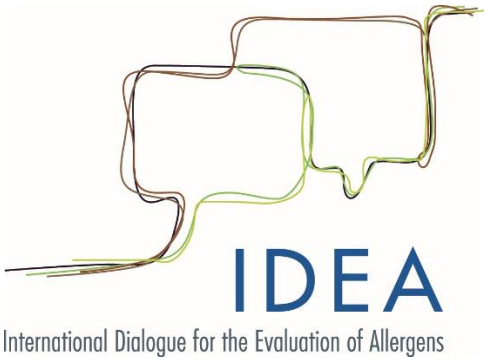

IDEA PROJECT

FINAL REPORT ON THE QRA2

Skin Sensitisation Quantitative Risk Assessment for Fragrance Ingredients

September 30, 2016

Executive Summary

The aim of skin sensitisation QRA is the prevention of induction of contact allergy. The fragrance industry has been widely using Quantitative Risk Assessment, referred in this report as QRA1, following its first description in the published literature (Api *et al*., 2008).

The authors proposed the following procedure for the risk assessment of individual fragrance ingredients:

- determination of the sensitisation induction threshold (no expected sensitisation induction level (NESIL)) involving a weight of evidence procedure and a check on this using human volunteers (human repeat insult patch testing, HRIPT).
- consumer exposure estimation through individual product use data;
- application of sensitisation assessment factors (SAF) to ensure conservatism in determining the consumer exposure limit (CEL) values;
- using a weight of evidence evaluation of these parameters, an acceptable exposure level (AEL) can be calculated and compared with the CEL. The ratio of AEL to CEL must be favourable to support safe use of the potential skin sensitiser.

In 2008 also, the SCCP provided constructive criticism on this proposed QRA.

In 2012, the Scientific Committee on Consumer Safety (SCCS, 2012a) published an opinion, which expressed its concerns about the number and nature of fragrance substances on the market capable of causing allergenic reactions on skin.

Prompted by this, the International Dialogue for the Evaluation of Allergens (IDEA) project (www.ideaproject.info) was started to establish a "broadly agreed, practically utilisable and transparent framework, based on high quality scientific and clinical findings, for assessing fragrance sensitisers". The project, from its outset, has involved the collaboration of academic scientists, clinicians and industry scientists from a number of countries and disciplines.

QRA 2

Initial priority areas (phase 1) for the development of the QRA, through the IDEA project were agreed based on their relative importance in improving utility and transparency and with a focus on exposure aspects:

(i) to carry out specific reviews of each of the uncertainty factors (SAFs);
(ii) to introduce dermal aggregate exposure, as replacement for the original individual product exposure assessment for fragrance ingredients;

(i) SAF review

In line with QRA1, QRA2 incorporates transparent and scientifically justified SAFs, some of which differ from those in QRA1. The reconsidered values are as follows namely:

- *Product Effects: Vehicle*

  The vehicle/matrix requires a SAF because of the influence on the delivery of the allergen into the skin. The consumer can be exposed to fragrance ingredients in products of varying complexity ranging from aqueous matrices, simple ethanol matrices to multi-phase creams. The SAF for matrix considerations is given a value of either 1 or 3 (3.16, the half log of 10 and not 2). This SAF is likely to be 1 for most product types.

- *Frequency/Duration*

  This SAF reflects the use of a product regularly and over a long time period, which may lead to a higher long-term exposure vs. the experimental situation. An additional factor of 1 or 3 is assigned to each of the various product types. This SAF was not originally considered in the QRA1.

- *Site of exposure*

  For each body site this SAF considers the state of the skin as well as the inherent susceptibility of each of these. It includes consideration of irritation as a contribution from both the product composition and the existing state of the skin site. A SAF of 1, 3 or 10 may be applied. This takes account of the state of the skin at each site as well as the inherent susceptibility of each of these. In particular the axillæ and the ano-genital region have been identified as requiring a SAF of 10.

- *Inter-Individual Variability*

  It is concluded that inherent the state of the skin dermal condition is more influential than age, sex and ethnicity. A SAF of 10 was concluded to be sufficient to account for this.

ii) Dermal aggregate exposure

The IDEA Project encouraged the incorporation of the Creme RIFM Exposure Model (Comiskey *et al*., 2015; Safford *et al.,* 2015) into QRA2. The model is based on the declared habits and practices data from 36,446 panellists across Europe and The United States of America (Kantar Database, 2011). To this end, each panellist supplied diary data on which products were used during the day for seven consecutive days, as well as the application sites of most products. The survey data listed specific body application sites for the panellists to select. The application of the QRA for fragrance ingredients detailed exposure information based on product usage, and takes into account:

- Amount of product used per application.
- The concentrations of the fragrance ingredient in each type of product.

