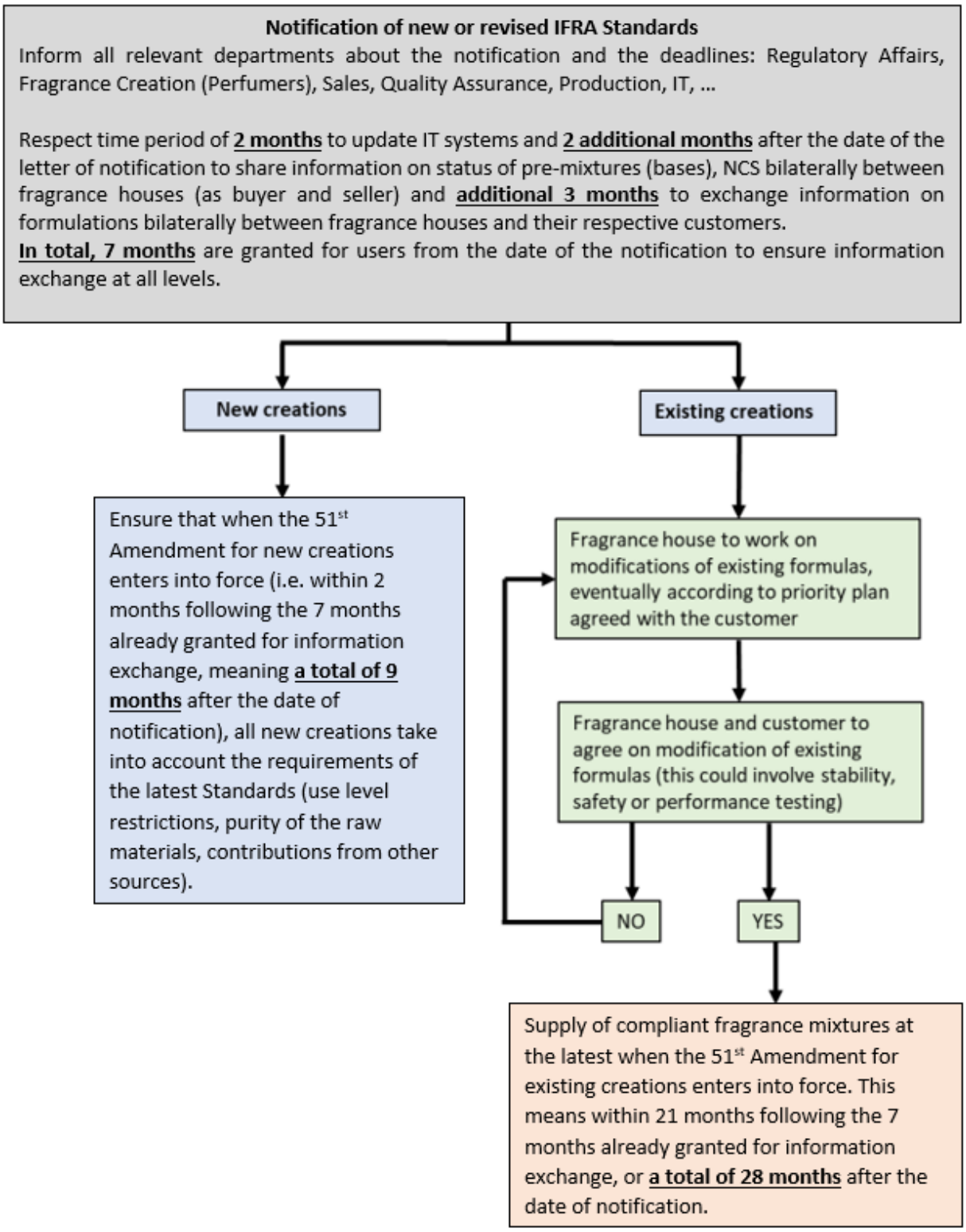
Food and Chemical Toxicology Fragrance Material Safety Assessment Center:
http://fragrancematerialsafetyresource.elsevier.com/

2.4. Standard Operating Procedure for handling Amendments to the IFRA Code of Practice

The Standard Operating Procedure (SOP) intends to help companies implement Amendments to the IFRA Code of Practice, which consists of new or revised Standards.

An updated version of the operating procedure reflecting the specific timelines of the 51st Amendment is provided in Figure 4.

Figure 4: Standard operating procedure for the 51st Amendment.



3. Quantitative Risk Assessment for fragrance ingredients

3.1 Introduction to the Quantitative Risk Assessment (QRA and QRA2) for fragrance ingredients

Although some substances in common use today may have the potential to cause dermal sensitization, they can still 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 been incorporated in the way dermal sensitization risk assessments are conducted for fragrance ingredients. This methodology reflects evolving risk assessment processes considering the latest scientific developments. 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 (Api *et al*., 2008). The QRA methodology as it exists today does not cover occupational use of consumer products, mainly due to missing exposure data to build into the risk assessment.

In a brief overview, key steps of the QRA process are the determination of benchmarks for the induction potential (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. The detailed methodology has been published in a peer-reviewed journal (Api et al 2020).

Based on the recommendation of the Expert Panel for Fragrance Safety and beginning with the 40th Amendment to the IFRA Code of Practice in May 2006, RIFM and IFRA formally adopted the QRA approach 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.

Further to the development of the QRA, and to its initial use for determining IFRA Standards, refinements have now been made to the QRA process to include:

1. Determination of aggregate exposure of consumers to fragrances used in personal care and household care products (Comiskey *et al*., 2015; Comiskey *et al.*, 2017), and use of the results from the aggregate exposure calculations to refine acceptable use levels of fragrance ingredients in products (and thus to define IFRA Standards) (QRA submissions)
2. Discussion and refinement of SAFs used in the QRA process (Basketter and Safford, 2016).

The QRA process for dermal sensitization incorporating these refinements, referred to as QRA2, is the outcome of the multi-stakeholder platform 'International Dialogue for Evaluation of Allergens' (IDEA)[4].

The use of aggregate exposure represents a key advancement in determining acceptable levels of use in IFRA Standards. This ensures that the levels consider the overall exposure of consumers to any fragrance from the use of multiple products as part of their normal daily routine. Aggregate exposure is determined using the Creme RIFM model, a Monte Carlo based model which uses extensive consumer survey data from several countries (Comiskey *et al*., 2015; 2017). The process of determining acceptable levels incorporates the following steps:

[4] IDEA QRA2 report: http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final--september-2016.pdf

1. Calculate the acceptable level of a fragrance in each product type using conservative deterministic CEL values and the fragrance NESIL, as previously used.
2. Incorporate these acceptable levels into the Creme RIFM Exposure model and calculate aggregate exposure to the fragrance (CEL_{agg}) for each body area.
3. Identify body areas for which the AEL/CEL_{agg} ratio is less than 1. If there are none go to step 7.
4. Apply an adjustment factor to reduce the acceptable levels for products used on the body area with the lowest AEL/CEL_{agg} ratio. The adjustment factor for each product was calculated based on its contribution to exposure to that body area (i.e., products with a higher contribution were reduced the most).
5. Determine aggregate exposure as in Step 2 using these modified acceptable levels.
6. Follow steps 3-5 until the AEL/CEL_{agg} ratio for all body areas is equal to or greater than 1 (in Step 3).
7. Determine the final acceptable levels for each product by applying the appropriate adjustment factor to the values determined in Step 1.

The adjustment factors have been calculated using this methodology for one fragrance ingredient only. It follows that the adjustment factors are the same for all fragrances since they are a function of product exposure, which is always the same regardless of the fragrance ingredient. Thus, exposure to a given fragrance ingredient is calculated as the product exposure multiplied by the concentration of fragrance ingredient in the consumer product. The initial acceptable levels calculated in the method (Step1) are a function of the product exposure and the NESIL, so although they will vary with the NESIL value, the relative values between products will not change.

As part of the refinements described above, particularly with respect to incorporating aggregate exposure, product categories have been redefined to better reflect consumer use of the products (e.g., rinse-off/leave-on, the general area of use). MAC levels used in the IFRA Standards are defined by category and driven by the product with the lowest acceptable level in that category.

Table 6: SAF and product type that drive the IFRA QRA2 category Consumer Exposure Levels (CEL).Table 6 provides the SAF and product type that drives the IFRA QRA2 category consumer exposure levels. These data are used with the NESIL to calculate the acceptable exposure levels to individual fragrance ingredients.

Table 6: SAF and product type that drive the IFRA QRA2 category Consumer Exposure Levels (CEL).

IFRA QRA2 category	SAF	Calculated Consumer Exposure Level (CEL) (mg/cm^2/day)	QRA2 Aggregate Adjustment factor	Product type that drives the category Consumer Exposure Level (CEL)
Category 1 – products applied to the lips	100	11.8	0.91	Lip products
Category 2 – Products applied to the axillae	300	9.1	0.63	Solid deodorants/antiperspirants
Category 3 – Products applied to the face using fingertips	100	2.17	1.00	Eye products
Category 4 – Fine fragrance products	100	2.21	0.95	Fine fragrance products
Category 5 – Products applied to the face and body using the hands (palms), primarily leave-on	100	3.02	0.33	Insect repellent (intended to be applied to the skin)
Category 6 – Products with oral and lip exposure	100	1.27	0.32	Toothpaste
Category 7 – Products applied to the hair with some hand contact	30	2.2	0.58	Hair sprays
Category 8 – Products with significant anogenital exposure	300	7.4	NA*	Baby wipes
Category 9 – Products with body and hand exposure, primarily rinse off	300	0.2	0.50	Bar soap
Category 10 – Household care products with mostly hand contact	100	0.2	0.60	Hand dishwashing detergent
Category 11 – Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate	300	0.2	NA*	Feminine hygiene liners
Category 12 – Products not intended for direct skin contact, minimal or insignificant transfer to skin	NA*	NA*	NA*	NA*

* Not Applicable (NA) – the product types in these categories are not included in the Creme RIFM model, and aggregate exposure is not considered when calculating the acceptable levels of fragrance ingredients.

3.2 Example: Coumarin

Coumarin has been chosen as an example to demonstrate the practical application of the principles of QRA2. 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 Coumarin include the availability of robust animal sensitization data, confirmatory human sensitization data as well as diagnostic patch test studies.

Table 7 shows the practical application of the dermal sensitization QRA approach for fragrance ingredients, in products in the 12 IFRA QRA categories. It lists the calculated upper concentration limits for Coumarin in each IFRA QRA category.

Table 7: Calculation of the aggregate exposure adjusted upper concentration limits for Coumarin using the aggregate adjustment factors from Table 6 (Coumarin: NESIL of 3500 µg/cm^2).

