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Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials

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ABSTRACT

In 2008, a proposal for assessing the risk of induction of skin sensitization to fragrance materials Quantitative Risk Assessment 1 (QRA1) was published. This was implemented for setting maximum limits for fragrance materials in consumer products. However, there was no formal validation or empirical verification after implementation. Additionally, concerns remained that QRA1 did not incorporate aggregate exposure from multiple product use and included assumptions, e.g. safety assessment factors (SAFs), that had not been critically reviewed. Accordingly, a review was undertaken, including detailed re-evaluation of each SAF together with development of an approach for estimating aggregate exposure of the skin to a potential fragrance allergen. This revision of QRA1, termed QRA2, provides an improved method for establishing safe levels for sensitizing fragrance materials in multiple products to limit the risk of induction of contact allergy. The use of alternative non-animal methods is not within the scope of this paper. Ultimately, only longitudinal clinical studies can verify the utility of QRA2 as a tool for the prevention of contact allergy to fragrance materials.

1. Introduction

Contact allergy to fragrance materials[1] is a topic of considerable interest for consumers, clinicians, industry and regulatory authorities. Mixtures of fragrance materials are used in a wide variety of consumer products at varying levels, leading to a wide range of exposures. Some of these fragrance materials have been identified as contact allergens and

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[1] The term "fragrance materials" is used throughout to designate chemically defined substances and complex mixtures such as botanical isolates that are used primarily for imparting odour.

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Abbreviations:

AEL:	Acceptable Exposure Level (quantity/unit skin area)
CEL:	Consumer Exposure Level - estimation of upper-level consumer exposure to individual perfumed products (quantity/unit skin area)
CEL_{agg}	Aggregate Consumer Exposure Level for a specific skin site
HRIPT	Human Repeat Insult Patch Test
IDEA	International Dialogue for the Evaluation of Allergens, www.ideaproject.info
LLNA	Local Lymph Nodes Assay
NESIL:	No Expected Sensitization Induction Level (expressed as the quantity of allergen in ug/cm^2 area of skin exposed)
QRA	Quantitative risk assessment (for dermal sensitization)
QRA1	Dermal sensitization quantitative risk assessment for fragrance materials (first version - Api et al., 2008)
QRA2	This revised version of the QRA for fragrance materials
SAF	Sensitization Assessment Factor
SCCP	Scientific Committee on Consumer Products
SCCS	Scientific Committee on Consumer Safety (successor to SCCP)
$UCL_{product}$	Upper concentration level in product

they express varying degrees of sensitizing potency. These potency differences, the demonstration of induction dose responses and the determination of induction thresholds have been explored in a number of publications. The concept of a risk assessment approach for the induction of skin sensitization has been described previously (Farage et al., 2003; Felter et al., 2002, 2003; Gerberick et al., 2001; Griem et al., 2003). In 2008, a first methodological scheme, herein referred to as QRA1, for the skin sensitization quantitative risk assessment of fragrance materials was published and subsequently implemented (Api et al., 2008; Api and Vey, 2008). However, there was no formal validation of the methodology or empirical verification after this implementation, but to place this in context, it should be noted that validation of any risk assessment process is particularly difficult.

The European Commission's Scientific Committee on Consumer Safety (SCCS) critiqued QRA1 and identified opportunities for important improvements in QRA1 such as refined exposure data, inclusion of aggregate exposure to multiple consumer products and re-examination and refinement of the Sensitization Assessment Factors (SAFs) (SCCP, 2008; SCCS, 2017, 2018b). These areas were subsequently explored and developed further in a series of workshops held as part of the IDEA project (International Dialogue for the Evaluation of Allergens, www.ideaproject.info). The workshops involved dermatologists, academics, technical representatives from industry and included observers and participants from the European Commission and its expert committees (IDEA) ((IDEA, 2013; 2014a; 2014b). The workshops also considered information from a recent literature review (e.g. Ter Burg et al., 2010). Concurrently, the scientific basis of QRA1 was critically reviewed, with proposals for revisions to be made to the uncertainty factors (i.e. the SAFs) (Basketter and Safford, 2016). Draft revisions of QRA1 were sent to the US Food and Drug Administration, European Commission, the SCCS and the EU Joint Research Centre and their suggested improvements were utilized in developing further the QRA2 (SCCS 2017; SCCS 2018b).

In the material that follows, the updating of the original QRA SAFs is presented alongside a detailed description of the revisions to exposure assessment. For clarity, a worked example of the implementation of QRA2 is given. Finally, some remaining challenges and uncertainties are discussed.

2. QRA2 methodology for fragrance materials

2.1. General principles of risk assessment and its applicability to skin sensitization

At the outset, it is important to note that QRA2 does not apply where there is no skin sensitization hazard and/or proposed levels of use of a fragrance material result in exposures that are below the Dermal Sensitization Threshold (DST)and thus will not be discussed further (e.g. Api et al., 2015). The DST was established below which there is no appreciable risk of sensitization, which precludes the need for sensitization testing of ingredients where dermal exposure is sufficiently low (Safford, 2008; Safford et al., 2011, 2015;Roberts et al., 2015). That said, the general methodology proposed in QRA2 (see Fig. 1) is consistent with other areas of toxicological risk assessment, where the aim is to avoid the expression of toxicity, such that it is not necessary to deal with its subsequent consequences. The wider approach to toxicological risk assessment has been outlined in many publications and is typically applied for identification and characterization of systemic health endpoints (for instance WHO, 2004; ECHA, 2012; ECETOC, 2009). The general principles of risk assessment have also been applied to induction of skin sensitization, itself a systemic endpoint (Robinson et al., 2000). These principles were described in a series of papers and then adapted specifically to fragrance materials (Gerberick et al., 2001; Felter et al., 2002, 2003; Farage et al., 2003; Griem et al., 2003; Api et al., 2008).

2.2. Purpose of QRA2

In keeping with the earlier QRA1, QRA2, addresses the risk of induction of skin sensitization; it is not designed to address the elicitation of an allergic response in subjects already sensitized. The general toxicological principles of quantitative risk assessment can be applied to sensitization, since it is known that the induction of dermal sensitization is also a threshold based phenomenon (Kimber et al., 1999; Robinson et al., 2000). Identifying the maximum exposure levels and ensuring they are not exceeded enables control of the risk of induction, which ultimately also controls the risk of elicitation. It is recognized that the elicitation process is complex, depending not only on the intrinsic potency of the sensitizer, but also on the susceptibility of the exposed individual and on the nature of the circumstances that led to sensitization (Hostynek and Maibach, 2004; Friedmann, 2007). Furthermore, in some cases, contact allergies may remain sub-clinical, not being manifested as allergic contact dermatitis throughout the lifetime of the subject (Hostynek and Maibach, 2004; Mortz et al., 2013).

2.3. Key stages in QRA2

The key stages described in QRA2 are equivalent to those in the original QRA (Api et al., 2008):

- Derivation of the NESIL: the starting point of departure for QRA2, termed the No Expected Sensitization Induction Level (NESIL) of the potential allergen (and equivalent to an induction maximum no observed adverse effect level in a 100 subject HRIPT (Politano and Api, 2008).
- SAFs: application of the SAFs to account for uncertainties in determining the NESIL; SAFs are derived for a product type and not for a fragrance material. The SAFs include assessment of inter-individual variability, consideration of product composition, frequency/duration of use, and skin condition (related to the skin site(s) where a product would be used).
- Determination of the Acceptable Exposure Level (AEL) calculated from the NESIL and the applied SAFs (i.e. AEL = NESIL/Total SAFs).
- Estimation of upper-level of aggregate consumer exposure to the fragrance material in perfume-containing product (Consumer Exposure Level - CEL).