- Use practices (e.g. distributions of how a consumer uses the product per application, including the area of application and frequency of use).
- The QRA2 SAF values.

This enables the calculation of the aggregate consumer exposure level (CEL) to be compared with the AEL value derived from the assessment of the threshold based on the evaluation of the induction dose response relationship.

FURTHER DEVELOPMENT OF THE QRA

The immediate priorities are:

- To complete the ongoing work to incorporate consideration of pro- and particularly pre-haptens into QRA2.
- Agreeing a protocol and conducting a critical evaluation of the effectiveness of QRA2 in minimising consumer sensitisation.

Other activities:

- Identifying suitable non-animal tests to replace the LLNA test for risk assessment purposes in line with EU regulatory requirements. It is recognised that this is a very challenging topic and one where close collaboration with other research organisations is being sought.
- A thorough re-evaluation of the weighing is necessary because of the changes in the hazard identification and characterisation methodology.
- Development of a suitable model to assess exposure in occupational settings.

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1. Introduction

Certain chemicals have an intrinsic ability to induce a state of delayed hypersensitivity in human skin. Chemicals identified with this property are referred to as skin sensitisers. With sufficient skin exposure, the induction of a state of immunological hypersensitivity can occur. This constitutes a relevant and important toxicological endpoint, which in humans can be identified using a diagnostic patch test and is described as contact allergy. Allergic contact dermatitis (ACD) is the consequence of exposure to a contact allergen exceeding an individual threshold concentration in a contact allergic person. The induction of skin sensitisation does not always lead to ACD (Mortz *et al*., 2013).

Contact allergy to fragrance ingredients is a topic of high interest for consumers, industry and Regulatory Authorities as expressed for example, through the 2012 SCCS Opinion on Fragrance Allergens (SCCS, 2012a) and the Technical Guidance of the European Chemicals Agency (ECHA, 2012). Industry is committed to addressing this issue and to providing solutions. This requires a broad, multi-stakeholder approach to reduce the burden on the general population and society of contact allergy and ACD associated with fragrance substances.

The IDEA project is designed to provide a broadly agreed, science based and transparent framework for assessing fragrance ingredient sensitisers globally (see Section 6, Appendix 1). Through a series of workshops, international scientists from various sectors (including leading dermatologists, industry, academic institutions and regulatory/governmental bodies) are working together to improve the safety assessment process of those fragrance ingredients that might have allergic potential and thereby to improve consumer protection.

Taking into consideration the constructive criticism of the original QRA methodology as expressed in the 2008 SCCP opinion (SCCP, 2008), the objective of the IDEA workshops on QRA has been to re-evaluate the skin sensitisation QRA (QRA1) and its use for risk management of potential fragrance allergens. To reach this objective, the participants of these workshops were mandated to review the methodology as used today by the fragrance industry and identify the areas needing further refinement.

The evolution of QRA as published in 2008 (Api *et al*., 2008) to the form presented here is largely the result of the agreed discussions and conclusions from these IDEA workshops (IDEA, 2013, 2014a, 2014b).

1.1. Scope of QRA2 as Described in this Document

The scope of the skin sensitisation QRA as presented here is the evaluation of the risk to consumers of the induction of contact allergy presented by fragrance ingredients in cosmetics

and other household consumer products. The original risk assessment methodology (QRA1) was implemented by IFRA (International Fragrance Association; www.ifraorg.org) into standards on the first three ingredients in 2006.

While IFRA membership accommodates about 90% (by volume) of the fragrances produced globally and used in consumer products, there are a number of product types and exposures to fragrance ingredients that are not under the scope of IFRA and therefore not covered by the IFRA Standards (e.g. aromatherapy, drugs and topical treatments, massage and spa therapies, occupational exposure, natural exposure, foods, etc.). Nonetheless it is important that these are taken into account in order to gauge the overall (aggregate) exposure.