Category	Product type driving the QRA2 upper concentration limits	Max QRA2 unadjusted use level by category (%)	QRA2 aggregate adjustment factor	QRA2 aggregate exposure adjusted upper concentration limits (%)**
1	Lip products	0.297	0.91	**0.27**
2	Deodorants and antiperspirants of all types including fragranced body sprays	0.128	0.63	**0.080**
3	Eye products	1.613	1.00	**1.6**
4	Fine fragrance (eau de toilette, parfum etc.)	1.584	0.95	**1.5**
5	Insect repellent (intended to be applied to the skin)	1.159	0.33	**0.38**
6	Toothpaste	2.756	0.32	**0.88**
7	Hair sprays	5.303	0.58	**3.1**
8	Baby wipes***	0.158	NA*	**0.16**
9	Bar soap	5.833	0.50	**2.9**
10	Hand dishwashing detergent	17.500	0.60	**11**
11	Feminine hygiene conventional pads, liners, interlabial pads***	5.833	NA*	**5.8**
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin	Not Restricted		

* Not Applicable (NA) – the product types in these categories are not included in the Creme RIFM model, and aggregate exposure is not considered when calculating the acceptable levels of fragrance ingredients.

** Expressed with two significant digits.

*** See section 6.5.11 for additional information

4. Systemic toxicity

Endpoints related to systemic toxicity (genotoxicity/carcinogenicity, reproductive and developmental toxicity, and repeated dose toxicity) are evaluated according to the RIFM Criteria II document (Api *et al*., 2015).

For systemic toxicity assessment, in order to define upper concentration limits in products, aggregate exposure is determined for total body exposure, as all fragrance ingredient that is absorbed through the skin becomes systemically available independently of the body site on which the fragrance ingredient was applied. This approach is therefore different from the one used for skin sensitization (QRA2), which considers body sites.

4.1 Calculation of upper concentration limits based on systemic toxicity considerations

For consideration of concerns related to **systemic toxicity** of a given material, several pieces of key information are needed. In order to determine the upper concentration limits based on systemic toxicity, the Optimization Tool in the Creme RIFM Aggregate Exposure Model is used.

For the given systemic product categories, the model provides upper concentration levels, such that the 95th percentile (P95) of aggregate exposure to each material stays below the designated reference dose (RfD). The RfD is approved by the Expert Panel for Fragrance Safety. Upper concentration level distribution follows the use level pattern reported to RIFM by the industry. This is achieved in reply to RIFM concentration of use surveys, where fragrance compounders report the use levels of a given fragrance ingredient in fragrance compounds (intended for a specific product type). These data are combined with the use concentrations of fragrance compounds in product types as reported by the consumer product manufacturers directly to Creme Global. The P95 exposure data are calculated using the Creme RIFM Aggregate Exposure Model for each product type and this ratio between different product types is used in the Optimization Tool to distribute the allowable upper concentration levels between product categories.

Therefore, all the concentrations resulting from the RIFM concentration of use surveys are used as starting points in the optimization tool. In case there is no reported use for a product category the default used in the optimization tool is 10 ppm unless there is another reported use for another product that is below 10 ppm, which will then become the starting point for running the Optimization Tool. When the RfD is low and every upper concentration limit falls below the 95th percentile use in every category, then the default for a no reported use for a product category is 0.1 ppm.

Other key data used in the optimization tool are skin absorption data. The calculated skin absorption data used are based on the skin absorption model (SAM) developed by RIFM (Shen *et al.*, 2014) unless measured data are available.

When there is a need for an IFRA Standard based on another adverse effect (typically dermal sensitization), the upper concentration levels (e.g., from QRA2) will be compared to the upper concentration levels based on the material's systemic effects (see Section 6).

4.2 IFRA categories based on systemic toxicity considerations

In order to consider aspects concerning systemic toxicity, the following IFRA categories subdivisions are applied:

- **Category 5** has been divided into 5A (body lotion), 5B (face moisturizer), 5C (hand cream), and 5D (baby products).

  The exposure data for Categories 5D, 8, and 11, if available, is often limited to regional studies and are so far not regarded as reliable enough to be used in the Creme RIFM model. The RIFM aggregate exposure Core Team, therefore, agreed that the upper concentration level of Category 5D should be derived from the lowest upper concentration level from Categories 5A, 5B, and 5C. To account for the uncertainty regarding the

exposure information, the level will be divided by 3. The upper concentration levels of Categories 8 and 11 should be the same as Category 5D. Consequently, **the upper concentration levels of Categories 5D, 8, and 11 are derived by taking the lowest upper concentration level from Categories 5A, 5B, and 5C divided by 3.**

- **Category 10** has been divided into 10A (household care products with mostly hand contact) and 10B (household care products with mostly hand contact, including household aerosol/spray products with potential leave-on skin contact). It should be pointed out that category 10A as well as 10B does contain spray products. The differentiation is linked to the likelihood of skin contact (10B) compared to minimal contact and/or the assumption of hands being washed after application – hence consideration more as rinse-off products (10A).

The final IFRA categories, including dermal sensitization (QRA2), phototoxicity, and systemic toxicity considerations are reflected in Table 8.

Table 8: IFRA Standard categories by product type.

Category	Product type
1	Products applied to the lips
2	Products applied to the axillae
3	Products applied to the face/body using fingertips
4	Products related to fine fragrance
5	Products applied to the face and body using the hands (palms), primarily leave-on:
5A	Body lotion products applied to the body using the hands (palms), primarily leave on
5B	Face moisturizer products applied to the face using the hands (palms), primarily leave on
5C	Hand cream products applied to the hands using the hands (palms), primarily leave on
5D	Baby Creams, baby Oils and baby talc
6	Products with oral and lip exposure
7	Products applied to the hair with some hand contact
7A	Rinse-off products applied to the hair with some hand contact
7B	Leave-on products applied to the hair with some hand contact
8	Products with significant anogenital exposure
9	Products with body and hand exposure, primarily rinse off
10	Household care products with mostly hand contact:
10A	Household care products with mostly hand contact
10B	Household care products with mostly hand contact, including aerosol/spray products (with potential leave-on skin contact)
11	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate
11A	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate without UV exposure
11B	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate with potential UV exposure
12	Products not intended for direct skin contact, minimal or insignificant transfer to skin

Coumarin has been chosen as an example to demonstrate the practical application of setting upper concentration levels based on systemic toxicity. The material is a weak sensitizer with a NESIL of 3500 µg/cm² and the reference dose 160 µg/kg/day. The comparison of the systemic exposure and the QRA2-derived upper concentration levels is provided in Table 9.

5. Environment

To support the IFRA Environmental Standards, a screening level risk assessment is performed following the RIFM Environmental Framework (Salvito, 2002) which provides three tiered levels of screening for aquatic risk.

- In Tier 1 only the material's regional volume of use, log Kow and molecular weight are needed to estimate a conservative risk quotient (RQ) expressed as the ratio: Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC)). In Tier 1 a general QSAR for fish toxicity is used with a high uncertainty factor as discussed in Salvito *et al.*, 2002.
- In Tier 2 the model ECOSAR (providing chemical class specific ecotoxicity estimates) is used allowing for a lower uncertainty factor to be applied to the PNEC.
- Finally, if necessary, Tier 3 is conducted using measured biodegradation and ecotoxicity data to refine the RQ, thus allowing for lower PNEC uncertainty factors.

A screening-level hazard assessment is also performed using EPISUITE[5] using a material's structure and physical-chemical properties. This screening level hazard assessment considers the potential for a material to be persistent and bioaccumulative and toxic or very persistent and very bioaccumulative. The screening criteria currently applied are those used in the European Union for REACH as per their guidance document of 2012. For persistence, if the EPISUITE models BIOWIN 2 or BIOWIN 6 <0.5 and BIOWIN 3 <2.2, then the material is considered potentially persistent. A material would be considered potentially bioaccumulative if the EPISUITE model BCFBAF predicts a fish BCF ≥ 2000 L/kg. Ecotoxicity is determined in the screening level risk assessment.

Should additional assessment be required, based on these model outputs, a weight-of-evidence based review is performed. This review considers available data on the material's physical-chemical properties, environmental fate (e.g., OECD Guideline biodegradation studies or die-away studies), fish bioaccumulation, and higher tier model outputs (e.g., USEPA's BIOWIN and BCFBAF found in EPISUITE).

[5] Last version released of EPISUITE: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

6. IFRA Standard categories

6.1 Introduction to the IFRA categories

For practical reasons, IFRA Standards are set per product category, each covering a range of product types that can be grouped together based on risk assessment considerations. Groupings have been derived for the skin sensitization endpoint resulting from the application of QRA2 and have been compared to groupings fitting with phototoxicity and systemic toxicity considerations.

With the new approach of combining the QRA2, phototoxicity and systemic toxicity assessment in one exercise, the number of categories in the IFRA Standard has changed from 11 categories for dermal sensitization Standards and 4 for systemic toxicity-based Standards to 12 (Table 8). Product categorization is achieved by grouping consumer product types based on functional type, and major factors in habits and practices of consumers such as area of use (head, face, axillae, etc.) and whether they are rinse-off or leave-on applications. This represents a change from the categorization used in previous amendments but was considered necessary to fully implement aggregate consumer exposure into the process.

The final list of IFRA categories is shown in Table 8.

6.2 General approach for deriving the maximum acceptable concentrations (MAC) for IFRA categories

The MAC reported in the Standards are derived from a RfD that is set by the Expert Panel for Fragrance Safety and are provided in the RIFM safety assessments. These values are the lower values of upper concentration levels derived from the comparison of the dermal sensitization and the systemic toxicity endpoints risk evaluation. When there is a need for an IFRA Standard based on several adverse effects (typically dermal sensitization and systemic toxicity) the upper concentration levels (maximum acceptable exposure levels) for dermal sensitization (e.g., by QRA2) will be compared to the upper concentration levels based on the material's systemic effects. The resulting comparison results in the MAC. **For each product category, the lowest exposure level (based on systemic toxicity, dermal sensitization, or any other endpoint) will be used to derive the MAC**. The MAC are expressed in the RIFM Safety Assessment and Standard with two significant digits.

It is possible that for some materials, the upper concentration level based on sensitization effects (i.e., derived by QRA2) is lower than that derived for systemic toxicity for a given product category, but not all categories. As a result, the use level will be restricted to the respective QRA2 limit for such product category. The resulting lowered total systemic exposure from all such product categories combined will be used to deploy the Creme-RIFM Aggregate Exposure Model's Optimization Tool once again to derive refined upper concentration levels for all other remaining product categories. In this way, a given proportion of the maximum acceptable aggregated exposure can be redistributed to those product categories that are not limited by the QRA2, i.e., this allows for higher upper concentration levels in such categories. If in a product category the upper concentration level reaches 100% (most likely in IFRA Standard category 12), the level is fixed to 100% and the optimization tool is applied again to allow redistribution of exposure over remaining not yet fixed categories. This process may have to go through several iterations to achieve the maximum allowable distribution amongst the different product categories. Table 9 uses the example of Coumarin to demonstrate how this is accomplished.

In general, when the **threshold of toxicological concern (TTC)** is used in the endpoint assessment, it will not be treated as a no-effect level, meaning that no risk management measures will be recommended based on the TTC values alone (if the current use is below the TTC). i.e., **In those cases, the MAC reported in the Standard are derived solely from the dermal sensitization endpoint evaluation**. A monitoring system is in place at RIFM to ensure that the current use does not exceed the TTC. This system re-surveys concentration data every 5 years for any fragrance ingredient that has a safety assessment that used either the TTC or the Dermal Sensitization Threshold (DST). If the monitoring system indicates that the current use levels are no longer

supported by the current RIFM safety assessment, a re-evaluation is conducted, and the safety assessment is revised. This process could result in a new IFRA Standard.