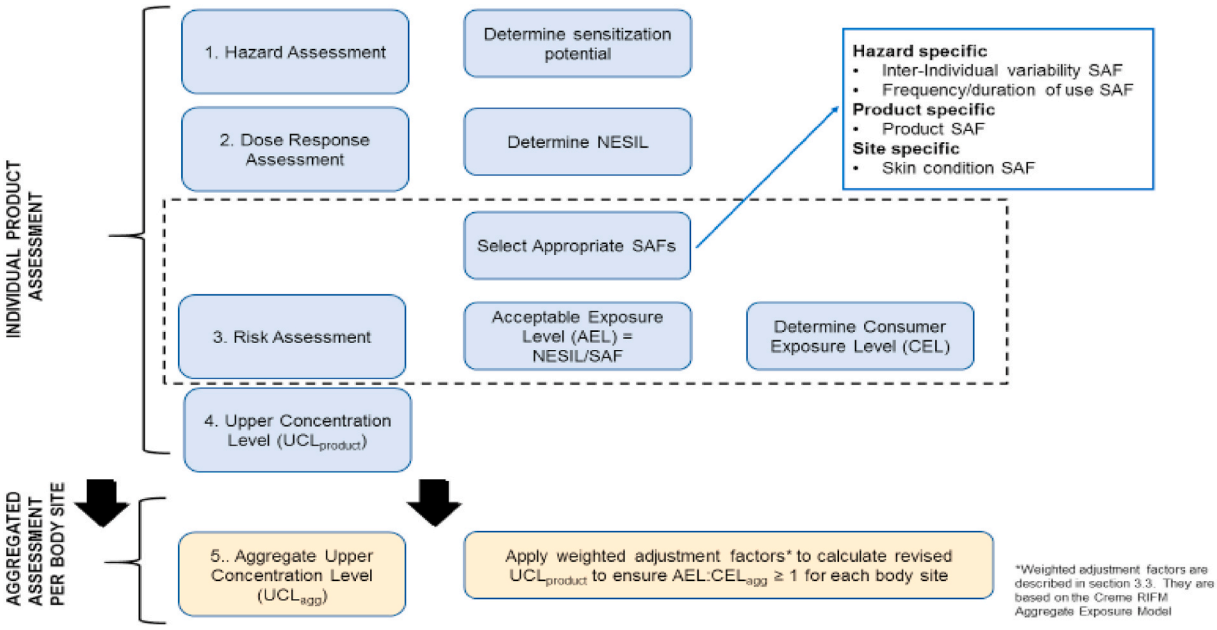

Fig. 1. Summary of QRA2 process.

- Comparison of AEL with CEL.

In subsequent paragraphs, the SAF and exposure stages of QRA2 will be discussed in more detail, with particular consideration given to the newer elements which distinguish it from the original version of skin sensitization QRA (QRA1).

2.3.1. *Derivation of a No Expected Sensitization Induction Level (NESIL)*

The starting point of QRA2, often referred to as the point of departure for the risk assessment of a potential fragrance allergen, as was the case with QRA1, remains the NESIL (Api et al., 2008). The NESIL employed in QRA2 is derived in much the same manner as before (Api et al., 2008). In the derivation of a NESIL, all available data are taken into consideration including all historical data as well as data generated from newer models (e.g. in chemico and in vitro assays). In this context it is to be noted that the existing data from the HRIPT as performed by RIFM play an important role in the derivation of the NESIL. It is realized that in many regions, specifically in Europe human volunteer testing of substances such as fragrance material is deemed unacceptable and new HRIPT data will no longer be accepted.

Although it is beyond the scope of this paper to provide a detailed practical guide on deriving the NESIL, it should be noted that extrapolation of all *in silico*, *in chemico*, *in vivo (animal),* and in vitro data to the human population requires careful consideration of uncertainties such as the need for intraspecies extrapolation or the accommodation of the possibility that a fragrance allergen constitutes a pre- or pro-hapten. Importantly, the elaboration and implementation of non-animal methods is currently in a state of active development and change and adjustment of non-animal data to derive a NESIL needs to be evaluated on a case-by-case basis. The use of such methods for NESIL determination will form the core of a subsequent complementary review paper, which will also consider the potential impact on elements of the QRA2 as presented e.g. on the SAFs. However, as an illustration, some of the potential data sources that may contribute to the NESIL derivation are shown in Fig. 2.

Once the NESIL has been established, it is subject to several SAFs to accommodate various areas of uncertainty. Accordingly, these SAFs will each be discussed in turn.

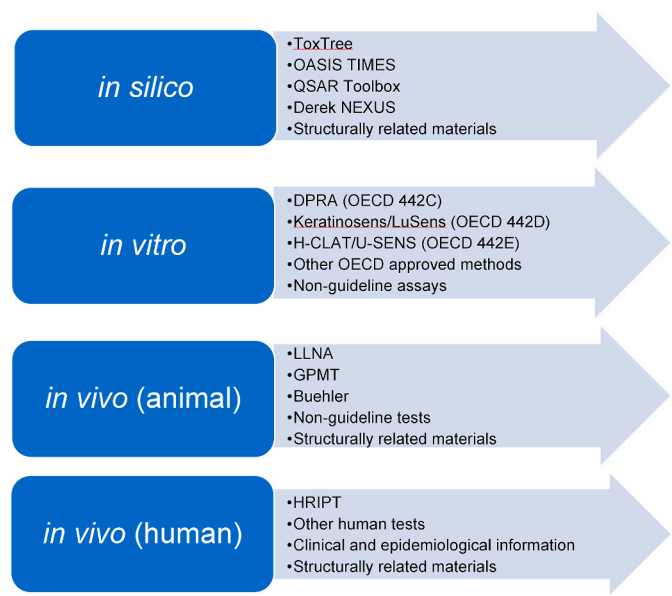

Fig. 2. Information sources that may be used in the derivation of a NESIL.

2.3.2. *Sensitization Assessment Factors (SAFs) for fragrance materials*

Extrapolation/uncertainty factors are commonly used in the QRA process (Api et al., 2008; ECHA, 2012). It is important to recognize that SAFs are specific to product types and are, therefore, the same for all fragrance allergens that are evaluated. Composite SAFs (that include a default intraspecies SAF) are the same for all fragrance materials within a product type group. This is because the default intraspecies SAF does not vary, fragrance specific uncertainties are incorporated into the NESIL and the remainder of the SAF components are based on product category specific use considerations. A detailed explanation of the SAFs originally used in QRA1 and the scientific literature used to support the decisions assigning the SAFs was provided (Api et al., 2008). Since then, publications with new data have become available and a full review of the underlying assumptions and the scientific basis for the selection of values for the SAFs has been published (Basketter and Safford, 2016. This review of the underlying assumptions, followed by extensive

discussion at IDEA workshops, has led to an updated and extended attribution of SAFs, summarized in Table 1.

Table 2 provides a summary of overall SAFs for categories containing an extensive number of consumer products containing fragrance materials. The rationale for selection is set out later in the paper. The SAFs should be reviewed again when using QRA for other types of skin sensitizing chemicals (e.g. preservatives, dyes, etc.).

2.3.2.1. Inter-individual variability. The uncertainty factor or SAF for inter-individual variability allows for additional variations in the sensitivity of individuals within the human population compared to the sample of approximately 100 subjects in a HRIPT conforming to RIFM guidelines (Politano and Api, 2008; Basketter and Safford, 2016). Some variables in the human population may favor susceptibility to induction of skin sensitization. For example, genetic effects, sensitive subpopulations (including poly-sensitized individuals) and the condition of the skin have been shown to be more influential than age, sex, ethnicity and most pre-existing disease states (Basketter and Safford, 2016; Api et al., 2008; Felter et al., 2002; Robinson, 1999). However, there is good evidence suggesting that subjects with common diseased skin types (e.g. atopic eczema, psoriasis) are not more predisposed to the induction of contact allergy (Basketter and Safford, 2016. Nevertheless, it is important to note that QRA2 is not intended to cover products used in the context of medicaments applied to chronic eczematous conditions or other skin conditions such as stasis dermatitis.