The aim of skin sensitisation QRA is the prevention of induction of contact allergy (primary prevention). If induction is prevented, elicitation will not occur. QRA is intended to deliver an output specifically in relation to induction. Elicitation thresholds are likely to be lower compared to induction thresholds. At present, the relationship between the potency of an allergen, the induction thresholds, and the ability of the substance to elicit responses has not been characterised (ECHA, 2012). In part this is due to the fact that elicitation thresholds depend not only on the intrinsic potency of a sensitiser, but also on the susceptibility of the exposed individual. This latter aspect being a function not only of potency, but also of the severity of the induction process (Hostynek and Maibach, 2004; Friedmann, 2007). Typically, substance-specific elicitation thresholds can only be derived from clinical studies using volunteers who are sensitised to the substance in question. Many examples of such work have appeared in the literature (e.g. Fischer *et al.*, 2009) and it has been suggested that the variation between the thresholds for contact allergens may be rather less than that for induction (Fischer *et al.*, 2011).

1.2. Induction of Contact Allergy

The immunological mechanisms involved in the induction of contact allergy are well understood and have been the subject of recent reviews (Martin, 2012; Honda *et al.*, 2013; McFadden *et al.*, 2013). Similarly, the mechanism associated with development of the inflammatory response characteristic of the elicitation of allergic contact dermatitis is described in these reviews. The initial aspects of induction and elicitation are similar, but there are also important differences. In both phases, a chemical has to come into contact with the skin, partition into the viable epidermis and once there, be sufficiently reactive (hapten) to bind covalently with skin protein (reviewed in Divkovic *et al.*, 2005; Basketter *et al.*, 2007). To act as a hapten, the chemical may be reactive *per se* or may require abiotic (pre-haptens) or biotic transformation (pro-haptens) following application to the skin. The same abiotic or metabolic processes will similarly apply in both phases of the immune response. However, the details of these processes, in terms of what are the key clinically relevant pre-/pro-haptens and how they are converted to a hapten, remain largely theoretical (e.g. Smith and Hotchkiss, 2001; Hewitt *et al.*, 2013). Assuming equivalent dosimetry, the non-specific effects necessary for the development of an adaptive immune/allergic response, e.g. irritancy, release of danger signals etc., will be the same in both phases (McFadden *et al.*, 2013). Thus, the essential difference in the two phases is that *induction* involves the migration of dendritic cells to the

draining lymph node and the subsequent activation of hapten-specific lymphocytes, whereas *elicitation* activates hapten-specific effector and memory T cells at the site of skin contact, thereby triggering a local inflammatory response. Most importantly, the induction of skin sensitisation is clearly a threshold-based phenomenon (Kimber *et al*., 1999; Robinson *et al*., 2000).

It is important to recognise that, except in the rare cases of exposure to highly potent allergens, (e.g. poison ivy, some industrial chemicals) multiple induction exposures (over a period which may span weeks, months or years) are generally required for the induction of contact allergy. In contrast, the elicitation of allergic contact dermatitis normally will occur in response to a single, or just a few, dermal exposures in a suitably sensitised individual.

1.3. Use of QRA2 beyond Current Scope

QRA2 has the potential to be extended to other types of contact allergens and other exposure scenarios. However, the use of this QRA2 approach for such ingredients (e.g. preservatives, sunscreens) can only occur once a separate review of all the elements of QRA for each class of ingredients in consumer products has been completed. In contrast to preservatives, fragrance ingredients have unique use-level distributions that contribute to the olfactory appreciation.

Many publications and new data have become available since the Api *et al*. (2008) publication. These publications have reduced to some extent the level of uncertainty that existed beforehand and which required a more cautious approach. As with any risk assessment methodology, as additional data becomes available from further targeted research, subsequent review of QRA2 will be required. Therefore, it is appropriate to remember the methodology as set out below is an important stage in an evolving and adaptive process.

2. General Principles of a Human Risk Assessment and its Applicability to Skin Sensitisation

The quantitative risk assessment methodology outlined in many publications (for instance WHO, 2004; ECHA, 2012; ECETOC, 2009) is the cornerstone of health-based exposure limits and used extensively by governmental agencies and industry. Safety assessments for chemicals that possess the ability to cause sensitisation by contact with skin have traditionally been conducted using an *ad hoc* comparative risk assessment technique (Robinson *et al*., 1989). Since it is known that the general principles of quantitative risk assessment can also be applied to induction of skin sensitisation, an alternative and potentially better quantitative risk assessment approach for skin sensitisation was developed (Robinson *et al.,* 2000) and described in a series of papers (Farage *et al.*, 2003; Felter *et al.,* 2002; Felter *et al*., 2003; Gerberick *et al*., 2001; Griem *et al*., 2003). This Quantitative Risk Assessment (QRA) methodology was subsequently described for use with fragrance ingredients (Api *et al*., 2008). The skin sensitisation QRA approach follows the same four steps outlined above for general toxicology risk assessment. It is implicit that the conduct of the full skin sensitisation QRA is necessary only for those ingredients identified as dermal sensitisers.