However, when the TTC is used in the safety assessment and the use of the material exceeds the TTC, an IFRA will set Standards based on the TTC.

6.3 Specific cases for deriving the upper concentration levels for IFRA categories

In some cases, specific ingredients have been the object of an ingredient defense activity in the context of regulatory developments (e.g., SCCS dossiers for the European Commission). In their defense, the industry may have provided upper concentration levels, which have been reflected in the application of the optimization tool as fixed values. This is the case, for example, of **Acetylated Vetiver oil** and **p-tert-Butyl-alpha-methylhydrocinnamic aldehyde (p-BMHCA)**, where the upper concentration levels for cosmetic product categories, as provided to the SCCS, have been implemented in these Standards. This approach will also be used for any ingredient in a similar situation in the future.

There are a few cases where existing IFRA Standard limits have been taken as fixed limits in the optimization tool as in the case of **3- and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (HMPCC), Oakmoss and Treemoss** as described below.

The Standard on **3- and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (HMPCC)** was not based on QRA1 but on a pragmatic approach establishing a restriction based on consideration of elicitation information instead of induction information (which is the one considered for Standards addressing dermal sensitization). As a result, the IFRA Scientific Committee (in charge of IFRA Standards at that time) recommended to the Expert Panel for Fragrance Safety to limit the use of HMPCC to 0.02% in lip products, deodorants and antiperspirants and 0.2% in other cosmetic products except for oral products. As such, when transferring the Standard to QRA2, the fixed levels were transferred to the different categories depending on the products included within each of the categories.

For **Oakmoss and Treemoss**, the restrictions in the Standards are directly linked to the presence of Atranol and Chloroatranol in the finished products. To ensure that those remain below trace levels, the upper concentration levels have not been increased (compared to QRA1).

6.4 Important information relevant to the product types included in each category

Several key considerations regarding the product types and categories must be noted:

- The QRA2 addresses the protection of human health and is specifically aimed at reducing as much as possible the induction of dermal sensitization to fragrance ingredients under their conditions of use. The QRA for dermal sensitization of fragrance ingredients 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. As such, upper concentration levels are determined for consumer use of these products only. End-uses that are not listed in this Guidance document have not been reviewed by RIFM in their safety assessment process and are therefore not included in the IFRA risk management.
- The QRA2 methodology and systemic toxicity risk assessment do not cover occupational use of consumer products, mainly due to missing exposure data to build into the risk assessment.
- Upper concentration levels of fragrance mixtures in medical devices and prescriptive drugs have not been determined. This is mainly due to the potential or intended application on compromised or diseased skin and therefore a different risk-benefit consideration than for typical consumer products is needed. In addition, these product types are under the scope of specific regulations with defined safety assessment requirements.
- In cases where a finished consumer product is marketed for applications that cross several uses, the most stringent restriction should apply.

Table 9: Combining QRA2 and systemic toxicity acceptable levels for Coumarin

Category	Product	QRA2 acceptable % in final product	Systemic acceptable % in final product	Combined systemic and QRA2 % in final product (this can be the result from various iterations in the optimization tool)
1	Products applied to the lips	0.27	0.089	0.089
2	Products applied to the axillae	0.080	0.080	0.080
3	Products applied to the face/body using fingertips	1.6	0.089	0.089
4	Products related to fine fragrances	1.5	1.5	1.5
5 (5A)	Products applied to the body using the hands (palms), primarily leave-on (Body lotion)	0.38	0.38	0.38
5 (5B)	Products applied to the face using the hands (palms), primarily leave-on (Face moisturizer)	0.38	0.11	0.11
5 (5C)	Products applied to the hands using the hands (palms), primarily leave-on (Hand cream)	0.38	0.16	0.16
5 (5D)	Products applied to babies using the hands (palms), primarily leave-on (Baby cream, oil, talc)	0.38	NA*	0.035
6	Products with oral and lip exposure	0.88	0.0024	0.0024
7 (7A)	Rinse-off products applied to the hair with some hand contact	3.1	0.18	0.18
7 (7B)	Leave-on products applied to the hair with some hand contact	3.1	0.18	0.18
8	Products with significant anogenital exposure (tampon)**	0.158	NA*	0.035
9	Products with body and hand exposure, primarily rinse off	2.9	0.52	0.52
10 (10A)	Household care products with mostly hand contact	11	NA*	0.52
10 (10B)	Household care products with mostly hand contact (including household aerosol/spray products with potential leave-on skin contact)	11	1.6	1.6
11 (11A)	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate without UV exposure	5.8	NA*	0.035
11 (11B)	Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate with potential UV exposure	5.8	NA*	0.035
12	Other air care products not intended for direct skin contact, minimal or insignificant transfer to skin	100	33	33

* Not Applicable (NA) – the product types in these categories are not included in the Crème RIFM aggregate exposure model, and aggregate exposure is not considered when calculating the acceptable levels of fragrance ingredients.
** See section 6.5.11 for additional information

- The target of the RIFM Safety Assessments is humans and their safety while handling the finished consumer products. Some finished products applied to pets are listed in Table 11 and are covered by the IFRA Standards (animal sprays or shampoos). However, the categorization of such products only relates to the human exposure during the application of such products, not to the pet exposure to the product. Consequently, the assessment of the safety of such finished consumer products regarding animals is outside the scope of IFRA/RIFM and is the responsibility of the manufacturer.
- Product types are placed into IFRA product categories based on their way of use (leave on or rinse off) and the area of the body on which they are used. This method of categorization was adopted to fit in with the use of aggregate exposure to derive acceptable levels in the QRA2 process and adjusted for systemic exposure considerations. 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 considering how the product is used and the body area on which it is used. 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 result in re-categorization of the product type.
- The NESIL is expressed in two significant figures and rounded down as a conservative approach. For example, a calculated NESIL of 3564 will be rounded to 3500.
- It should be noted that the AELs will be expressed as accurate to two decimal places unless the NESIL is low enough that the AEL needs to be expressed to three decimal places. 1ppm (0.0001%) will be the lowest level reported as AEL.

6.5 Important information relative to specific product types

6.5.1 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, including the propellant.

Specially concentrated products:

For any concentrated product, Standards for maximum concentrations of restricted materials have been based on upper levels of consumer product exposure from published surveys. In cases where specially concentrated products have been specifically designed to ensure lower delivery of the concentrated product, proportionately higher levels of restricted materials than those specified in the Standards may be used providing that the manufacturer certifies to the fragrance suppliers the exact degree to which exposure has been reduced. (For an example see the note on concentrated aerosol products below)

Concentrated aerosol products:

For aerosol products to be applied to the axillae, Standards for maximum concentrations of restricted materials have been based on upper levels of consumer product exposure from published surveys (e.g., deodorant products with a product exposure of 9.1 mg/cm^2/day [Cowan- Ellsberry *et al.*, 2008]). In cases where concentrated aerosol products in this category have been specifically designed to ensure lower product delivery (e.g., lower spray rate), proportionately higher levels of restricted materials than those specified in the Standards may be used providing that the manufacturer certifies to fragrance suppliers the exact degree to which exposure has been reduced.

Incidental aerosol skin contact:

Incidental skin contact from aerosol products (e.g., aerosol air freshener) as defined in Category 10A 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, including Category 10B.

Concentrated aerosol air fresheners:

These air fresheners are differentiated from other aerosol air fresheners by the following two characteristics:

- These air fresheners are part of a device that either delivers the fragrance automatically or the device has an activation mechanism that is not located near where the aerosol is discharged, so there is essentially no dermal exposure from activation and at best incidental through exposure. Such concentrated aerosol air fresheners deliver a metered spray (typically 0.05 – 0.5 ml/spray) and are placed in Category 12.
- Other aerosol air fresheners deliver a continuous spray at 1-1.5 ml/second spray for as long as the consumer manually pushes the activation button, which is typically 2 to 10 seconds for a total volume of 2 – 15 ml/spray. Those products are placed in Category 10B, as they are typically manually activated by a push-button near the spray, which can result in some dermal exposure.

6.5.2 Aftershaves

Products marketed as aftershave products are all included in Category 4 along with other fine fragrance products. Some aftershave products are cream and lotion products and may be categorized as face moisturizers (Category 5B). It is recommended that the fragrance supplier and the customer company consult on the appropriate category for these types of aftershave products.

6.5.3 After sun and self-tanning products

After sun and self-tanning creams, lotions, foams, and other product applications are not addressed separately, but are included in the appropriate 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 appropriate major product categories without amendment to their MAC which is already sufficiently conservative. The use of products for severely sunburned skin could constitute a different exposure scenario, but since these borders on needing professional medical advice for treatment, this is outside the scope of this -risk assessment activity.

6.5.4 Sunscreens

Products that contain UV filters are not listed separately but are included in the appropriate major product type (e.g., lip creams containing sunscreen are included in the lip products category).

6.5.5 Animal sprays

The target of the RIFM Safety Assessments is humans and their safety while handling the finished consumer products. Some finished products applied to pets are listed in Table 11 are being covered by the IFRA Standards (animal sprays or shampoos). However, the categorization of such products only relates to the human exposure during the application of such products, not to the pet exposure to the product. Therefore, the assessment of the safety of such finished consumer products regarding animals is outside the scope of IFRA/RIFM and is the responsibility of the manufacturer.

Animal sprays (or pet sprays) are categorized in Category 10B due to the possibility of minimal exposure to (human) skin while operating the products.

6.5.6 Body sprays (including body mists)

Although Category 2 targets products that are mainly applied to the axillae, body sprays (including body mists) have been placed in this category as, in many regions, the intended and/or foreseeable use does go beyond the application on the body only.

If a body spray (body mist) is clearly labelled that it should not be applied to the axillae (meaning it should not be used as a deodorant), then this product can be considered under Category 4. It is recommended that the fragrance supplier and the customer company consult on the appropriate category for each specific body spray (body mist) product.

6.5.7 Body and face paint (for adults and children)

Due to insufficient habits and practice information that would allow differentiation of these products, body and face paint (for adults and children, which sometimes are even marketed as one product for both applications) are included in Category 3.

6.5.8 Children's toys

As stated in Section 1.6.3, IFRA prohibits the use of fragrance ingredients and mixtures in toys or other children's products where there is a likelihood of mouth contact. Following the criteria established by the toy industry, these include:

1) toys for children less than 3 years of age;
2) any toy designed and intended to go into the mouth; and/or
3) those toys for which mouth contact is reasonably foreseeable.

If these conditions do not apply, fragrance ingredients may be used according to the MAC levels described Category 1 of IFRA Standards. These toys have been placed in Category 1 (leave-on products generally applied to the lips) due to the potential for ingestion of minute amounts of fragrance ingredients. Should exposure data become available, these product types may be re-categorized.

Due to non-foreseeable exposure, Olfactive Board Games have been categorized in Category 12.

6.5.9 Dental products

Toothpaste and Mouthwash Products:

With the implementation of the QRA approach, the IFRA Standards includes oral care products. Mouthwash and toothpaste 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.

See section 1.6.2 'Oral care products and other products with the potential for ingestion' for specifics related to the flavor material status needed for fragrances used in oral care products.

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.

6.5.10 Oral intake of products

The IFRA policy on the inclusion of fragrance ingredients in consumer products with the potential of ingestion is described in Section 1.6.2.