There are data showing that children are not more susceptible to the induction of skin sensitization than adults (Cassimos et al., 1980; Epstein, 1961). Indeed, young children are less sensitive, such that a risk assessment for adults is a conservative substitute for children. A review found that the risk of sensitization appears to increase a little with age, although this may be confounded by an increase in exposure with age (Militello et al., 2006). Recent reviews argue that an assessment factor of 10 should adequately cover inter-individual variability in the general population for induction of sensitization and is also protective for infants and children, but may not be adequate to protect 'at risk' groups yet to be fully characterized (Basketter and Safford, 2016; Felter et al., 2018).

2.3.2.2. Product composition. The ability of the chemical composition of certain product matrices to enhance the induction process has also been examined. Previously overlooked data reviewed indicate that enhancement of penetration through the epidermis does not necessarily enhance the induction of sensitization (Basketter and Safford, 2016). The balance of the available data does not indicate that there is any substantial synergistic outcome when allergens are combined, the reality being that combined effects are additive (e.g. McLelland and Shuster, 1990; Johansen et al., 1998; Jowsey et al., 2008; Kleinhuis et al., 2015). It must be borne in mind that much of the available evidence derives from studies (either of induction or elicitation) using skin sensitizing doses close to the threshold of detection of an allergic effect in order to maximize the chance of seeing any synergy. Nevertheless, it has to be taken into account that the presence of inflammatory danger signals (Gilmour et al., 2019), e.g. released by irritants or concomitant allergen application, will have the potential to increase the allergic response to individual skin sensitizers (e.g. Kligman, 1966; Cumberbatch et al., 1993; McFadden and Basketter, 2000). Results in mice of an enhanced, even synergistic, inflammatory response to the application of multiple allergens are not inconsistent with these observations, in that the effects observed though strictly greater than additive are far from logarithmic (Johansen et al., 1998; Bonefeld et al., 2011).

The standard vehicle used in the HRIPTs for fragrance materials is a mixture of diethyl phthalate and ethanol, which is known to be optimal for the induction of sensitization in the local lymph node assay (Lalko et al., 2004; Politano and Api, 2008). The diethyl phthalate and ethanol combination in use by RIFM was selected because the majority of fragrance materials are soluble in this combination and it is representative of the matrix often used in commercial products Politano and Api, 2008). Thus, for products based on these or similar solvents, a factor of 1 is considered appropriate to account for the composition effects. For aqueous products, the same factor of 1 is applied even though it is a sub-optimal vehicle in the LLNA. For solid matrices such as talc or residues on clothing, the allergen could migrate from the solid substrate to

Table 2
QRA2 product categories.

QRA2 category	Overall SAF[1]
1 – Products applied to the lips	100
2 – Products applied to the axillae	300
3 – Products applied to the face using finger tips	100
4 – Fine fragrance products	100
5 – Products applied to the face and body using the hands (palms), primarily leave-on	100
6 – Products with oral and lip exposure	100
7 – Products applied to the hair with some hand contact	30
8 – Products with significant anogenital exposure[2]	300
9 – Products with body and hand exposure, primarily rinse-off	300
10 – Household care products with mostly hand contact	100
11 – Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate[2]	300
12 – Products not intended for direct skin contact, minimal or insignificant transfer to skin (e.g. fragranced candles)	Not Restricted

[1]See Table 1 for individual contributing SAFs.

Table 1
Summary of SAF values for QRA2 (adapted from Basketter and Safford, 2016).

Factor	Consideration	Influence	SAFs*	Comments (comparison of the experimental condition with the product use condition).
Inter-individual	There can be large differences between individuals in response to a chemical exposure due to several different parameters.	Increase of susceptibility to induction	10	The inter-individual variability not accommodated in the NESIL requires a SAF of 10.
Product composition	Role of constituents of the product	Enhancement of induction	0.3 or 1 or 3	The predicted effect of product formulation versus the experimental conditions; 0.3 (inert objects with no direct contact, e.g. candles or detergent pods or no vehicle/matrix) or 1 (most products) or 3 (increased irritation)
Frequency/ duration of product use	Products may be used over extended periods resulting in bio-accumulation	Increase of susceptibility to induction	1 or 3	Products may be used frequently over extended periods of time resulting in accumulation (chemical or biological accumulation) or reservoir effect.
Skin site condition	Inflammation	Increase of susceptibility to induction	1 or 3 or 10	Inflammation for body site: body areas that are specifically prone to increased level of inflammation such as contribution to inflammation from use of the product itself or of other products to the body site (such as use of depilatories on axillae and legs).

*Values of 0.1, 0.3, 1, 3, 10, 30, 100 and 300 are used such that when multiplying SAF values, 3 is treated as an integer when multiplied with 1, 10, 100 to give 3, 30, 300; when multiplied by itself it is taken as $\sqrt{10}$ (approx. 3.16) such that $3 \times 3 = 10$.

sweat and sebum on the skin, which, due to its oily nature, would justify a factor of 1 being used.

A SAF of either 0.3 or 1 or 3 could be used on a case by case basis (e.g. 0.3 for objects with no direct contact such as candles or detergent pods). Although this SAF will be 1 for all products evaluated in this paper, a SAF of 3 is retained for special cases where the risk evaluator judges that the product contains strong irritants or other substances of established potential for enhancing induction that exceed the considerations included in the category default SAFs.

2.3.2.3. Occlusion. Full occlusion of the skin where the area of application is impermeably covered, results in multiple effects, including increases in the hydration of the stratum corneum, increases in skin temperature, microbial count, pH, and increased susceptibility to dermal irritation. The overall effect of full occlusion has been shown to enhance sensitization (Basketter and Safford, 2016). The HRIPT as practiced by RIFM, employs a series of 24-h exposures under full occlusion (Politano and Api, 2008). Typically, exposures to fragrance materials in consumer products involve at most only partial occlusion to a much lower degree than occurs in the HRIPT.

Experimental data indicate that the potential for induction of sensitization from partially occluded or non-occluded exposures may be lower than from full occlusion (Basketter and Safford, 2016). However, as a conservative approach, the worst-case experimental conditions (full occlusion) applied to all exposure situations and no correction (i.e. using a SAF smaller than 1) has been introduced for non-occluded exposures. For this reason, occlusion does not appear as a separate SAF in Table 1, nor in the example that follows later in this paper.

2.3.2.4. Frequency/duration. With regard to the period/frequency of exposure, it is recognized that many products will be used on a daily basis over extended periods of time (months, years). The exposure regimen involved in RIFM's HRIPT involves nine 24-h exposures over a 3-week period, and whether this is an adequate simulation of longer-term use must be addressed (Basketter and Safford, 2016). There is limited experimental evidence to show that sensitization may be increased when the normal dosing regimens of predictive tests are extended over longer periods. A prolonged LLNA (13 open applications over 57 days) was found to be more effective at induction than the standard conditions involving 3 applications over 3 days producing an average of a 2.65-fold increase in stimulation indices in 8 separate studies (DeJong et al., 2007). The exposure regimen of the HRIPT is, of course, intermediate in the time and frequency to the two extremes used in this LLNA study. Therefore, a frequency/duration SAF of 3 are considered to cover adequately higher use frequency and longer-term exposure from consumer products compared to experimental studies.

2.3.2.5. Skin site condition. There is little evidence from the scientific literature that particular skin areas of the body are inherently more prone to the induction of skin sensitization than others (Basketter and Safford, 2016). However, the presence of compromised/inflamed skin may have an effect although deeper damage may also increase the rate at which the allergen passes through the epidermis where the key cellular processes of induction occur, to be completely bypassed. There is little evidence that compromising the skin barrier by physical or chemical means, in the absence of inflammatory danger signals (Gilmour et al., 2019), significantly increases the potential for the induction of sensitization (Basketter and Safford, 2016); the review also noted that a predisposition of different skin sites to irritant contact dermatitis that may enhance induction (e.g. intimate regions and axillae). Ultimately, it was concluded that a SAF of 1, 3 or 10 should be assigned based on the use of products on skin sites that have different susceptibilities to inflammation.