The different phases of risk assessment (as described in detail in WHO, 2004) are as follows:

- **Hazard Identification**

This involves the use of experimental data to determine the skin sensitisation potential of the fragrance ingredient. Historically, this has involved a murine Local Lymph Node Assay (LLNA) or the use of other assays such as the guinea pig maximization test or Buehler guinea pig test (Kimber *et al*., 2003, ECETOC 2003). Moving forward it will rely on the integrated assessment of data based on a weight of evidence analysis using all available data, including non-animal test methods.

- **Dose–Response Assessment or Hazard Quantification**

The dose response for induction of skin sensitisation, from a previously executed LLNA, is used to identify an EC3 value (Estimated Concentration required to result in a threshold positive response; i.e. a Stimulation Index = 3). The EC3 value is used define the relative sensitisation potency. A good correlation between the EC3 and the NOAEL in the Human Repeat Insult Patch Test (HRIPT) has been established (Gerberick *et al*., 2001; Basketter *et al*., 2005a; Api *et al*., 2014).

- **Exposure Assessment**

The amount of fragrance ingredient that remains on the skin under the conditions of product use in terms of quantity per unit area (e.g. µg/cm^2) is assessed. Exposure to the fragrance ingredient is determined using habits and practice data for consumer product use, human parameters data, the level of perfume in the finished product and the level of the individual fragrance ingredients in the perfume.

- **Risk Characterisation**

The data from the previous steps are used to determine an acceptable exposure level to a fragrance ingredient against which the real-life exposure of consumers to that fragrance ingredient in a specific product type can be compared. The acceptability or unacceptability of real-life exposures can then be determined.

In developing a methodology for quantitative risk assessment for skin sensitisation of fragrance ingredients based on the above approach new terms were adopted. “No Expected Sensitisation Induction Level” (NESIL) and “Sensitisation Assessment Factors” (SAFs) replaced the terms NOAEL and uncertainty factors, generally used in toxicological risk assessments. The Acceptable Exposure Level (AEL = NESIL/total SAFs) is equivalent to the ‘reference dose (RfD)’ used in general toxicology. These terms have been adopted to take into account unique elements of quantitative risk assessment for skin sensitisation and are described in detail in the sections within this dossier.

The overall skin sensitisation QRA2 is presented in Figure 1 and its use in conjunction with aggregated exposure is shown in Figure 2 and is detailed in the remaining sections of this report. Finally, the risk characterisation process is explained and some worked examples given (see Section 2.3.3).

2.1. Hazard Characterisation

Historically, several animal models have been used to determine the potential for a fragrance ingredient to induce sensitisation. Guinea pig tests (adjuvant and non-adjuvant) were used for many years to assess the inherent contact sensitisation potential of chemicals. These tests can assess potency to a certain extent or antigen cross-reactivity of structurally related chemicals. Later, the murine local lymph node assay (LLNA) was approved by the OECD (OECD, 2002). This not only determines the potential of an ingredient to induce contact sensitisation, but also makes further use of these data for assessment of the relative sensitisation potency. The cut off value of 3 was supported by a detailed retrospective evaluation (Basketter *et al*, 1999), which actually demonstrated that the best accuracy was achieved with a threshold of 3.6. However, the cut off value of 3.0 was retained to ensure that the decision making contained an element of conservatism.

2.1.1. Derivation of the EC3 Value

The most appropriate method for the routine calculation of EC3 values is by linear interpolation from the dose response data. This results in similar estimations when compared to more complex statistical approaches (Basketter *et al.,* 1999). Using linear interpolation, the EC3 value is calculated by taking two data points on the dose response curve, one immediately above (a = % concentration, b = Stimulation Index) and one below (c = % concentration, d = Stimulation Index) the Stimulation Index value of three. Where there is any