6.5.11 Baby diapers, Feminine hygiene conventional pads, liners, Interlabial pads, Tampons, Incontinence pants/pads, Cleaning wipes, Baby wipes, Dryer sheets, and Wet toilet paper

Regarding the assembled products, two situations need to be considered:

1. Product types for which the MAC levels apply to the finished consumer product. This includes Baby diapers, Feminine hygiene conventional pads, liners, Interlabial pads, Tampons, and Incontinence pants/pads.
   In these cases, the fragrance mixture is often included in the finished product based on weight rather than percent concentration (as is the case for the formulated products). Therefore, MAC levels reflect the ratio of fragrance ingredient weight and product weight.

2. Product types for which the MAC levels apply to the lotion/formulation carrier that is then added to the finished consumer product. This includes Cleaning wipes (such as toilet seat wipes and wipes in household cleaning products), Baby wipes, Dryer sheets, and Wet toilet paper.
   This is because the fragrance mixture is part of a lotion/carrier formulation that is then added to the finished product. Therefore, MAC levels reflect the percent concentrations of the fragrance ingredient in the lotion/carrier formulation rather than the finished product.

6.5.12 Scent pads and foil packs

Scent pads and foil packs are two types of fragrance sampling technology that contain the hydroalcoholic product on a pad or in a foil pack. As such these product types are categorized in Category 4.

6.5.13 Scent strips

The concentration of the fragrance mixture 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) in the consumer product for which the scent strip is meant to be sampled. For example, if the consumer product is a fine fragrance product containing 15% of a fragrance mixture, then the concentration of the fragrance mixture to be used in the scent strip should be 15% (Category 4).

6.5.14 Tissues *vs*. wipes

Tissues or facial tissues are soft (dry) tissues (Category 11) that are usually contained in boxes. Wipes or refreshing tissues (Category 3) are moist towels and are usually contained in (re)sealable plastic packages.

6.5.15 Wheat bags

Heating pads of various shapes or sizes filled with grain to be applied on different areas of the body and presented as providing a soothing effect by applying it either warm or cold.

6.5.16 Attars and attar-type fragrances

On a global scale, it has been determined that ***attar*** has a broad definition as a concentrated fragrance oil format with various uses by consumers (similar to an oil, lotion, or spray format), rather than a single specific use in one product type [recognizing it being described as such[6]].

Because it is free from the ethanol used in traditional colognes and Eau de Toilette (EDT), the undiluted attar is preferred by various religious groups as a personal fragrance product. It may be applied in very small amounts to small skin surface areas like a fine fragrance on pulsation points or in larger amounts over a more extensive body surface like body oil. Most often attar is used neat. However, the term “attar type fragrance” is also used to describe diluted products. For example, when religious concerns about ethanol are not an issue, Attar can be diluted for typical fine fragrance or Eau de Toilette uses or as a fabric spray.

Attar can also be used in/as air care products. Examples include incense or reed diffusers. The smoke from the incense may be used to fragrance clothing or the air.

Therefore, user exposure can vary based on the actual use pattern of the product as/in which the Attar is used.

Because of the various potential uses of consumer products labelled as attar or “attar type fragrances” (as outlined above) and the wide range of potential exposures, it is not feasible to assign it to a single QRA category. It is therefore up to the final product manufacturer to select the proper IFRA category for a compliance assessment. The decision criteria should include the intended or reasonably foreseeable use of the product (body part, the amount used, etc.). Both doses per unit area for the dermal QRA and total daily exposure for systemic risk assessment should be considered. Possible options are included in Table 10.

Table 10: Possible categorization of Attar products depending on the potential uses of consumer products labelled as Attar or “Attar type fragrances”

Type of finished consumer product	Proposed categorization
Fine fragrance type use	4
EDT use (oil with alcohol)	4
Body oil/lotion like use	5A
With intimate exposure	8
Fabric Spray / reed diffuser	10A
Incense / other non-skin	12

IFRA recommends using the most stringent outcome of the safety assessment (in terms of dermal and systemic effects) in case no clear end product for the use of attar is specified.

6.5.17 Categorization of multiple uses products

The 49th Amendment to the IFRA Code of Practice included two major updates:

1) implementation of QRA2 and,

2) implementation of systemic toxicity considerations.

One or a combination of both can drive the maximum acceptable concentrations (MACs) derived from the RIFM Safety Assessments which have been approved by the Expert Panel for Fragrance Safety and presented in the IFRA Standards. As a result, many materials that had existing IFRA Standards have different MACs compared to their previously issued Standards. Some materials now have more restrictive limits in IFRA Categories, which could either be driven by QRA2 or systemic toxicity considerations. Given that the process is now more complex, it may be counterintuitive to

[6] Garry Dix, Perfumer and Flavorist, Vol. 40, 38-43, Jan. 2015

the previously derived MACs in the Standards presented with the 48th Amendment which were derived from QRA1.

This is best explained by using examples. Utilizing QRA2 and solely taking into consideration dermal sensitization risk as the driver for a Standard, the allowable limit would be approximately 2x lower in Category 4 (Products Related to Fine Fragrance) vs. Category 7B (Leave-on Products Applied to the Hair with Some Hand Contact) based on differences in SAF's (100 vs 30) and adjustment factors (0.95 vs 0.58) respectively.

As an example, the Standard for Longifolene CAS # 475-20-7 (based solely on dermal sensitization risk) provides the following limits:

Category 4 = 1.5%

Category 7B = 3.1%

On the other hand, the IFRA Standard for 1-(1,2,3,4,5,6,7,8 Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl) ethanone (OTNE) CAS # 54464-57-2 (based on dermal sensitization and systemic toxicity risk), provides the following limits:

Category 4 = 20%

Category 7B = 0.67%

(for comparison, the MACs based on dermal sensitization only would be: Category 4 Fine Fragrance – 20.4% and for Category 7B Hair Care Products = 41.1%)

To categorize a product requested to be "dual use" such as a fine fragrance & hair mist it would be necessary to apply the more restrictive of the two different categories that such a product could be assigned to (Category 4 or 7B in these examples).

As done in the past when sensitization was the sole driver of standards, intuitively this would mean applying the more restrictive Category 4 level covering both uses of the dual use product as would be the case with Longifolene where 1.5% would then be the limit.

However, this does not hold when the Standard for a material is not driven solely by dermal sensitization but rather driven by dermal sensitization and systemic toxicity. This can lead to lower limits in other IFRA Categories, that if solely based on dermal sensitization would be higher.

This is demonstrated with OTNE, where in the above case, the lower limit for Hair mist (Category 7B = 0.67%) would be applied as the overall Maximum Acceptable Concentration (MAC) for the dual use product.

The explanation lies in how the MACs for the different categories that you find in the Standard are derived when systemic toxicity is considered. Here the main driver that determines maximum concentration use level is the distribution of the existing use levels of the material as reported to RIFM in the regular concentration surveys. Therefore, if the material has been reported to be used at higher levels in one category (e.g., Category 4) it is possible that the subsequent Standard limit (MAC) of this material is higher in this category compared to what one would expect to find for other categories with generally lower skin or systemic exposure (e.g., Category 7B). However, the maximum use level derived from systemic considerations can never exceed the upper use limit based on QRA2. This process is taking place at RIFM and the MACs reported in the Standard are the final outcome of this exercise. To follow the example from above with OTNE, the MAC in Category 4 is close to the QRA2 value because the systemic toxicity allows the level influenced by the 95th percentile reported use of the material in this category, which is 62% higher than the reported use in Category 7.

As such, it is extremely important for companies to report the concentration used for fragrance ingredients in the RIFM Concentration Surveys so that those uses will be represented, as they impact the attribution of permitted uses in the Standard. This means that reported exposures will accurately reflect real-life exposures and that the MAC will be derived from those same real-life exposures. If a material is used in a product that has a dual use, the concentration should therefore be reported for both products.

To conclude, it is necessary to always take the following approach for dual use products: compare the limits in both categories the product shall be used in, for all ingredients within the fragrance, and identify the lowest limit for all ingredients in both categories to drive the overall MAC for the dual use product. The same principle and rules apply for products with more than 2 intended uses (in different product categories).

Additional considerations of multiple uses products involving lips exposure are described in item 1.6.2.2.

6.5.18 Reed diffusers

The rationale for the categorization of reed diffusers was shared via the IFRA IL 1107 and is as follows:

Reed diffusers and some related products [fragranced oil for lamp ring, pot-pourri, and liquid refills for air fresheners (non-cartridge systems), etc.] with the implementation of QRA2 in the 49th Amendment, were placed in Category 10A. This more restrictive categorization was chosen by IFRA and RIFM to reflect the potential exposure during manual handling (flipping) of the soaked reeds and/or the refill. Similar concerns exist for other product types sharing the same fate (like lamp oils). This decision was confirmed by the QRA Expert Team at RIFM.

Another comprehensive review of product types in Category 10, 11 and 12 is foreseen as part of the preparation of the 52nd Amendment.

6.5.19 Sprays for facial masks (protective face coverings)

Questions have been addressed to IFRA and RIFM about how to categorize sprays for facial masks. It was determined that the appropriate characterization and assessment of the safety of this product type needs to be left to the responsibility of the producer.

6.5.20 Pillow spray

Rational for placing pillow spray in Category 11: The industry QRA expert group did look at the information provided. To our information, the instructions to the consumer provided in the categorization form do not indicate that the surface of the pillow should be allowed to dry before laying on it. It is assumed that the product will be sprayed on the top surface of the pillow, the consumer will lay its face on the pillow before the fabric dries and there is the aspect of occlusion when putting the face on the pillow. It was assumed that it would be too conservative to assume 100% transfer to skin. The surrogate application was a wet facial wipe which assumes a factor of 20% for amount of product remaining on skin. As such assuming 20% of the product remains on the skin then, Category 11 would be appropriate without additional data from the applicant

6.6 IFRA categories: list of finished consumer products per category

Table 11 gives the products placed in the 12 IFRA Categories and subcategories with detailed comments for specific product types.

Table 12 is an alphabetical list of product types and their corresponding IFRA Category.