2.3.3. Assigning SAFs to different products

The total SAF for a specific cosmetic or household product is calculated by multiplying the factors assigned to account for inter-individual variability, product effects, frequency of exposure and skin condition SAFs. A complete list of consumer products listed with their individual and total SAFs is given in a Table in the supplementary data/information. It details the values assigned to each of the components of the total SAF for fragrance materials in a non-exhaustive range of product types. A rationale is provided for the attribution of the product composition and skin condition SAFs.

2.3.4. Determination of the Acceptable Exposure Level (AEL)

The AEL value is determined simply by applying, as a divisor, the accumulated SAFs from Table 2 to the figure that has been determined as the NESIL for the skin sensitizer under consideration. The AEL can then be compared to the level to which consumers may be exposed (the CEL). To define the CEL, it is necessary to carry out an exposure assessment, the details of which follow.

3. Exposure assessment

The Consumer Exposure Level (CEL) (expressed as quantity of substance/unit area of exposed skin) was an essential element of QRA1 and has been subjected to important enhancement for QRA2. Consumer exposure occurring under intended and foreseeable conditions of use, but not deliberate misuse, is addressed. It includes parameters such as frequency, use practices (e.g. how a consumer actually uses the product), duration of use, amount of product used per application/use, co-use with other products and the level of fragrance in product. The ultimate output, termed the Consumer Exposure Level (CEL_{agg}), is the aggregated daily exposure which is compared to the AEL mentioned above. This value is inextricably linked with individual product concentrations, such that for QRA2 purposes there is a primary need to derive an upper concentration limit (UCL) for each product from which aggregate exposure can then be derived. Understanding the complex interplay between these entities is at the core of the proactive establishment of safe exposure levels.

3.1. Consumer aggregate exposure model (Creme RIFM exposure model)

Consumers generally use several products each day, and some of these will be applied to the same skin site. If the same fragrance material is used in each of these products, then it becomes important to consider aggregating exposure from each product on the same body site. A special feature of QRA2 has been the introduction of aggregate exposure into the risk assessment methodology. Deterministic calculations that simply accumulate exposures from all product usage scenarios are considered to provide unrealistic estimates since:

- Consumers are unlikely to use all products under consideration, and even less likely to use them all, together, on a daily basis.
- Consumers do not use the same amounts of each of the products.
- The ingredient will not be included in products at the same concentration; some products will not include the ingredient at all.

Probabilistic modeling helps overcome these issues since it uses consumer reported habits data and manufacturers' product data, and is,

therefore, considered to be a more accurate, method for estimating aggregate exposure. The use of probabilistic exposure models to assess cosmetics and consumer product exposure is gaining attention (McNamara et al., 2007; Hall et al., 2007, Meek et al., 2011; Vilone et al., 2014; Dimitroulopoulou et al., 2015a,b; Dimitroulopoulou et al., 2015a; Dimitroulopoulou et al., 2015a; Delmaar et al., 2015; Dudzina et al., 2015; Nijkamp et al., 2015; Tozer et al., 2015; Safford et al., 2015; Aylward et al., 2020; Tozer et al., 2019). The general application of probabilistic models to the safety assessment of chemicals is being discussed by regulatory agencies and their acceptance into regulatory frameworks is growing (e.g. USFDA, 2006; OECD, 2018; EFSA, 2012, 2019, 2020; AGES, 2019; RIVM, 2015; van der Voet et al., 2015; ECETOC, 2016). Recently, the SCCS have also received and discussed data on the use of probabilistic models for fragrance substances and cosmetics (SCCS 2017; SCCS, 2018a). Models using the Creme Global™ methodology, on which the RIFM fragrance model is based, are being used by the United States Environmental Protection Agency (US EPA caresng.org) and the Food Safety Authority of Ireland (FSAI) in their food safety risk analyses (FSAI, 2016).

In 2010 a fragrance model was developed to estimate the aggregate dermal and systemic exposure to fragrance materials resulting from the use of consumer products. This model has now been modified for use in QRA2 for dermal sensitization. It was developed using declared detailed habits and practices data from 36,446 panelists across Europe and the United States of America (Kleinstreuer et al., 2018,[2]) (Comiskey et al., 2015, 2017; 2017; Safford et al., 2015, 2017). The model was updated with habits and practices data from more than 42,000 panelists across the two regions (Kienhuis et al., 2015). These habits and practices data are updated every 6–8 years and data on individual fragrance ingredients are updated every 5 years. Each panelist supplied diary data on which cosmetic products were used during the day for seven consecutive days, as well as information on the application sites of most products. The model uses probabilistic (Monte Carlo) simulations to integrate full distributions of data sets, including statistical surveys of amounts used (Tozer et al., 2004; Loretz et al., 2005, 2006, 2008; Hall et al., 2007, 2011). These provide a realistic estimate of aggregate exposure for individuals across a population (Comiskey et al., 2015, 2017; 2017; Safford et al., 2015, 2017).

Statistical distributions of the quantities per use of each product were obtained from separate surveys (Tozer et al., 2004; Loretz et al., 2005, 2006, 2008; Hall et al., 2007, 2011). In this way, information obtained on the amount of product used per application and the distributions of the frequency of use of different products could be probabilistically combined to derive 95th percentile Aggregate Consumer Exposure Levels (CEL_{agg}). Whilst this sounds relatively simple, thought is required to decide which skin sites should have their exposure aggregated.

3.2. Choice of skin sites for exposure aggregation

A set of 18 non-overlapping product application sites covering the entire body, previously established for the Creme RIFM exposure model, was employed in the QRA2 calculations of aggregate dermal exposure - see Table 3. This set was adapted from the list of application sites recorded by participants in a survey of consumer habits and practices (Kantar Database. The criteria for selecting the application sites was that the whole body be covered, that no sites overlap, and that the sites be broad enough usefully to describe the behavior of consumers, but specific enough that exposure in terms of quantity per unit area is not underestimated due to assigning too large a surface area.

Table 3
Body sites used for aggregate exposure calculation.

Body site	Additional definition
Scalp	
Face	Does not include: eyes, lips, mouth, behind ears
Peri-ocular	The eyelid and surrounding skin around the eyes.
Lips	
Inside mouth	Buccal/inside cheek: does not include: lips
Neck	Does not include: behind ears
Behind ears	
Chest	Does not include: axillae, abdomen
Abdomen	Stomach region
Back	Does not include: axillae
Axillae	Under arm region
Arms	Does include: shoulder, forearm, upper arm; Does not include: wrists, hands, palms, axillae
Wrists	
Back of hand	Does not include: palms, wrists
Palms	
Anogenital	
Legs	Does include: buttocks, thighs, calves; Does not include: feet
Feet	

Body skin is divided into separate regions since regional (draining) lymph nodes critical for the acquisition of skin sensitization function largely independently. Thus, where possible, aggregation of exposures to sites served by completely different draining lymph nodes has been avoided (Epstein et al., 1963; Kligman, 1966; Uren et al., 2003; Kimber et al., 2008). For these reasons, the calculation of aggregated exposure is made separately for each of the 18 non-overlapping skin sites listed in Table 3.)

The model's output is dermal exposure expressed as the amount of product and/or fragrance material per skin surface area ($\mu g/cm^2$) for the 18 application sites, derived from the highest product use day for each consumer over a 7-day period. Conservatism includes the assumption that the investigated fragrance material is always present in every consumer product, taking a random selection from the concentration-per-product distribution data provided by the fragrance industry (zero use concentrations are not included thus contributing to the conservatism of the model). The 95th percentile of exposure is used as a standard in many domains of regulatory risk assessment and is considered appropriate in this case, particularly in light of the conservative nature of the Creme RIFM aggregate exposure model.