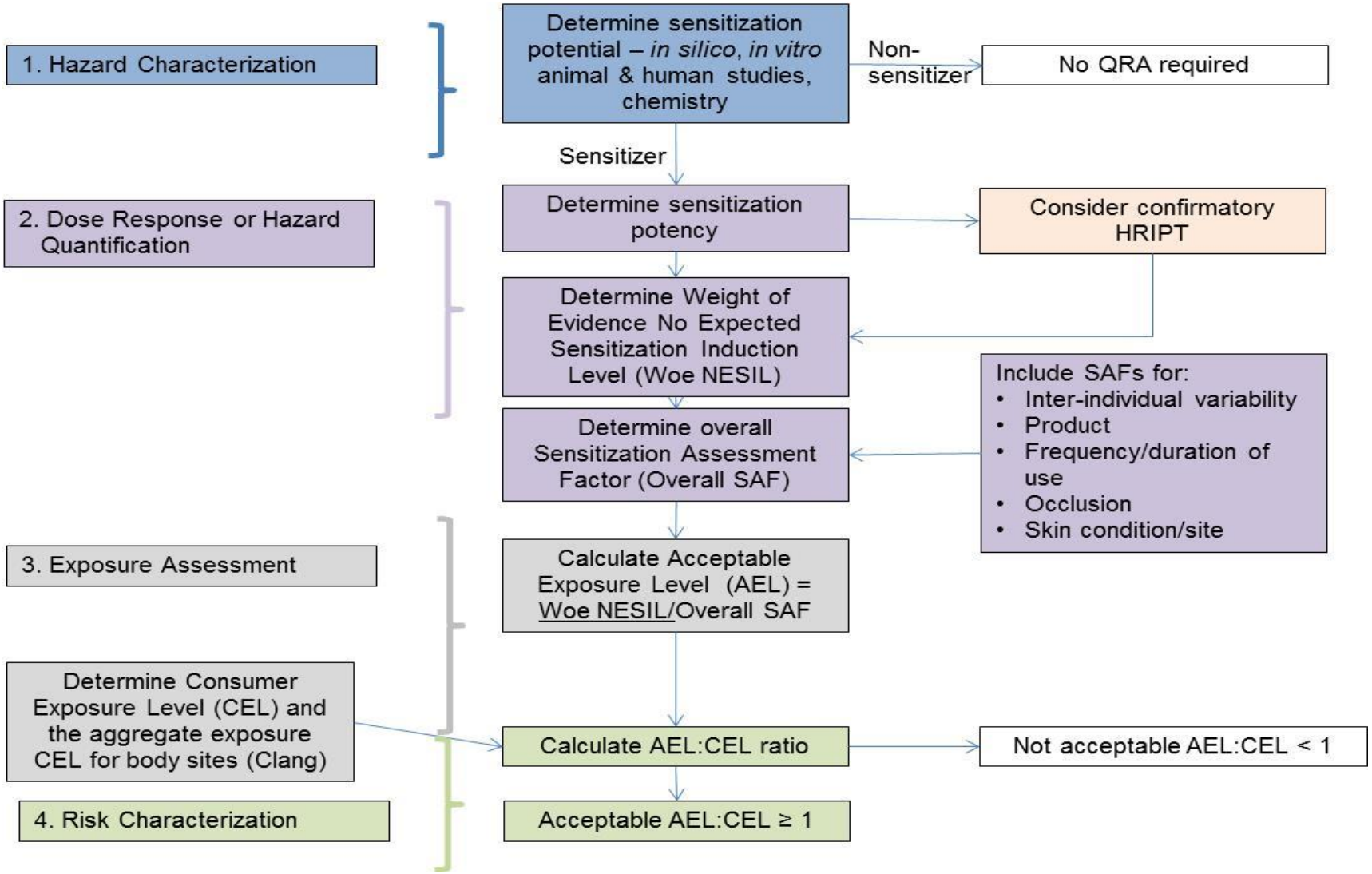

Figure 1: Skin Sensitisation QRA2 for Fragrance Ingredients

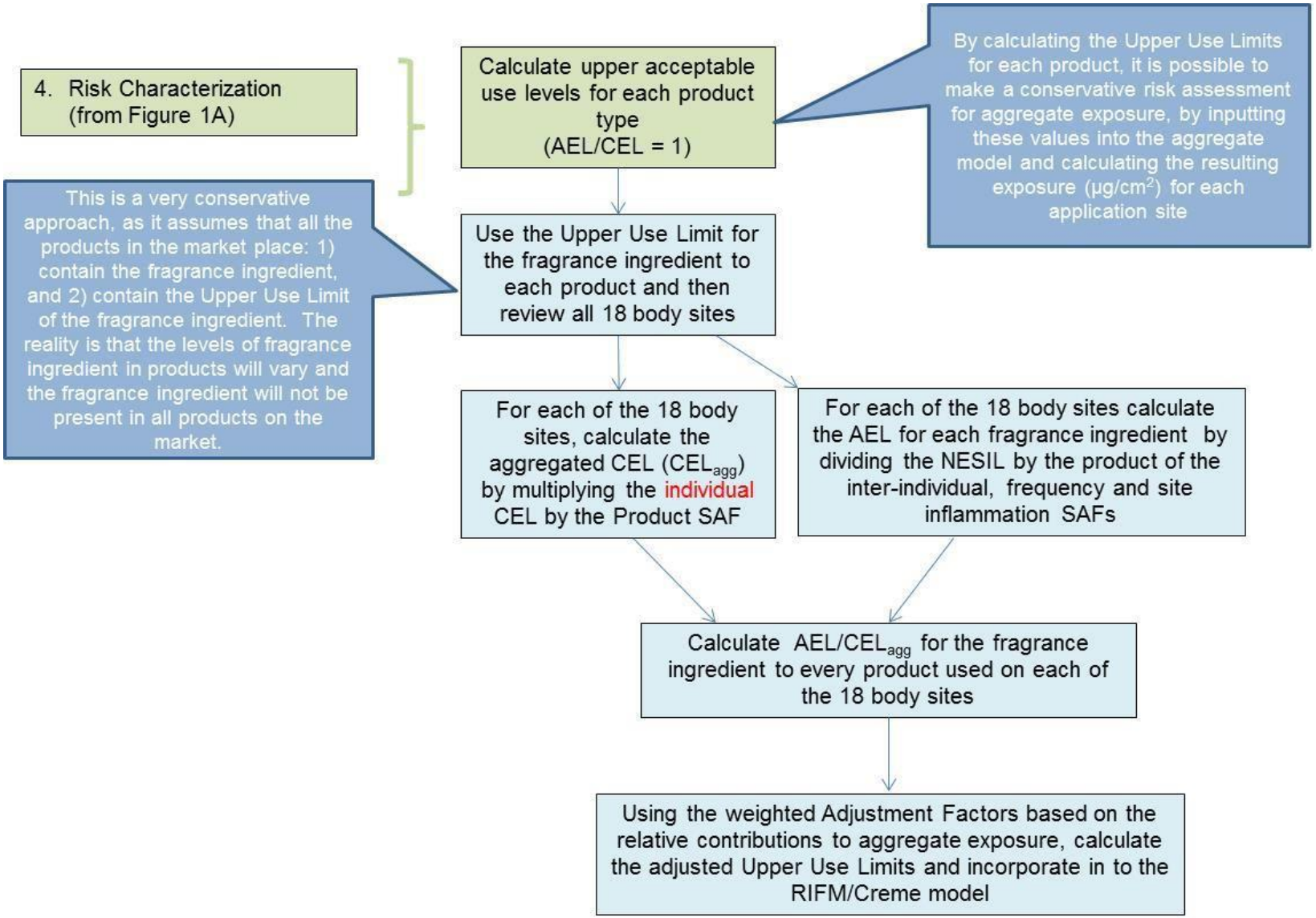

Figure 2: Use of QRA2 with Aggregate Exposure for Skin Sensitisation for Fragrance Ingredients

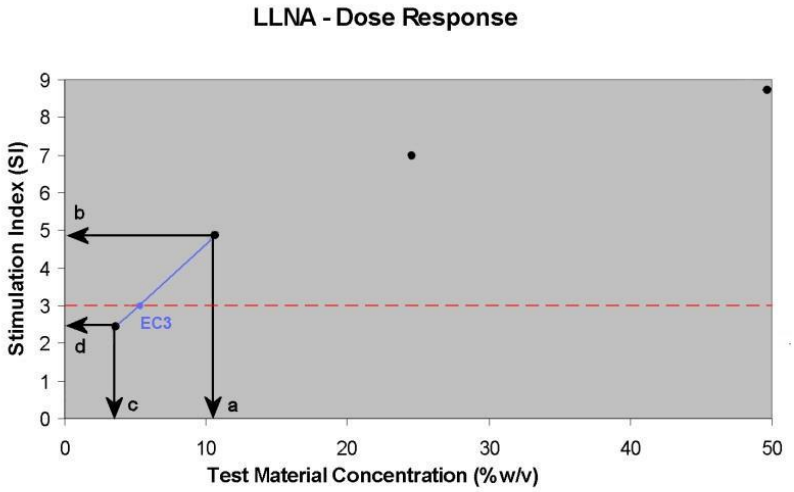

Figure 3: A Graphic Demonstration of the EC3 Calculation

suspicion from the weight of other evidence that the substance might not be a true non-sensitiser, it would be prudent to assume an EC3 value of 100%. The vehicle-treated control value cannot be used for the latter. The EC3 value is then calculated utilising the following equation and is illustrated in Figure 3:

$$EC3 = c + [(3-d)/(b-d)] * (a-c)$$

Historically, for non-cancer risk assessments based on a threshold, a default 10- fold uncertainty factor, to take into account toxicokinetic and toxicodynamic differences, has been used to extrapolate from laboratory animal species to humans. However specific information on toxicokinetics and/or toxicodynamics can reduce the uncertainty (but are not further discussed here). When tests are performed using, *in silico* or *in vitro* methods or results of tests on analogous substances are used in read-across, a weight of evidence approach needs to be developed to derive an indication of potency/hazard class which may require confirmation by conducting an HRIPT. The approach is somewhat different when using LLNA data to derive the relative potency of contact sensitisers. Initial use of LLNA data has focused on adding to the weight of evidence for ranking dermal allergens as to their relative potency. Much work has been done to correlate the dose-response data obtained in the LLNA with what is known about potency in humans. The EC3 value has been demonstrated to closely correlate with the NOAEL from human sensitisation tests designed to confirm lack of induction, in an extensive chemical dataset that embraces a range of chemistry and skin sensitising activity. The chemical diversity of this data set includes for example aldehydes, ketones, aromatic amines, quinones and acrylates (Api, 2008; Api *et al*., 2009; Basketter *et al*., 2000; 2005b; Gerberick *et al*., 2001; 2001a; 2004; Griem *et al*., 2003; Schneider and Akkan, 2004).

After a thorough review of the data, it was agreed at the IDEA workshops that an interspecies

assessment factor for extrapolation from the LLNA to humans was not needed. Strictly speaking, the EC3 value is not a true NOAEL in mice; it provides an indication of potency that correlates very well with the NOAEL in the confirmatory HRIPT. However, given the caution used to ensure that the selected dose levels avoid the induction of skin sensitisation in panellists, in most cases these HRIPTs do not determine maximum no effect levels. This may impact on the quality of the correlation between the LLNA EC3 value and experimental HRIPT NOAELs. The true maximum HRIPT NOAEL is generally somewhere well above the dose levels chosen for this confirmatory test and for ethical reasons, is not determined in the QRA process. The HRIPT according to strict and harmonized criteria (McNamee *et al*., 20008; Politano and Api, 2008) is used to confirm the 'no effect level' based on the total amount of material applied to the skin expressed as a dose per unit area (e.g. µg/cm^2).

2.2. Dose-Response or Hazard Quantification

2.2.1. No Expected Sensitisation Induction Level (NESIL)

The NESIL is defined as the quantitative threshold exposure level that is considered not to induce skin sensitisation in humans. A Weight of Evidence (WoE) approach is used to determine each NESIL. WoE introduces a scientifically more valid means for estimating the allergenic potency of a substance for its risk assessment than approaches used in the past. WoE has the advantage, over formerly used risk assessment practices, by specifically addressing the elements of exposure-based risk assessment that are unique to the induction of dermal sensitisation while being consistent with the principles of general toxicological risk assessment. WoE is used increasingly by regulatory authorities both in Europe and in the USA (where it is commonly called 'systematic review'). As such, it is a clear improvement over an earlier risk management strategy used by industry, under which each specific fragrance ingredient identified as an allergen was limited to the same concentration across all skin contact product types categorized as either 'leave-on' or 'rinse-off' (Api *et al.,* 2008). The determination of the NESIL, expressed as a dose per unit area (e.g. µg/cm²) is explained in detail by Api *et al*. (2008) with the scientific rationale to support use of this dose metric described by Kimber *et al*. (2008).

Briefly, there are several criteria that can assist in determining the NESIL. All the data that are available for a chemical should be considered. Quantitative Structure-Activity Relationship (QSAR) models or *in silico* models and read-across to data for structurally/mechanistically related chemicals that are determined to be suitable analogues of the chemical of interest can be important. An assessment of all the historical animal and human data is also essential.

For many fragrance raw materials sufficient test data (laboratory animal and human) already exist to allow estimation of skin sensitisation potential and potency classification. These data provide information permitting the establishment of a NESIL.