Table 11: List of IFRA categories and subcategories with corresponding product

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Category 1	**Leave on products generally applied to lips**				
Lip Products of all types (solid and liquid lipsticks, balms, clear or colored, etc.)	Products that contain UV filters 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).		YES	Applicable (leave-on products)	Category 1
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.		YES	Applicable (leave-on products)	Category 1
Category 2	**Leave on products generally applied to axillae**				
Deodorant and antiperspirant products of all types including any product with intended or reasonably foreseeable use on the axillae or labelled as such (spray, stick, roll-on, under-arm, deo-cologne, etc.)			NO	Applicable (leave-on products)	Category 2
Body sprays (including body mist)			NO	Applicable (leave-on products)	Category 2
Category 3	**Products generally applied to the face using fingertips**				

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Eye products of all types (eye shadow, mascara, eyeliner, eye make-up, eye masks, eye pillows, etc.) including eye care and moisturizer			NO	Applicable (leave-on products)	Category 3
Facial make up and foundation			NO	Applicable (leave-on products)	Category 3
Make-up remover for face and eyes			NO	Applicable (leave-on products)	Category 3
Nose pore strips			NO	Applicable (leave-on products)	Category 3
Wipes or refreshing tissues for face, neck, hands, body	These product types have been placed in Category 3 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.		NO	Applicable (leave-on products)	Category 3
Body and face paint (for children and adults)	This product type has been placed in Category 3 based on the absence of exposure data, with the assumption that this product is applied with fingertips and not with the palms. Should exposure data become available, this product type may be re-categorized.		NO	Applicable (leave-on products)	Category 3

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Facial masks for face and around the eyes			NO	Applicable (leave-on products)	Category 3
Category 4	**Fragrancing products generally applied to neck, face and wrists**				
Hydroalcoholic and non-hydroalcoholic fine fragrance of all types (Eau de Toilette, Parfum, Cologne, solid perfume, fragrancing cream, etc.), aftershaves of all types (except creams and balms)			NO	Applicable (leave-on products)	Category 4
Fragranced bracelets	These product types have been placed in Category 4 based on the absence of exposure data and on assumptions which include the leave-on use on the wrists. Should exposure data become available, this product type may be re-categorized.		NO	Applicable (leave-on products)	Category 4
Ingredients of perfume kits and fragrance mixtures for cosmetic kits			NO	Applicable (leave-on products)	Category 4
Scent pads, foil packs			NO	Applicable (leave-on products)	Category 4
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.		NO	Applicable (leave-on products)	Category 4

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Category 5	**Leave on products applied to the face and body using the hands (palms)**				
Body creams, oils, lotions of all types	Products that contain UV filters 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).	A	NO	Applicable (leave-on products)	Category 5A
Foot care products (creams and powders)		A	NO	Applicable (leave-on products)	Category 5A
Insect repellent (intended to be applied to the skin)		A	NO	Applicable (leave-on products)	Category 5A
All powders and talc (excluding baby powders and talc)		A	NO	Applicable (leave-on products)	Category 5A
Facial toner		B	NO	Applicable (leave-on products)	Category 5B
Facial moisturizers and creams (including care products for beard and mustache)		B	NO	Applicable (leave-on products)	Category 5B
Hand cream		C	NO	Applicable (leave-on products)	Category 5C
Nail care products including cuticle creams, nail lacquer remover, etc.		C	NO	Applicable (leave-on products)	Category 5C
Hand sanitizers		C	NO	Applicable (leave-on products)	Category 5C
Baby cream/lotion, baby oil, baby powders and talc		D	NO	Applicable (leave-on products)	Category 5D
Category 6	**Products with lip and oral exposure**				
Toothpaste	Exposure limits for these products are established to reduce the risk of peri-oral skin sensitization and phototoxicity and as such, are not related to considerations of safe levels for ingestion. For the systemic		YES	Applicable (rinse-off products)	Category 6
Mouthwash, including breath sprays			YES	Applicable (rinse-off products)	Category 6

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Toothpowder, strips, mouthwash tablets	toxicity assessment, only incidental ingestion is considered.		YES	Applicable (rinse-off products)	Category 6
Category 7	**Products applied to hair with hand contact**				
Hair permanent or other hair chemical treatments (rinse-off) (e.g., relaxers), including rinse-off hair dyes	Fragrance ingredients in hair permanent and other hair chemical treatments have been placed in Category 7. 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.	A	NO	Applicable (rinse-off products)	Category 7A
Hair sprays of all types (pumps, aerosol sprays, etc.)		B	NO	Applicable (leave-on products)	Category 7B
Hair styling aids non sprays (mousse, gels, leave-on conditioners)		B	NO	Applicable (leave-on products)	Category 7B

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Hair permanent or other hair chemical treatments (leave-on) (e.g., relaxers), including leave-on hair dyes	Fragrance ingredients in hair permanent and other hair chemical treatments have been placed in Category 7. 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.	B	NO	Applicable (leave-on products)	Category 7B
Shampoo - Dry (waterless shampoo)		B	NO	Applicable (leave-on products)	Category 7B
Hair deodorizer, hair perfume*		B	NO	Applicable (leave-on products)	Category 7B
Category 8	**Products with significant anogenital exposure**				
Intimate wipes			NO	Applicable (leave-on products)	Category 8
Intimate deodorant spray			NO	Applicable (leave-on products)	Category 8
Tampons			NO	Applicable (leave-on products)	Category 8
Baby wipes			NO	Applicable (leave-on products)	Category 8
Toilet paper (wet)			NO	Applicable (leave-on products)	Category 8
Category 9	**Rinse off products with body and hand exposure**				

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Bar soap			NO	Applicable (rinse-off products)	Category 9
Shampoo of all types			NO	Applicable (rinse-off products)	Category 9
Cleanser for face (rinse-off)			NO	Applicable (rinse-off products)	Category 9
Conditioner (rinse-off)			NO	Applicable (rinse-off products)	Category 9
Liquid soap			NO	Applicable (rinse-off products)	Category 9
Body washes and shower gels of all types			NO	Applicable (rinse-off products)	Category 9
Baby wash, bath, shampoo			NO	Applicable (rinse-off products)	Category 9
Bath gels, foams, mousses, salts, oils and other products added to bathwater (such as bath bombs)			NO	Applicable (rinse-off products)	Category 9
Foot care products (feet are placed in a bath for soaking)			NO	Applicable (rinse-off products)	Category 9
Shaving creams of all types (stick, gels, foams, etc.)			NO	Applicable (rinse-off products)	Category 9
All depilatories (including facial) and waxes for mechanical hair removal			NO	Applicable (rinse-off products)	Category 9
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.		NO	Applicable (rinse-off products)	Category 9
Category 10	**Household care products with mostly hand contact**				

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Hand wash laundry detergent (including concentrates)		A	NO	Applicable (rinse-off products)	Category 10A
Laundry pre-treatment of all types (e.g. paste, sprays, sticks)		A	NO	Applicable (rinse-off products)	Category 10A
Hand dishwashing detergent (including concentrates)	In an abundance of caution, the exposure for liquid soaps (0.2 mg/cm^2/day) is being used for the Hand Dishwash Liquid products (the HERA value is 0.01 mg/cm^2/day). This considers consumers who use hand dishwash liquids as a liquid soap.	A	NO	Applicable (rinse-off products)	Category 10A
Hard surface cleaners of all types (bathroom and kitchen cleansers, furniture polish, etc.)		A	NO	Applicable (rinse-off products)	Category 10A
Machine laundry detergents with skin contact (e.g., liquids, powders) including concentrates		A	NO	Applicable (rinse-off products)	Category 10A
Toilet seat wipes		A	NO	Applicable (rinse-off products)	Category 10A
Fabric softeners of all types excluding fabric softener sheets		A	NO	Applicable (rinse-off products)	Category 10A

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Household cleaning products, other types including fabric cleaners, soft surface cleaners, carpet cleaners, furniture polishes sprays and wipes, leather cleaning wipes, stain removers, fabric enhancing sprays, treatment products for textiles (e.g., starch sprays, fabric treated with fragrances after wash, deodorizers for textiles or fabrics)		A	NO	Applicable (rinse-off products)	Category 10A
Floor wax		A	NO	Applicable (rinse-off products)	Category 10A
Fragranced oil for lamp ring, reed diffusers, pot-pourri, liquid refills for air fresheners (non-cartridge systems), etc.		A	NO	Applicable (rinse-off products)	Category 10A
Ironing water (Odorized distilled water)		A	NO	Applicable (rinse-off products)	Category 10A
Dry cleaning kits (involving manual application on the textile)		A	NO	Applicable (rinse-off products)	Category 10A
Animal sprays – sprays applied to animals of all types		B	NO	Applicable (leave-on products)	Category 10B
Air freshener sprays, manual, including aerosol and pump		B	NO	Applicable (leave-on products)	Category 10B
Aerosol/spray insecticides		B	NO	Applicable (leave-on products)	Category 10B
Category 11	**Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate**				

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Feminine hygiene conventional pads, liners, interlabial pads		A	NO	Not applicable (leave-on products without UV exposure)	Category 11A
Baby diapers		A	NO	Not applicable (leave-on products without UV exposure)	Category 11A
Incontinence pant, pad		A	NO	Not applicable (leave-on products without UV exposure)	Category 11A
Toilet paper (dry)		A	NO	Not applicable (leave-on products without UV exposure)	Category 11A
Tights with moisturizers		B	NO	Applicable (leave-on products)	Category 11B
Scented socks, gloves		B	NO	Applicable (leave-on products)	Category 11B
Facial tissues (dry tissues)		B	NO	Applicable (leave-on products)	Category 11B
Napkins		B	NO	Applicable (leave-on products)	Category 11B
Pillow spray		B	NO	Applicable (leave-on products)	Category 11B
Paper towels		B	NO	Applicable (leave-on products)	Category 11B
Wheat bags		B	NO	Applicable (leave-on products)	Category 11B
Facial masks (paper/protective) e.g., surgical masks not used as medical device		B	NO	Applicable (leave-on products)	Category 11B
Fertilizers, solid (pellet or powder)		B	NO	Applicable (leave-on products)	Category 11B
Category 12	**Products not intended for direct skin contact, minimal or insignificant transfer to skin**				

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Candles of all types (including encased)	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 negligible. As such, the concentration of fragrance ingredient is not restricted in the finished product.		NO	Not applicable (non-skin contact products)	Category 12
Laundry detergents for machine wash with minimal skin contact (e.g. Liquid tabs, pods)			NO	Not applicable (non-skin contact products)	Category 12
Automated air fresheners and fragrancing of all types (concentrated aerosol with metered doses (range 0.05-0.5mL/spray), plug-ins, closed systems, solid substrate, membrane delivery, electrical, powders, fragrancing sachets, incense, liquid refills (cartridge), air freshening crystals, solid non aerosol car diffuser)			NO	Not applicable (non-skin contact products)	Category 12
Air delivery systems			NO	Not applicable (non-skin contact products)	Category 12
Cat litter			NO	Not applicable (non-skin contact products)	Category 12
Cell phone cases			NO	Not applicable (non-skin contact products)	Category 12
Deodorizers/maskers not intended for skin contact (e.g., fabric drying machine deodorizers, carpet powders)			NO	Not applicable (non-skin contact products)	Category 12
Dry cleaning kits (placed in the dryer)			NO	Not applicable (non-skin contact products)	Category 12
Dryer sheets and fabric softener sheets			NO	Not applicable (non-skin contact products)	Category 12

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Fuels			NO	Not applicable (non-skin contact products)	Category 12
Insecticides (e.g., mosquito coil, paper, electrical, for clothing) excluding aerosols/sprays			NO	Not applicable (non-skin contact products)	Category 12
Joss sticks or incense sticks			NO	Not applicable (non-skin contact products)	Category 12
Dishwash detergent and deodorizers – for machine wash			NO	Not applicable (non-skin contact products)	Category 12
Olfactive board games			NO	Not applicable (non-skin contact products)	Category 12
Paints			NO	Not applicable (non-skin contact products)	Category 12
Plastic articles (excluding toys)			NO	Not applicable (non-skin contact products)	Category 12
Scratch and sniff			NO	Not applicable (non-skin contact products)	Category 12
Scent pack			NO	Not applicable (non-skin contact products)	Category 12
Scent delivery system (using dry air technology)			NO	Not applicable (non-skin contact products)	Category 12
Shoe polishes			NO	Not applicable (non-skin contact products)	Category 12
Rim blocks (toilet)			NO	Not applicable (non-skin contact products)	Category 12
Toilet gel			NO	Not applicable (non-skin contact products)	Category 12

IFRA Category Product Type	IFRA Category rationale Comments	IFRA Sub-category	Flavour use	Phototoxicity	IFRA category for Certificate of Conformity of fragrance mixtures with IFRA Standards
Scent beads			NO	Not applicable (non-skin contact products)	Category 12

For questions related to multiple use products see section 1.6.2.2

* Hair perfume has been placed in Category 7 as a general entry. Please take note that this applies if the product is marketed specifically for hair. If it is a product that can be sprayed on hair as well as other parts of the body or if the marketing/label is not explicit, then some consumers might spray the product directly onto the skin, and therefore the application would be similar to a fine fragrance and the product should be treated as a product in Category 4.