3.3. Upper concentration limits (UCLs) and the role of weighting

The UCL for each product is the maximum acceptable concentration level for fragrance material in each product based on the potential for inducing dermal sensitization to the fragrance material. QRA2 upper limits for fragrance concentration are established by 1) setting initial fragrance material UCL for each product deterministically (as per QRA1), 2) estimating aggregate exposures at each application site based on those initial levels, and 3) adjusting the UCLs based on those aggregated exposures. The second and third steps are repeated iteratively until AEL/CEL_{agg} levels >1 are established for all application sites. Fig. 3 shows the iterative algorithm, and the following section explains each step in detail.

Initially, the QRA-derived upper use levels for each product were calculated without aggregation, based on the NESIL for the fragrance material, the total SAF for the product type and application site and the high percentile product exposure (Api et al., 2008). Such calculations of

[2] The Creme RIFM Aggregate Exposure model is available via a paid for licence to Creme Global (www.cremeglobal.com). Aggregated concentration data on fragrance materials are available in the model. The model has been published (see particularly Comiskey et al., 2015, 2017; Safford et al., 2015, 2017). The Kantar data are available for interested parties directly from Kantar (http://www.kantarworldpanel.com/global). All other data are freely available.

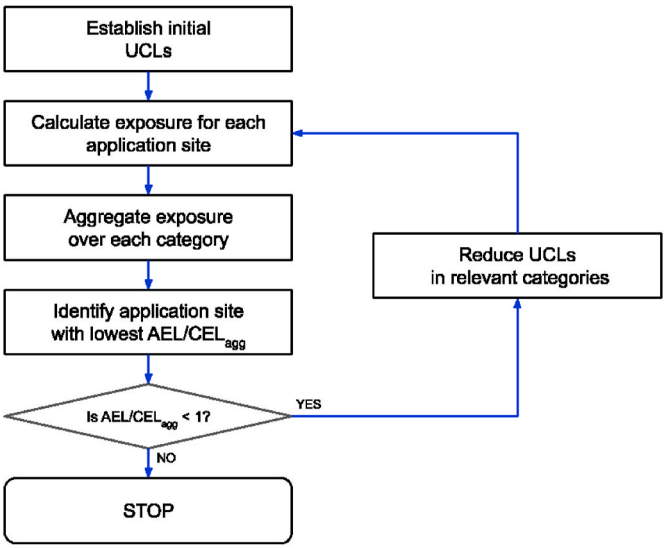

Fig. 3. Schematic illustration of QRA2 UCL calculations.

the upper use level in a given product type used the following formula[3]:

$$Upper\ Concentration\ Level\ (\%) = \frac{NESIL(\mu g/cm^2)}{1,000 \times Total\ SAF \times Exposure\ (mg/cm^2/day)} \times 100$$

Aggregated exposure for all products, at each application site (CEL_{agg}), is estimated using the Creme RIFM exposure model and compared to the AEL for that application site. The key consideration is that CEL_{agg} must be less than the AEL, i.e. where $AEL/CEL_{agg} \geq 1$ for all application sites. Whenever new products are added to the model, calculations including their contributions to the aggregated exposure has to be reconsidered. If the lowest AEL/CEL_{agg} is below 1, the UCL for those product types that the application site is exposed to must be reduced, thereby reducing CEL_{agg}. The reduction is determined as follows: for each product category, estimate the exposure at the application site to the fragrance material aggregated over all products within the category. Then calculate the sum of all these category-level exposures.

$$Category\ Sum = Exposure\ Category_1 + Exposure\ Category_2 + \ldots + Exposure\ Category_n$$

Then for each product category, the exposure for the category is divided by the sum above to obtain a Relative Contribution to the total skin site exposure for the category. This term will have a value in the range (0–1).

$$Relative\ Contribution\ Category_i = \frac{Exposure\ Category_i}{Category\ Sum}$$

A Weighting Factor for each category is calculated by subtracting its Relative Contribution from 1.

$$Weighting\ Factor\ Category_i = 1 - Relative\ Contribution\ Category_i$$

The Weighting Factor is applied to the initial (or current, as the process is iterative) UCL to reduce it and to produce a new UCL.

$$Adjusted\ UCL\ Category_i = Initial\ UCL\ Category_i * Weighting\ Factor\ Category_i$$

Weighting Factors are used to ensure that the UCLs are appropriate and do not exceed the AEL. The nature of the Weighting Factor is such that the UCLs of each category are reduced in proportion to the size of its Relative Contribution. In other words, UCLs of categories with a low contribution to exposure are reduced only a little, while the UCLs of those with a high contribution are reduced much more. The aim is to ensure that the categories most likely to lead to the induction of contact allergy are subject to the greatest reduction in UCL.

At this point, the new UCLs can be tested by re-calculating CEL_{agg} using the Creme/RIFM model and then re-examining AEL/CEL_{agg}. It can happen that the adjustment undershoots or overshoots (i.e. AEL/CEL_{agg} is still below 1 or greatly exceeds 1). In either case the solution is to re-calculate the Weighting Factor by applying a Multiplication Factor to the Relative Contribution of all categories to determine more exact UCLs ($AEL/CEL_{agg} \geq 1$).

$$Weighting\ Factor\ Category_i = 1 - (Relative\ Contribution\ Category_i \times Multiplication\ Factor)$$

where the adjustment has undershot, the Multiplication Factor is assigned a value greater than 1 to amplify the effect of each category's Relative Contribution. Where the adjustment has overshot, the Multiplication Factor is assigned a positive value less than 1 to temper the effect. The particular value assigned is established empirically using iterative calculations. Importantly, no one category is treated differently compared to the other categories, maintaining the principle of applying the most reduction to the UCL of categories with high exposures.

As most products are applied at more than one site, several iterations of checking AEL/CEL_{agg}, identifying the application site with the lowest AEL/CEL_{agg}, and adjusting UCLs may be required before the AEL/CEL_{agg} for all application sites is greater than 1. Thus, a product category's UCL may be adjusted repeatedly. The ratio for each product category of the final UCL divided by the initial UCL provides the QRA2 aggregate adjustment factors.

3.4. Independence of QRA2 aggregate adjustment factors from fragrance material

From Fig. 3 it can be seen that there are three important calculations in the process of determining QRA2 aggregate adjustment factors.

1) **Determining the initial UCL.** In the formula from Section 3.2.2.3, the terms Total SAF and Product Exposure are properties of the product types and are independent of the fragrance material in question. The only term that can vary from one fragrance material to another is the NESIL.
2) **Checking exposure by comparing AEL/CEL_{agg} to 1.** AEL is defined as NESIL/Total SAF. Again, note that the Total SAF term is a function of the product types and is independent of the fragrance material. Further, CEL_{agg} is proportional to the concentration of fragrance material which, in turn, is proportional to the NESIL (while all other factors relevant to CEL_{agg} do not vary with fragrance material). This means that in the ratio AEL/CEL_{agg}, by being included in both terms, the NESIL is cancels itself out and the ratio is therefore independent of the fragrance material.

[3] Factors of 1000 and 100 are for converting mg to μg and a fraction to a percentage respectively.

Table 4
SAF and product type driving QRA2 category Consumer Exposure Levels.

QRA2 category	SAF	Calculated CEL (mg/cm^2/day)	QRA2 aggregate adjustment factor	Product type that drives the category 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	Deodorants/ antiperspirants of all types including fragranced body sprays
Category 3 – Products applied to the face using finger tips	100	2.17	1.00	Eye products
Category 4 – Fine fragrance	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*	Products not intended for direct skin contact, minimal or insignificant transfer to skin

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

3) **Adjusting UCL.** The Relative Contribution of each category, being a ratio of exposures, is a function of product exposure, and is independent of the concentration of the fragrance material in question. This being so, the Weighting Factors and any necessary Multiplication Factors are also independent of the fragrance material.

3.5. *Implementation of weighted adjustment factors*

Due to the QRA method of calculating concentrations in products, the relative contribution of exposure from each product to the dermal aggregate exposure to each application site for all fragrance ingredients is the same. Therefore, when adjustment factors are applied to fragrance materials, the same AEL/CEL$_{agg}$ ratios will emerge. Table 4 shows the adjustment factors resulting from applying the method detailed above. Using the adjustment factors from the example below (section 4), UCLs can be derived that give acceptable AEL/CEL ratios on all body sites taking into account aggregate exposure.