Table 12: IFRA categories and subcategories arranged alphabetically by product type.

Product Type	IFRA Category
Aerosol/spray insecticides	Category 10B
Air delivery systems	Category 12
Air freshener sprays, manual, including aerosol and pump	Category 10B
All depilatories (including facial) and waxes for mechanical hair removal	Category 9
All powders and talc (excluding baby powders and talc)	Category 5A
Animal sprays – sprays applied to animals of all types	Category 10B
Automated air fresheners and fragrancing of all types (concentrated aerosol with metered doses (range 0.05-0.5mL/spray), plug-ins, closed systems, solid substrate, membrane delivery, electrical, powders, fragrancing sachets, incense, liquid refills (cartridge), air freshening crystals)	Category 12
Baby cream/lotion, baby oil, baby powders and talc	Category 5D
Baby diapers	Category 11A
Baby wash, bath, shampoo	Category 9
Baby wipes	Category 8
Bar soap	Category 9
Bath gels, foams, mousses, salts, oils and other products added to bathwater (such as bath bombs)	Category 9
Body and face paint (for children and adults)	Category 3
Body creams, oils, lotions of all types	Category 5A
Body sprays (including body mist)	Category 2
Body washes and shower gels of all types	Category 9
Candles of all types (including encased)	Category 12
Cat litter	Category 12
Cell phone cases	Category 12
Children's toys	Category 1
Cleanser for face (rinse-off)	Category 9
Conditioner (rinse-off)	Category 9
Deodorant and antiperspirant products of all types including any product with intended or reasonably foreseeable use on the axillae or labelled as such (spray, stick, roll-on, under-arm, deo-cologne, etc.)	Category 2
Deodorizers/maskers not intended for skin contact (e.g., fabric drying machine deodorizers, carpet powders)	Category 12
Dishwash detergent and deodorizers – for machine wash	Category 12
Dry cleaning kits (involving manual application on the textile)	Category 10A
Dry cleaning kits (placed in the dryer)	Category 12
Dryer sheets and fabric softener sheets	Category 12
Eye products of all types (eye shadow, mascara, eyeliner, eye make-up, eye masks, eye pillows, etc.) including eye care and moisturizer	Category 3
Fabric softeners of all types excluding fabric softener sheets	Category 10A
Facial moisturizers and creams (including care products for beard and mustache)	Category 5B
Facial toner	Category 5B
Facial make up and foundation	Category 3
Facial masks (paper/protective) e.g., surgical masks not used as medical device	Category 11B

Product Type	IFRA Category
Facial masks for face and around the eyes	Category 3
Facial tissues (dry tissues)	Category 11B
Feminine hygiene conventional pads, liners, interlabial pads	Category 11A
Fertilizers, solid (pellet or powder)	Category 11B
Floor wax	Category 10A
Foot care products (creams and powders)	Category 5A
Foot care products (feet are placed in a bath for soaking)	Category 9
Fragranced bracelets	Category 4
Fragranced oil for lamp ring, reed diffusers, pot-pourri, liquid refills for air fresheners (non-cartridge systems), etc.	Category 10A
Fuels	Category 12
Hair deodorizer, hair perfume	Category 7B
Hair permanent or other hair chemical treatments (leave-on) (e.g., relaxers), including leave-on hair dyes	Category 7B
Hair permanent or other hair chemical treatments (rinse-off) (e.g., relaxers), including rinse-off hair dyes	Category 7A
Hair sprays of all types (pumps, aerosol sprays, etc.)	Category 7B
Hair styling aids non sprays (mousse, gels, leave- on conditioners)	Category 7B
Hand cream	Category 5C
Hand dishwashing detergent (including concentrates)	Category 10A
Hand sanitizers	Category 5C
Hand wash laundry detergent (including concentrates)	Category 10A
Hard surface cleaners of all types (bathroom and kitchen cleansers, furniture polish, etc.)	Category 10A
Household cleaning products, other types including fabric cleaners, soft surface cleaners, carpet cleaners, furniture polishes sprays and wipes, leather cleaning wipes, stain removers, fabric enhancing sprays, treatment products for textiles (e.g., starch sprays, fabric treated with fragrances after wash, deodorizers for textiles or fabrics)	Category 10A
Hydroalcoholic and non-hydroalcoholic fine fragrance of all types (Eau de Toilette, Parfum, Cologne, solid perfume, fragrancing cream, aftershaves of all types, etc.), aftershaves of all types (except creams and balms)	Category 4
Incontinence pant, pad	Category 11A
Ingredients of perfume kits and fragrance mixtures for cosmetic kits	Category 4
Insect repellent (intended to be applied to the skin)	Category 5A
Insecticides (e.g., mosquito coil, paper, electrical, for clothing) excluding aerosols/sprays	Category 12
Intimate wipes	Category 8
Intimate deodorant spray	Category 8
Ironing water (Odorized distilled water)	Category 10A
Joss sticks or incense sticks	Category 12
Laundry detergents for machine wash with minimal skin contact (e.g. Liquid tabs, pods)	Category 12
Laundry pre-treatment of all types (e.g., paste, sprays, sticks)	Category 10A

Product Type	IFRA Category
Lip Products of all types (solid and liquid lipsticks, balms, clear or colored, etc.)	Category 1
Liquid soap	Category 9
Machine laundry detergents with skin contact (e.g., liquids, powders) including concentrates	Category 10A
Make-up remover for face and eyes	Category 3
Mouthwash, including breath sprays	Category 6
Nail care products including cuticle creams, nail lacquer remover, etc.	Category 5C
Napkins	Category 11B
Nose pore strips	Category 3
Olfactive board games	Category 12
Paints	Category 12
Paper towels	Category 11B
Pillow spray	Category 11B
Plastic articles (excluding toys)	Category 12
Rim blocks (Toilet)	Category 12
Scent beads	Category 12
Scent delivery system (using dry air technology)	Category 12
Scent pack	Category 12
Scent pads, foil packs	Category 4
Scent strips for hydroalcoholic products	Category 4
Scented socks, gloves	Category 11B
Scratch and sniff	Category 12
Shampoo - Dry (waterless shampoo)	Category 7B
Shampoo of all types	Category 9
Shampoos for pets	Category 9
Shaving creams of all types (stick, gels, foams, etc.)	Category 9
Shoe polishes	Category 12
Tampons	Category 8
Tights with moisturizers	Category 11B
Toilet gel	Category 12
Toilet paper (dry)	Category 11A
Toilet paper (wet)	Category 8
Toilet seat wipes	Category 10A
Toothpaste	Category 6
Toothpowder, strips, mouthwash tablets	Category 6
Wheat bags	Category 11B
Wipes or refreshing tissues for face, neck, hands, body	Category 3

6.7 QRA categorization of a new product type or review of an existing product categorization

Due to innovative new uses of fragrances or existing fragrance applications that are considered not (adequately) covered by the QRA Categories in the IFRA Code of Practice, in these cases, companies request RIFM to review additional information for such uses and assign them to the appropriate QRA Category. RIFM consults with a team of experts familiar with various product types who are also experts in applying the QRA methodology.

Companies are requested to supply information, exposure data and habits and practices data on the new product type using a standardized form: Data Needed for IFRA QRA Categorization of a New Product Type or To Review an Existing Product Categorization (ifrafragrance.org). These data are examined by experts to make a balanced judgement. Any unpublished data will remain on file at RIFM but will be submitted to government authorities upon request.

If certain exposure data points are not available, a conservative approach will be taken – e.g. it will be assumed that 100% of the fragrance will be transferred to the exposed sites. If data are missing, it may not be possible to categorize the product.

When applicable, the resulting categorization will be updated in the next version of the RIFM/IFRA Guidance for the use of the IFRA Standards.

6.8 Certificate of Conformity of fragrance mixtures with IFRA Standards

IFRA does not provide certification of compliance with the IFRA Standards. This is an issue for suppliers and their customers. However, to ease the process and to ensure that consumer goods companies and people using fragranced products can be confident that fragrances conform with the IFRA Standards, IFRA has developed a template for Certificates of Conformity with the IFRA Standards.

The certificate of conformity of fragrance mixtures with IFRA Standards hereafter "Certificate of Conformity" declares compliance with the requirements expressed in the IFRA Standards, and confirms that a specific fragrance mixture up to a certain concentration can be used in a specified consumer product in compliance with up to and including a specific Amendment (the number and the Notification date of the Amendment should be stated in the Certificate). The Certificate of Conformity does not replace a safety assessment and does not dismiss companies from complying with the national/local regulations in place in the countries they operate and market. Additional information can also be provided by the supplier on a voluntary basis, such as the concentration in the fragrance mixture or the finished consumer product of the ingredients subject to IFRA Standards being part of the fragrance mixture.

IFRA classes were used in the past to define the group of consumer products for which the fragrance mixture can be used at the MAC level determined by the Certificate of Conformity. Such classes are considered systemic toxicity and phototoxicity considerations. As of the 49th Amendment, IFRA Categories already consider skin sensitization, systemic toxicity and phototoxicity considerations. Consequently, the nomenclature of ‘classes’ becomes obsolete, as they already match with the IFRA categories (see also Table 11). The Certificate of Conformity is a document established by the fragrance mixture manufacturer and based on a trusting relationship between the fragrance supplier and its customer (fragrance supplier or finished product manufacturer). IFRA is not involved in its preparation and takes on no responsibility with respect to the content or format of any such Certificate of Conformity.

Figure 5 provides an example of a Certificate of Conformity. This template is also available at the IFRA website:

https://ifrafragrance.org/docs/default-source/ifra-code-of-practice-and-standards/ifra-certificate-template/certificate-of-conformity-to-ifra-standards-template-december-12-2019.doc?sfvrsn=20664815_2

The previous information letter on Certificates of Conformity (IL768) is becoming obsolete and the information is replaced by what is contained in this Guidance for the use of IFRA Standards. Relevant information on the role of Certificates can be found in IL896.

Figure 5: Example of Certificate of Conformity of fragrance mixtures with IFRA Standards.

[Logo of the CERTIFYING PARTY]

CERTIFICATE OF CONFORMITY OF FRAGRANCE MIXTURES WITH IFRA STANDARDS

This Certificate assesses the conformity of a fragrance mixture with IFRA Standards and provides restrictions for use as necessary. It is based only on those materials subject to IFRA Standards for the toxicity endpoint(s) described in each Standard.

CERTIFYING PARTY:
Name of the fragrance supplier delivering the certificate
Address of the fragrance supplier

CERTIFICATE DELIVERED TO:
Customer: Name of the fragrance supplier or finished product manufacturer

SCOPE OF THE CERTIFICATE:
Product: Name of the product/fragrance mixture

COMPULSORY INFORMATION:

We certify that the above mixture is in compliance with the Standards of the INTERNATIONAL FRAGRANCE ASSOCIATION (IFRA), up to and including the xx Amendment to the IFRA Standards (published *Month, Year*), provided it is used in the following category(ies) at a maximum concentration level of:

IFRA Category(ies) [see Table 12 in Guidance for the use of IFRA Standards for details]	Level of use (%)*
Category 4	***12%***
Category 5.C	***2.1%***

**Actual use level or maximum use level*

For other kinds of application or use at higher concentration levels, a new evaluation may be needed; please contact (name of the fragrance supplier).

(OPTIONAL INFORMATION):

Information about presence and concentration of fragrance ingredients subject to IFRA Standards in the fragrance mixture (name of the product) is as follows:

Materials under the scope of IFRA Standards:	CAS number(s):	Recommendation from IFRA Standard:	Concentration (%) in fragrance mixture or finished product:
trans-2-Hexenal (example)	*6728-26-3 (example)*	*Restriction (example)*	*to be completed*
Citral (example)	*5392-40-5 (example)*	*Restriction (example)*	*to be completed*
……...	……...	……...	*to be completed*

Disclaimer: This Certificate provides restrictions for use of the specified product based only on those materials restricted by IFRA Standards for the toxicity endpoint(s) described in each Standard. This Certificate does not provide certification of a comprehensive safety assessment of all product constituents. This certificate is the responsibility of the fragrance supplier issuing it. It has not been prepared or endorsed by IFRA in anyway.

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[Logo of the CERTIFYING PARTY]

Materials under the scope of IFRA Standards:	CAS number(s):	Recommendation from IFRA Standard:	Concentration (%) in fragrance mixture or finished product:
Toluene (example)	*108-88-3 (example)*	*Specification: level that should be lower than 100ppm in fragrance mixture (example).*	*to be completed*
Safrole, Isosafrole, Dihydrosafrole (example)	*94-59-7* *120-58-1* *94-58-6 (example)*	*Specification: level should be lower than 0.01% in finished consumer product, only if such level is due to natural contributions containing Safrole, Isosafrole and/or Dihydrosafrole (example).*	*to be completed*

Signature *(If generated electronically, no signature)* Date

Disclaimer: This Certificate provides restrictions for use of the specified product based only on those materials restricted by IFRA Standards for the toxicity endpoint(s) described in each Standard. This Certificate does not provide certification of a comprehensive safety assessment of all product constituents. This certificate is the responsibility of the fragrance supplier issuing it. It has not been prepared or endorsed by IFRA in anyway.

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7. Frequently asked questions

7.1 Why was QRA2 developed?

The QRA approach was initially 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). QRA2 was developed to further refine the QRA process by incorporating:

1. Discussion and refinement of SAFs used in the QRA process. This process involved individual experts from industry and academia as well as independent experts from the fields of dermatology, contact allergy and risk assessment.
2. Aggregate exposure to fragrances from a range of personal and household care products.

This approach, particularly the inclusion of aggregate exposure estimation, is seen as a step-change in the risk assessment of fragrance ingredients and will ensure a more robust process for determining IFRA Standard upper concentration levels.

7.2 Do I have to calculate the NESIL and AELs for each of my fragrance ingredients?

In the context of setting IFRA Standards, NESILs and AELs are already determined by RIFM and approved by the Expert Panel for Fragrance Safety. This information is included in the RIFM safety assessments publicly available. It could happen that the safety assessment of a specific ingredient covered by an IFRA Standard is not yet publicly available on the Fragrance Material Safety Resource website at the time of the consultation. If this is the case, it will be clearly communicate in the documentation distributed with the consultation including information where to get a copy of the final draft safety assessment.

If a company would like to use fragrance ingredients that are not part of the RIFM Safety Assessment process, it remains the responsibility of the company to ensure the safe use of the ingredient. In the case of the skin sensitization endpoint, QRA2 may be used to derive safe use levels.

More details on the scope of the RIFM Safety Assessment program are available at www.rifm.org.

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

While 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 based on additional relevant exposure data becoming available. Such changes would be incorporated into future IFRA Amendments.

7.4 Where can I get help in understanding the QRA approach, including QRA2, and making the appropriate procedural changes?

This Guidance document is the first interface for global fragrance suppliers and users. For more in-depth understanding of the approaches now used, the following documents should be consulted:

QRA1:

Api *et al*., (2008), Dermal sensitization Quantitative Risk Assessment (QRA) for fragrance ingredients. Regulatory Toxicology and Pharmacology, 52; 3-23.

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://rifm.org/publications-sort-title.php and http://www.ifraorg.org/en-us/guidelines/).

QRA2:

Api et al. 2020

IDEA project (International Dialogue for the Evaluation of Allergens) Final Report on the QRA2: Skin Sensitisation Quantitative Risk Assessment for Fragrance Ingredients, September 30, 2016 (http://www.ideaproject.info/uploads/Modules/Documents/qra2-dossier-final--september-2016.pdf).

Refinements of SAFs:

Basketter, D. and Safford B. (2016). Skin sensitization quantitative risk assessment: A review of underlying assumptions. Regul Toxicol Pharmacol. 74; 105-16.

Aggregate exposure:

Comiskey *et al.*, (2015). Novel database for exposure to fragrance ingredients in cosmetics and personal care products. Regulatory Toxicology and Pharmacology. 72(3); 660-72.

Comiskey, *et al.*, (2017). Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regulatory Toxicology and Pharmacology, 88:144-156.

Safford *et al.*, (2017). Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regulatory Toxicology and Pharmacology 86; 148-156.

Safford *et al.*, (2015). Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regulatory toxicology and pharmacology, 72; 673-682.

7.5 Why was the Optimization Tool for systemic toxicity developed?

The total safety profile of a fragrance ingredient must be taken into consideration when deriving acceptable exposure levels.

Most fragrance ingredients are weak or extremely weak sensitizers. As such, the NESIL values will be higher which in turn will result in higher acceptable levels than for stronger sensitizers.

If the material has a safety profile with a lower reference dose, then the acceptable levels derived from the sensitization risk assessment may not be acceptable systemically. As such it is important to compare the acceptable exposure levels from all endpoints. To allow the distribution of safe use levels from a systemic point of view in the context of aggregate exposure, RIFM has developed an approach that is based on the reported exposure of the respective fragrance ingredient. This approach, which is happening through the Creme-RIFM aggregate exposure model, is called the Optimization Tool. Through iteration, this Optimization Tool distributes the acceptable use levels across the different IFRA Categories depending on the exposure reported.

The reported exposure of the respective fragrance ingredient is provided by companies participating in the RIFM concentration of use surveys. Should you like to receive such surveys, please contact RIFM (amapi@rifm.org). Companies' participation in this survey is strongly encouraged to obtain an adequate representation of the current uses of fragrance ingredients (including their contributions from naturals).

For more details on the Optimization Tool, please refer to Sections 4.1.

7.6 Where can I consult the RIFM safety assessments that drive the IFRA Standards?

As explained in Section 2, the RIFM safety assessments are the basis for deriving IFRA Standards as industry self-regulatory risk measures.

The Expert Panel for Fragrance Safety reviews and approves the RIFM safety assessments, which are then made publicly available on the website Fragrance Materials Safety Resource (http://fragrancematerialsafetyresource.elsevier.com/). It could happen that the safety assessment of a specific ingredient covered by an IFRA Standard is not yet publicly available on the Fragrance Material Safety Resource website at the time of the consultation. If this is the case, it will be clearly communicate in the documentation distributed with the consultation including information where to get a copy of the final draft safety assessment.

7.7 How do the IFRA Classes relate to the IFRA Standards categories?

In the past, the IFRA Classes have been established to take into account considerations of all types of IFRA restrictions (skin sensitization, phototoxicity and systemic toxicity) that can apply to ingredients in a fragrance mixture. With the 49th Amendment, a harmonization has been carried out, and the IFRA Standard Categories are identical to the IFRA classes. Therefore, there is no further need to differentiate them and to keep the specific terminology of classes.

The IFRA Categories are summarized in Table 11).

7.8 Why does the QRA2 no longer differentiate between products applied to shaved skin and non-shaved skin?

The first version of the Quantitative Risk Assessment methodology applied by the fragrance industry since 2006 (QRA1) included a specific category for products applied to recently shaved skin (Category 3), specifically to lower cheek and neck skin, the areas where male facial hair removal occurs. As part of the review of the safety assessment factors leading into QRA2, new data were reviewed, and it was concluded that such a differentiation was no longer needed.

Shaving does not cause significant chronic damage or inflammation to the skin in the shave zones. Mechanical irritation, which occurs immediately post-shaving (i.e., acute shaving irritation), the immediate post-shave razor burn, which is often experienced to occur in both the lower cheek and neck is more transient. Increasing shave strokes over a given area of skin can impact the barrier function of the stratum corneum by removing successive cell layers with each razor stroke. Irritation from shaving may produce an acute transient response. Consumer Shaving products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation.

Shaving may or may not affect dermal penetration. If a shaving product is used, then dermal penetration is minimal or even decreased. If no shaving product is used, then dermal penetration may be increased. However, the recent review of the Sensitization Assessment Factors (SAFs) used in the QRA2 shows that the importance of skin penetration is typically greatly overstated for the types of fragrance ingredients that cause skin sensitization. Further, in the QRA2 as with QRA1 it was assumed that the fragrance ingredient would be completely (100%) absorbed in the skin. In the QRA2 SAFs, consideration of substantive levels of inflammation as a co-factor has been considered. As a result, in QRA2, all fine fragrance products including after-shave products, are now covered under one single category (Category 4).

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7.9 What happens if I have a product that is not in an IFRA Category?

Table 11 and Table 12 contain a non-exhaustive illustrative list of consumer products available in the market. Given the diversity and variety of existing consumer products and new types introduced into the market, IFRA cannot provide a detailed list of product categorization for all consumer products.

It is recommended that the fragrance supplier and the customer company consult on the appropriate category for consumer products that are not included in any of the IFRA Categories.

If a stakeholder wishes a product type to be officially included in the IFRA Standard Categories (and therefore in this Guidance), it requires the engagement of the QRA Expert Group. It is indispensable that a detailed dataset (including exposure information) is provided to allow the QRA Expert Group to decide on the categorization of the product. The data form can be downloaded from the IFRA website[7] and should be sent to RIFM (rifm@rifm.org) with copy to IFRA (mvey@ifrafragrance.org).

7.10 Are any other oral care products included in IFRA Category 6?

Mouthwash and toothpaste are the principal oral care products currently identified in the respective category. Other oral care products like toothpowder, strips, and mouthwash tablets are also in scope.

Other oral care products such as 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.

Exposure limits for mouthwash and toothpaste resulting from the QRA process are established to reduce the risk of peri-oral skin sensitization. Regarding systemic exposure based on incidental ingestion, only the use of the ingredient from oral care products is considered (i.e., concomitant use as a flavor ingredient in foods is not considered).