4. Example of application of QRA2 to a fragrance material: methyl octine carbonate

The fragrance material methyl octine carbonate (methyl 2-nonynoate; CAS 111-80-8) has been chosen to demonstrate QRA2 in practice as historically all of its concentration limits had been set exclusively on the basis of sensitization. The NESIL for methyl octine carbonate is set at 24 μg/cm^2 (Api et al., 2019). Table 4 provides a summary of the total SAF for each product category, the product type driving the category CEL, and the CEL and QRA2 aggregate adjustment factors for each category. Table 5 shows the practical application of the QRA2 approach for fragrance ingredients, in products across the 12 QRA2 product categories. It lists the calculated maximum concentrations for methyl

Table 5
Calculation of aggregate exposure adjusted upper concentration levels for methyl octine carbonate.

Product type driving the QRA2 UCL	**QRA 2 unadjusted use level by category (%)**	**QRA 2 aggregate** adjustment factor	**QRA 2 aggregate exposure adjusted upper concentration levels (%)**
Lip products	0.0020	0.91	0.0018
Deodorants and antiperspirants of all types including fragranced body sprays	0.00088	0.63	0.00055
Eye products	0.011	1.00	0.011
Fine fragrance (eau de toilette, parfum etc.)	0.011	0.95	0.010
Insect repellent (intended for skin application)	0. 0080	0.33	0.0026
Toothpaste	0.019	0.32	0.0061
Hair sprays	0.036	0.58	0.021
Baby wipes	0.0011	NA*	0.0011
Bar soap	0.040	0.50	0.020
Hand dishwashing detergent	0.12	0.60	0.072
Feminine hygiene conventional pads, liners, interlabial pads	0.040	NA*	0.040
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 taken into account when calculating the acceptable levels of fragrance ingredients.

$$Upper\ Concentration\ Level\ (\%) = \frac{NESIL(\mu g/cm^2)}{1,000 \times Total\ SAF \times Exposure\ (mg/cm^2/day)} \times 100$$

$$Upper\ Concentration\ Level\ (\%)\ Lip\ Products = \frac{24\ \mu g/cm^2}{1,000 \times 100 \times 11.8\ mg/cm^2/day} \times 100$$

octine carbonate in each category. The following equation provides an example on how the QRA 2 unadjusted use level by category (%) in Table 5 is calculated using lip products as an example.

$$Upper\ Concentration\ Level\ (\%)\ Lip\ Products = 0.0020\%$$

For some fragrance materials, additional limits for systemic toxicity may be applied and these may impact final acceptable maximum concentrations, e.g. for some fragrances and exposure scenarios the limit for systemic toxicity could be lower than the limit for skin sensitization, in these cases the systemic toxicity limit would drive the risk assessment. As previously mentioned, the largest changes, or where the adjustment factors are the greatest, arise from situations where multiple products are used on a particular body site. As such, adjustment factors for products applied to, or applied with, the hands typically have received the greatest adjustment factors.

The practical outcome of the application of QRA2 to methyl octine carbonate is to reduce the allowable upper level of exposure in several product categories, including deodorants and antiperspirants, fine fragrance, body lotion and hand cream - by more than 50% for the last mentioned.

5. Remaining uncertainties

Subsequent to its implementation, QRA1 was not formally tested for its efficacy in preventing the induction of contact allergy to fragrance materials. Whilst it is anticipated that such an evaluation will occur for QRA2, it is worth bearing in mind that several uncertainties remain, despite the improvements it offers compared to the original version. In their opinion in 2018, the SCCS (2018b) provided valuable comments on exposure aspects that required further refinement for QRA2, many of which have been addressed in this update (SCCS, 2018b). Gilmour et al. (2019) identified areas of uncertainty when assessing the risk of induction of skin sensitization, including those associated with the use of non-animal methods, better understanding of the impact of exposure variables such as frequency and duration, and the role of inflammation. Although conservative positions have been taken on exposure assessment whenever appropriate, inevitably as with any toxicology risk assessment, QRA2 contains areas of uncertainty that need to be identified and borne in mind when it is being applied. Therefore, case-by-case adjustments may be made when consumer use or product use is involved that are not covered in this paper.

The ban on the use of animal studies for the hazard assessment of cosmetics has also resulted in a reconsideration of the framework for the hazard assessment of fragrance materials. Thus, a priority for the future work of IDEA is to characterize potential areas of uncertainty associated with the use of non-animal-based methods for hazard assessment that would be different from those associated with the use of historical *in vivo* test methods.

The move towards new approach methodologies (NAMs) as a major source for deriving the NESIL will bring along the need to review a number of assumptions made in QRA2, including the suitability of certain SAFS.

6. Discussion

In 2008, a proposal for the quantitative risk assessment (QRA1) of fragrance materials was published (Api et al., 2008). The general principles of risk assessment can be applied to the induction of dermal sensitization as it is a threshold phenomenon. However, these general principles required tailoring to take into account unique elements of dermal sensitization as a toxicity endpoint. QRA methodology was a major improvement over the former approach because it specifically addresses the elements of exposure-based risk assessment that are unique to the induction of dermal sensitization, while being consistent with the principles of general toxicology risk assessment. In this revision (known as QRA2), the updated SAFs used within the QRA and aggregate exposure at different body sites have been integrated in the risk assessment framework. They provide an improved method for assessing the risk of induction of contact allergy to sensitizing fragrance materials. The issues considered are faced by other sectors whose products come into contact with human skin, but care must be taken before wholesale adoption of the present methodology into other sectors.

QRA2, in the version presented here, is now being used by RIFM in its safety assessments and is being implemented by the International Fragrance Association (IFRA) as a basis for setting concentration limits for fragrance materials in consumer products in its endeavor to manage the risk of induction of sensitization. In the future this method could also be applied to other exposures and product types (e.g. occupational exposures, aromatherapy, topical medicaments, massage oils, etc.) if comprehensive habits and practices data are available and a review of the SAFs are completed for those applications (Gilmour et al., 2019).

Non-animal test methods are increasingly employed for the assessment of the induction of skin sensitization. While the utility of these methods to determine potency is not yet fully established, these methods are continually being updated and new tools to help determine potency are being developed (OECD, 2016, 2017). The detail of how these NAMs will fit into the determination of a NESIL, including how they will impact the uncertainties associated with such determination, remains to be seen and forms part of ongoing work programs within the fragrance industry (e.g. www.ideaproject.info/news-events/idea-workshop-on-qra-based-on-nams-building-trust.)

It seems obvious that any observed failure of risk assessment and risk management measures must be fed back as part of the evaluation of the utility of QRA2. Usually, risk assessment methodologies are, by their nature, difficult to verify in general toxicology. It could be argued that such might arise via a cosmetovigilance process. However, as the aggregate exposure assessment in QRA2 specifies upper concentration levels, it is possible to evaluate the efficacy of the application of these

limits in preventing induction of new contact allergies to fragrance materials. Longitudinal clinical studies (in specialist dermatology centers) are now required to evaluate the efficacy of QRA2 as a tool for the prevention of contact allergy to fragrance materials. There are obstacles to overcome in this regard. These include being able to distinguish between allergies induced prior to, and after, the application of these concentration limits, or even from exposures not within their control. However, as well as monitoring contact sensitization rates to established fragrance substances in the clinical setting as a surrogate for the general consumer, prospectively monitoring sensitization to novel fragrance materials will be required. The findings from such work will be essential in determining whether further changes should be incorporated into the QRA2. It is also pertinent to bear in mind that the impact of the implementation of QRA2 will take several years to become apparent.

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Important improvements in skin sensitization Quantitative Risk Assessment (QRA) for fragrance materials QRA1 such as refined exposure data, inclusion of aggregate exposure to multiple consumer products and re-examination and refinement of the Sensitization Assessment Factors (SAFs) were explored and developed further in a series of workshops held as part of the IDEA project (www.ideaproject.info). The workshops involved dermatologists, academics, technical representatives from industry and included observers and participants from the European Commission and its expert committees.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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APPENDIX. APPLICATION OF SAFs

Appendix Table 1: SAFs for Fragrance materials in Different Product Types. Contribution of different SAFs and Rationale for Product SAF and Skin Condition SAF

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Category 1 - products applied to the lips						
Lip products[a]	10	1	3*	3*	A SAF of 3* is applied because the site is applied to the lips (highly vascular and there is exposure to mucous membranes and possible exposure to dry or chapped lips). Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Toys	10	1	3*	3*	These products are placed have been placed in Category 1. There are no exposure data available; should exposure data become available, then the products will be re-categorized. Due to the possibility of ingestion of small amounts of fragrance materials 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 must not only comply with IFRA Standards but must also have an approved flavor materials status as defined by the IOFI Code of Practice.	100
Category 2 - Products applied to the axillae						

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Deodorants & antiperspirants of all types including fragranced body sprays[a]	10	1	3*	10	The SAF is 10 as these products are applied to the axillae where the skin is easily irritated due to a combination of factors including the unique environment of the axillae (humid, oil-rich sebum production and site for perspiration). There may also be acute transient irritation due to product application or mechanical irritation. Shaving may produce an acute transient response.	300
Category 3 - Products applied to the face using fingertips						
Eye products (Includes: eye shadow, mascara, eyeliner, eye make-up)	10	1	3*	3*	The SAF is 3* because product is applied to the peri-ocular site and face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Makeup (foundation) [a]	10	1	3*	3*	SAF is 3* because the product is applied to the face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Make-up remover[b]	10	1	3*	3*	SAF is 3* because the product may be applied to eyelids (peri-ocular region) and face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Nose pore strips	10	1	3*	3*	SAF is 3* because the product is applied to the nose with minimal skin contact. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Wipes or refreshing tissues for faces, neck, hands, body	10	1	3*	3*	SAF is 3* because the product may be applied to eyelids (peri-ocular region) and face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Body paint	10	1	3*	3*	SAF is 3* because the product may be applied to eyelids (peri-ocular region), face and body. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Make-up remover for face, eyes, and lips[b]	10	1	3*	3*	The SAF is 3* because product is applied to the peri-ocular site, lips and face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Masks: face and lips and around the eyes mask	10	1	3*	3*	SAF is 3* because the product may be applied to the face, lips and peri-ocular region. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Facial masks (facial treatment)	10	1	3*	3*	SAF is 3* because the product may be applied to eyelids (peri-ocular region) and face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Category 4 - Fine Fragrance						
Fine fragrance all types (eau de toilette, perfume, cologne etc.) [a]	10	1	3*	3*	The area is the neck, wrists, antecubital fossa. Irritation from shaving may produce an acute transient response. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Fragranced bracelets	10	1	3*	3*	The area is the wrists. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Ingredients of perfume kits	10	1	3*	3*	The area is the neck, wrists, antecubital fossa. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Scent pads, foil packs	10	1	3*	3*	The area is the neck, wrists, antecubital fossa. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Scent strips for hydroalcoholic products	10	1	3*	3*	The area is the neck, wrists, antecubital fossa. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hair perfume	10	1	3*	3*	The SAF is 3* because when the product is applied to the hair there may also be exposure to the scalp. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Category 5 - Products applied to the face and body using the hands (palms), primarily leave-on						
Facial cream (moisturizing)/facial balm[a]	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Moisturizer face, eyes, and lips	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face, peri-ocular site and lips. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hand cream[a]	10	1	3*	3*	The SAF is 3* because the product is applied to the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Body creams, lotions[a]	10	1	3*	10	The SAF is 10 because the area is the entire body which may include areas of inflamed skin, i.e.: intimate regions and axillae. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300
Nail care products including cuticle creams etc.	10	1	3*	3*	The SAF is 3* because some nail care products are applied to the fingers and the back of the hands.	100
Foot care products (creams & powders)	10	1	3*	3*	The SAF is 3* because the product is applied to the feet and may be applied with the palms of the hands.	100
Baby cream	10	1	3*	10	The SAF is 10 because the area is the entire body which may include areas of inflamed skin, i.e.: intimate regions and axillae. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300
Baby oil	10	1	3*	10	The SAF is 10 because the area is the entire body which may include areas of inflamed skin, i.e.: intimate regions and axillae. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Baby powder/talc	10	1	3*	10	The SAF is 10 because the area of exposure will possibly include the whole body[33] including the peri-anal region. The skin integrity of some exposed areas may be compromised (diaper rash) [62].	300
Insect repellent (intended to be applied to the skin)	10	1	3*	3*	The SAF is a 3*. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hand sanitizers	10	1	3*	3*	The SAF is 3* because the product is applied to the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Face toner/astringent/anti-bacterial cleansers[b]	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face and peri-ocular site. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
All powders and talcs (except baby powders and talcs)	10	1	3*	10	The SAF is 10 because the area of exposure will possibly include the whole body[33] including the peri-anal region. The skin integrity of some exposed areas may be compromised (diaper rash) [62].	300
Category 6 - Products with oral and lip exposure						
Toothpaste[a]	10	1	3*	3*	The SAF is a 3*. The sites are the lips and mouth. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Mouthwash[a]	10	1	3*	3*	The SAF is a 3*. The sites are the lips and mouth. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Category 7 - Products applied to the hair with some hand contact						

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Hair sprays[a]	10	1	3*	1	The SAF is 1 because it is applied to the hair with minimal exposure of the scalp and hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	30
Hair styling aids (mousse, gels, leave-in conditioners) [a]	10	1	3*	3*	The SAF is 3* because when the product is applied to the hair there will also be exposure to the scalp and the palms of the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hair permanent or other hair chemical treatments (e.g. relaxers) but not hair dyes	10	1	3*	3*	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 hair styling aids.	100
Dry shampoo or waterless shampoo	10	1	3*	3*	The SAF is 3* because when the product is applied to the hair there will also be exposure to the scalp and the palms of the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hair deodorizer	10	1	3*	3*	The SAF is 3* because when the product is applied to the hair there may also be exposure to the scalp and the palms of the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hair dyes	10	1	3*	3*	The SAF is 3* because when the product is applied to the hair there will also be exposure to the scalp and the palms of the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Category 8 - Products with significant ano-genital exposure						
Intimate wipes	10	1	3*	10	The skin site SAF is 10 because peri-anal region is involved.	300
Tampons	10	1	3*	20	SAF is 20 because close, occluded contact occurs with non-keratinized mucosa (vaginal mucous membrane)[37,40-48] and exposure may occur for extended periods of time. This area may be prone to irritation. Farage, 2003	600
Baby wipes	10	1	3*	10	The SAF is 10 because the peri-anal region may be exposed. The area is primarily the baby's buttocks, groin, lower stomach and upper thighs where the skin integrity may be compromised (diaper rash) [62] and could involve mucous membrane exposure[37,40-48].	300
Wet toilet paper	10	1	3*	10	The SAF is 10 because the peri-anal region may be exposed.	300
Category 9 - Products with body and hand exposure, primarily rinse off						
Bar soap[a]	10	1	3*	10	The SAF is 10 because product may be used all over the body including the axillae and intimate regions. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300
Shampoo[a]	10	1	3*	10	The SAF is 10 because the product is applied to the head (hair) and scalp with the hands and may also be used over the entire body as a shower gel. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Face washes, gels, scrubs[b]	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Conditioner (rinse-off) [a]	10	1	3*	3*	SAF is 3* because the product is applied to the head (hair) and scalp with the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Liquid soap[a]	10	1	3*	3*	The SAF is 3* because product may be used on the hands and face. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Body wash/shower gels[a]	10	1	3*	10	The SAF is 10 because product may be used all over the body including intimate regions and axillae. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300
Bath gels, foams, mousses	10	1	3*	10	The SAF is 10 because product may be used all over the body including intimate body regions and the axillae. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300
Baby wash, bath, shampoo	10	1	3*	10	The SAF is 10 because product may be used all over the body including intimate body regions and the axillae. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	300