[7] https://ifrafragrance.org/docs/default-source/ifra-code-of-practice-and-standards/background-scientific-information-and-guidelines/qra-data-categorization-form.pdf?sfvrsn=f47ca8fd_0

7.11 How are naturals covered by the IFRA Standards and what is the role of Annex on contributions from other sources?

Annex on contributions from other sources to the IFRA Standards provides indicative levels of restricted substances in a non-exhaustive list of various fragrance ingredients of complex composition, including essential oils. The IFRA NCS TF is in charge of agreeing on the typical levels of constituents in Natural Complex Substances (NCSs) representative of the current market.

These typical levels should be considered when determining the compliance of a fragrance mixture under its conditions of use. However, if the company is in possession of detailed analytical data for the specific quality of NCS that will be part of the mixture, this data can be used instead of the typical levels provided in the Annex on contributions from other sources.

Additionally, some natural substances have their own IFRA Standard. In this case, the Standard on the natural substance itself as well as the IFRA Standards applicable to its constituents should be applied.

7.12 How do I determine a safe use level for an NCS?

Two cases can apply regarding NCS:

- An NCS is part of the fragrance mixture and this NCS contains constituents that are covered by IFRA Standards.

The company should know at which concentration the constituents covered by an IFRA Standard are present in the NCS. This information is provided by Annex on contributions from other sources or by analytical data derived by the company. Once the respective concentrations are known, the company should calculate the maximum allowed the use of NCS in the finished consumer product (and consequently in the fragrance mixture) to ensure that the concentration of constituents in the finished consumer product does not exceed the upper concentration levels established by the IFRA Standards, for a specific IFRA Category.

For example, a customer has requested a perfumer to create a fragrance mixture intended to be used in a fine fragrance at 20%. The perfumer would like to use Hay absolute as a fragrance ingredient in this mixture. Annex on contributions from other sources reports the presence of 8% Coumarin in Hay absolute. Coumarin can be used at a maximum use level of 1.3% in Category 4.

As there is a dilution factor of 5, the total amount of Coumarin in the fragrance mixture should not exceed 6.5% to reach such a level (assuming there are no other sources of Coumarin in the mixture), the concentration of Hay absolute in the mixture should be lower than 16.25%.

In this example, the NCS only contains one constituent covered by an IFRA Standard. If more than one constituent is covered by an IFRA Standard, this exercise should be repeated for each of them. The lowest resulting maximum permitted use level of the NCS will drive its use in the mixture.

- An NCS is covered by an IFRA Standard (e.g. Ylang ylang).

In this case, there are two restrictions to consider: the one resulting from the constituent approach and the one resulting from the NCS itself. Both need to be compared, and the lowest one will drive the maximum allowed use of the NCS in the fragrance mixture.

7.13 How do I apply the IFRA policy of Furocoumarins?

The IFRA Standards on phototoxic ingredients have been set based on:

- The phototoxicity potential of the fragrance ingredient itself (Table 2).

- The phototoxicity potential of furocoumarins present in certain NCS (Table 3).

The IFRA policy on Furocoumarins only applies to the fragrance ingredients listed in Table 2 of this Guidance and only for those finished consumer product applications that are exposed to the sunlight (see Table 11).

For such fragrance ingredients (individually or in combination), the total amount of the furocoumarin marker 5-MOP (this can come from one or several extracts containing furocoumarins – a non-exhaustive list is provided in the Standard) should not exceed 15ppm. The amount of Furocoumarins can be analytically quantified – IFRA has a method in the guidelines section of the public website.

In case the concentration of 5-MOP is unknown, the upper concentration levels indicated in the individual Standards apply.

Work is ongoing on updating the IFRA policy. For more information, please see the IFRA Information Letter 1050.

7.14 What does the Certificate of Conformity of fragrance mixtures with IFRA Standards mean and what not?

The Certificate of Conformity of fragrance mixtures with IFRA Standards is a document established by the companies creating fragrance mixtures and based on a trusting relationship between the fragrance supplier and its customer. It means that, by using this Certificate, a fragrance supplier assures its customer that the product they supply follows the requirements set by the IFRA Standards for the intended use.

The Certificate of Conformity confirms that a specific fragrance mixture up to a certain concentration can be used in a specified consumer product in compliance with up to and including a specific Amendment to the IFRA Code of Practice (the number and the Notification date of the Amendment should be stated in the Certificate).

The Certificate of Conformity declares compliance with the requirements expressed in the IFRA Standards, it does not replace a safety assessment.

The Safety Assessment reflects the internal expertise of the company with regards to the full safety assessment of all ingredients in the fragrance mixture (i.e., not just those with IFRA Standards). It cannot be issued in the name of IFRA but follows its compliance philosophy as reflected in the IFRA Code of Practice (i.e., all substances used in a fragrance have justification that supports its safe use).

As stated in the IFRA Code of Practice, it is the responsibility of each IFRA member to ensure that the fragrance mixtures or ingredients they supply comply with applicable laws and are safe for their intended uses. Thus, IFRA does not elaborate the Certificates of Conformity and there is no certifying company providing Certificates of Conformity on behalf of IFRA. Every supplier of fragrance mixtures is responsible for establishing and providing an IFRA Certificate of Conformity (template is available on the IFRA website.https://ifrafragrance.org/docs/default-source/ifra-code-of-practice-and-standards/ifra-certificate-template/certificate-of-conformity-to-ifra-standards-template-december-12-2019.doc?sfvrsn=20664815_2).

When there is an IFRA Standard on a raw material (e.g., citrus essential oil), the supplier should not issue an IFRA certificate as such. Instead, suppliers should communicate to their clients the conformity of the raw material with the corresponding IFRA Standard in a different format. It is relevant to note that important information on essential oils that need to be exchanged between supplier and user is about the presence of IFRA-restricted materials in the NCS, as it is relevant for the calculation of the maximum use of the NCS. Indicate information is provided in the IFRA Annex on contributions from other sources (see section 1.4 of this guidance).

7.15 Who can issue a Certificate of Conformity of fragrance mixtures with IFRA Standards?

The Certificate of Conformity is a document established by the fragrance mixture manufacturer and based on a trusting relationship between the fragrance supplier and its customer. IFRA is not involved in its preparation of a Certificate of Conformity of fragrance mixtures with IFRA Standards and takes on no responsibility for the Certificates issued by companies.

The Certificate of Conformity can be issued by anybody who is familiar with the Code of Practice and the associated Standards. It can therefore also be used by **non-members** to declare that they comply with the IFRA Standards.

Computational software solutions from third parties are commercially available to provide support for individuals and companies to issue Certificates of Conformity.

7.16 What is the scope of the Certificate of Conformity of fragrance mixtures with IFRA Standards?

The Certificate of Conformity is only applicable for fragrance ingredients and/or fragrance mixtures intended to be directly included in a finished consumer product. In practice, the Certificate of Conformity is also used by fragrance suppliers to fragrance suppliers for the acquisition of fragrance ingredients and/or bases.

The requirements to comply with the IFRA Standards are less onerous for raw material suppliers compared to fragrance compounders, as most of the Standards restrict the use of ingredients in the finished consumer product. Nevertheless, there are several Standards that establish Specification requirements that apply to individual raw materials.

Raw material suppliers are encouraged to collaborate with the fragrance houses by providing the composition of the essential oil if required by them, particularly for those constituents that have an IFRA Standard. However, if their fragrance ingredients (essential oils) are used as such in the final consumer product, the supplier should ensure that the NCS's constituents which have an IFRA Standard do not exceed the concentration limit in the finished consumer product established by the Standard. For this purpose, the raw material supplier can use its own analytical data or use the data provided in the Annex on contributions from other sources as approximative concentration information.

7.17 How to establish the level of use of a fragrance mixture intended to be used in different applications?

If a finished consumer product is marketed for applications that cross several uses, the most stringent restriction should apply.

7.18 Are products in compliance with IFRA Standards safe for pets?

The target of the RIFM Safety Assessments is humans and their safety while handling the finished consumer products. Some finished products applied to pets are listed in Table 11 (page 43), being covered by the IFRA Standards (animal sprays or shampoos). However, the categorization of such products only relates to the human exposure during the application of such products, not to the exposure of the product the pet. Therefore, the assessment of the safety of such finished consumer products regarding to animals is outside the scope of IFRA/RIFM and is the responsibility of the manufacturer.

7.19 Why it is not possible to find an IFRA category for some product applications?

A list of IFRA categories is available in Table 11 and Table 12 of this guidance. The list of product types provided in the guidance is illustrative and can help companies to make their decision on where to place product types that are not listed.

If you cannot categorize your specific product in any of those categories, please inform IFRA or RIFM to send an IFRA-RIFM categorization form to fill in to try to provide a suitable IFRA category for that product.

The form can be found IFRA website: Data Needed for IFRA QRA Categorization of a New Product Type or To Review an Existing Product Categorization (ifrafragrance.org).

7.20 What does it mean a "substantial amount of" on the IFRA Standard specifications "natural products containing substantial amounts of linalool/limonene" (depending on the corresponding IFRA Standard)?

We did not consider being in a position to define a specific cut off representative for all kinds of NCS, as it is difficult to establish and, not only depends on the amount of linalool or limonene in the NCS, but also on its general susceptibility to oxidize, which itself depends on various factors. Therefore, companies should understand their portfolio and, based on information from their suppliers or on their own measurement of peroxide values, they should be in the best position to understand which NCS need careful quality control.

8. Abbreviations

AEL	Acceptable Exposure Level
AISE	International Association for Soaps, Detergents and Maintenance Products
AWG	IFRA Analytical Working Group
CEL	Consumer Exposure Level
CoP	Code of Practice
DST	Dermal Sensitization Threshold
EdT	Eau de Toilette
EFSA	European Food Safety Authority
ETC	IFRA Executive Technical Committee
EU	European Union
FAQ	Frequently Asked Question
FDA	US Food and Drug Administration
FEMA	US Flavor and Extract Manufacturers Association
FSC	Food Safety Commission of Japan
GRAS	Generally Recognized As Safe
IDEA	International Dialogue for Evaluation of Allergens
IFRA	International Fragrance Association
IOFI	International Organization of the Flavor Industry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MAC	Maximum Acceptable Concentration
NA	Not applicable
NCS	Natural Complex Substance
NCS TF	IFRA Natural Complex Substances Task Force
NESIL	No Expected Sensitization Induction Level
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
OECD	Organization for Economic Co-operation and Development
OTC	Over the Counter
PBT	Persistent, Bioaccumulative, Toxic
PCPC	US Personal Care Products Council
PEC	Predicted Environmental Concentration
PNEC	Predicted No Effect Concentration
QRA	Quantitative Risk Assessment
QSAR	Quantitative Structure–Activity Relationship
REACH	Registration, Evaluation, Authorization of Chemicals

RfD	Reference Dose
RIFM	Research Institute for Fragrance Materials
RMTF	IFRA Risk Management Task Force
RQ	Risk quotient
SAF	Sensitization Assessment Factor
SAM	Skin Absorption Model
SOP	Standard Operating Procedure
TTC	Threshold of Toxicological Concern
VoU	Volume of Use
vPvB	Very Persistent, very Bioaccumulative
WoE	Weight of Evidence

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