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Foot care products (feet are placed in a bath for soaking)	10	1	3*	3*	The SAF is 3* because product is used on the feet. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Shaving creams, foams, gels[b]	10	1	3*	3*	The SAF is a 3* because the area is a part of the face.	100
Depilatory, hair removal creams, foams, gels (including facial) [b]	10	1	3*	10	The SAF is 10. It has been judged that the use of depilatories may lead to an irritation that requires 10-fold assessment factor compared to the conditions of the confirmatory tests (e.g. HRIPT).	300
Waxes for mechanical hair removal[b]	10	1	3*	3*	The SAF is 3* because many skin sites could be exposed. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation as the wax is inert and contact time with skin is brief.	100
Face and lips scrubs	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face and lips. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Facial cleansing wipes and cleanser wipe-off products[b]	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face, peri-ocular site and lips. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Cleanser for face, eyes, and lips	10	1	3*	3*	The SAF of 3* has been attributed because the product is applied to the face, peri-ocular site and lips. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Shampoos for pets	10	1	3*	3*	The SAF is 3* because the product is exposed to the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Category 10 - Household care products with mostly hand contact						
Aerosol air fresheners[a]	10	1	3*	1	SAF is a 1 because the exposure may include the upper extremities of the body.	30
Hand wash laundry detergent[b]	10	1	3*	3*	The SAF is 3* because the product is exposed to the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Laundry pre-treatment (all types)[b]	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, there is limited contact with the hands.	100
Hand dishwashing detergent[b]	10	1	3*	3*	The SAF is 3* because the product is exposed to the hands. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation	100
Hard surface cleaner (all types)[b]	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, there is limited contact with the hands.	100
Laundry detergents with skin contact (e.g. liquids, powders)[b]	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, there is minimal contact with the hands.	100

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Dry cleaning kits	10	1	3*	3*	The SAF is 3* because although the stain removing components of this product category may be more aggressive/irritating than surfactant based personal care products, there is minimal contact with the hands.	100
Toilet seat wipes	10	1	3*	3*	The SAF is 3* because contact with the hands is anticipated.	100
Fabric softeners - liquids[b]	10	1	3*	3*	The SAF is 3* because contact with the hands is anticipated.	100
Fabric Softeners - dryer sheets[b]	10	0.3	3*	3*	The SAF is 3* because limited contact with the hands is anticipated.	30
Bath cleaners, bleach, disinfectants, floor cleaner, kitchen cleaner, multi-purpose cleaner, soft surface cleaners, cleaner, window cleaner, furniture polishes (sprays and wipes), limescale removers[b]	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, there is minimal contact with the hands.	100
Washing up liquids[b]	10	1	3*	3*	The SAF is 3* because limited contact with the hands is anticipated.	100
Other household cleaning products (fabric cleaners, carpet cleaners, leather cleaning wipes, starch sprays, stain removers, fabric enhancing sprays)	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, there is minimal contact with the hands.	100
Animal sprays (all types)	10	1	3*	3*	The SAF is 3* because contact with the hands is anticipated.	100
Floor wax	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, minimal contact with the hands is anticipated.	100
Fragranced oil for lamp rings, reed diffusers, etc.	10	1	3*	3*	The SAF is 3* because contact with the hands is anticipated.	100
Odored distilled water (that can be added to steam irons)	10	1	3*	3*	The SAF is 3* because contact with the hands is anticipated.	100

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
In-wash scent booster pastilles	10	1	3*	3*	The SAF is 3* because although this product category may be more aggressive/irritating than surfactant based personal care products, there is minimal contact with the hands.	100
Category 11 - Products with intended skin contact but minimal transfer of fragrance to skin from inert substrate						
Feminine hygiene conventional pads, liners, interlabial pads	10	1	3*	10	The SAF is 10 because the contact is predominantly with stratified, squamous keratinized epithelium (Farage et al. 2003).	300
Diapers (baby and adult)	10	1	3*	10	The SAF is 10 because the peri-anal region may be exposed. The area of exposure will possibly include the whole body[33]. The skin integrity may be compromised (diaper rash) [62]. There may also be mucous membrane exposure [37,40-48].	300
Tights with moisturizers	10	1	3*	10	The SAF is 10 because contact with skin is anticipated and will be longer than brief. The ano-genital area may be exposed.	300
Scented socks, gloves	10	1	3*	3*	The SAF is 3* because contact with skin is anticipated and will be longer than brief.	100
Facial tissues (dry tissues)	10	0.3	3*	3*	The SAF is 3* because contact with the hands, lips, and face is anticipated.	30
Napkins	10	0.3	3*	3*	The SAF is 3* because contact with the hands, lips, and face is anticipated.	30
Paper towels	10	0.3	3*	3*	The SAF is 3* because contact with the hands is anticipated.	30
Toilet paper (dry)	10	0.3	3*	10	The SAF is 10 because the peri-anal region may be exposed. The area of exposure will possibly include the whole body[33]. The skin integrity may be compromised[62]. There may also be mucous membrane exposure [37,40-48].	100

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Wheat bags	10	1	3*	3*	The SAF is 3* because contact with skin is anticipated and will be longer than brief.	100
Solid fertilizers (pellet or powder)	10	1	3*	3*	The SAF of 3* has been attributed because the product may come into contact with the hand and uncovered extremities. No additional contribution to skin condition is expected from product irritation	100
Face Masks (paper/protective, e.g. surgical mask)	10	1	3*	3*	The SAF is 3* because contact with skin is anticipated and will be longer than brief.	100
Category 12 - Products not intended for direct skin contact, minimal or insignificant transfer to skin						
Candles[a]	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Closed air fresheners[a]	10	0.3	3*	1	The SAF is 1 because there is only rare accidental contact with the skin.	10
Laundry detergents with minimal skin contact (e.g. pods)[b]	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Air fresheners and fragrancing of all types (*concentrated aerosol with metered doses (range 0.05-0.5mL/spray)*, plug-ins, solid substrate, membrane delivery, electrical, potpourri, powders, fragrancing sachets, incense, liquid refills, air freshening crystals) [a]	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Air delivery systems	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Cat litter	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10

Product Type	Inter-individual SAF	Product Composition SAF	Frequency/ Duration SAF	Skin Condition SAF	Rationale for Skin Condition SAF	QRA2 SAF
Deodorizers/maskers not intended for skin contact (e.g. fabric drying machine deodorizers, carpet powders)	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Fuels	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Insecticides (e.g. mosquito coil, paper, electrical, for clothing)	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Joss sticks or incense sticks	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Machine dishwash detergent, deodorizers and rinse aids[b]	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Paints	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Plastic articles (excluding toys)	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Scratch and sniff	10	1	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Scent pack	10	1	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Scent delivery system (using dry air technology)	10	1	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Shoe polishes	10	1	3*	1	The SAF is 1 because there is limited exposure to the skin.	10
Toilet blocks	10	0.3	3*	1	The SAF is 1 because there is limited exposure to the skin.	10

*In keeping with convention, values of 0.1, 0.3, 1, 3, 10, 30, 100 and 300 are used such that when multiplying SAF values, 3 is treated as an integer when multiplied with 1, 10, 100 to give 3, 30 300 but when multiplied by itself it is considered as the number 3 approximates √10 (c. 3.16) such that 3 x 3 = 10.

Note: Products that contain sunscreens are not addressed separately but are included in the major product types (e.g. lip creams with sunscreen are included in lip product category).

[a]Consumer products in the Creme RIFM Aggregate Exposure Model, Version 2.0 (2018)

[b]Consumer products in the next version of the Creme RIFM Aggregate Exposure Model Version 3.0 (expected to launch Q3, 2019).