For newly developed ingredients, information to assess potency, (which is an essential

requirement of the QRA), may need to draw on non-animal experiments. Recently, significant advances in the use of non-animal test methods in hazard classification of ingredients have been made. The development of non-animal methodologies to provide information to estimate potency is an area of extensive ongoing research both within the fragrance industry and other sectors.

2.2.2. Human Data

Human sensitisation testing is not used in this process to determine hazard, but rather it is used to confirm the lack of sensitisation in the relevant species at a fixed exposure level that has been identified as highly unlikely to induce sensitisation.

Human repeat insult patch testing (HRIPT) methodology has a long history of development. In every method a number of potential induction exposures are followed by a rest period and then a challenge exposure. Variations exist as to patch type, number of subjects, skin site, number of induction patches, patch application period, duration and rest period prior to challenge. In all, enhancement of the skin response after challenge, over that seen during early induction exposures, has been the criterion by which induction of contact allergy is measured. Test volunteers are typically healthy adults who are enrolled without restriction as to sex or ethnicity. The test most typically conducted for confirming the absence of sensitisation responses under consumer relevant conditions is the HRIPT (McNamee *et al.,* 2008).

In HRIPTs, the size of the test population is important with regard to interpretation of findings. The sample size of test subjects must be sufficient so that results are likely to be valid for the population at large, yet small enough to be logistically feasible to conduct the study. For ethical reasons, a HRIPT is only conducted to confirm a dose level that is considered on the basis of solid evidence to be unlikely to cause reactions in the participating volunteers. Despite running many LLNAs and confirmatory HRIPTs, we are not aware of any false negative results (i.e. negative in the LLNA and confirmatory HRIPT, but clinical case reports of positive patch tests). There are certainly materials where there are potency differences between LLNA and HRIPTs (Api *et al*, 2014). A number of factors are incorporated in the protocol to further increase the sensitivity and reliability of the test (e.g. exaggeration through possible minor skin irritation of a test ingredient and use of occluded patches) (McNamee *et al.*, 2008).

To eliminate potential variations in methodology, the industry standard protocol (Politano and Api, 2008) has been adopted as the optimal approach to generate confirmatory human data for use in QRA.

It is generally agreed that HRIPT should not be conducted for hazard identification. Thus, a HRIPT is only conducted to confirm a dose level that is considered to be a NOAEL, where there is adequate data to support that the chosen dose will not result in the induction of skin sensitisation. A high degree of caution is used to ensure that the dose levels chosen for these tests will not produce reactions in the panellists. The HRIPT is conducted following Good Clinical Practices (GCP), with full informed consent and review by an external ethical review

board. RIFM has conducted 71 HRIPTs since 2005 (the first Standards based on the QRA were issued in 2006) on over 7,000 volunteers with only 24 reactions (0.3%) which includes 12 reactions with one material. As such the confirmatory HRIPT is used. It is pertinent to note that the critique by Basketter (2009) related to the testing of formulations and indicated that probably the only ethical use of the HRIPT was to confirm the NOAEL for a substance. He concluded that where there is a specific rationale for testing, for example, to substantiate a no-effect level for a sensitising chemical or to ensure that matrix effects are not making an unexpected contribution to sensitising potency, then rigorous independent review may confirm that an HRIPT is ethical and scientifically justifiable. The possibility that sensitisation may be induced in volunteers dictates that HRIPTs should be conducted rarely and in cases where the benefits overwhelmingly outweigh the risk.

2.2.3. Examination of the value of QRA1 in consumer protection

Api *et al*. (2010) reviewed clinical data from 2000 to 2007 for three fragrance ingredients – cinnamal, citral and isoeugenol – to assess the utility of the QRA approach. This assessment indicated that, had the QRA approach been available at the time IFRA Standards were originally established for these fragrance ingredients, the clinical data might have shown lower prevalence rates (i.e. reduced contact allergy). The data thereby provides some support that the QRA approach should be a useful tool for primary prevention of contact allergy.

Since the Api *et al*. (2010) publication, additional retrospective clinical data on fragrance ingredients have been reviewed for the years 2008-2012 from a sponsored survey of the patch test database at the Contact Allergy Unit, University Hospital Leuven, Belgium and presented at the IDEA workshops. This limited survey is summarised in Table 1. The survey focused on the number of positive clinical-patch test reactions to the fragrance ingredients in Fragrance Mix I and Fragrance Mix II in the different product types covering the period 2008-2012. Each year there were approximately 500 patients patch tested and the table provides the number of confirmed positive patch test reactions to individual fragrance ingredients in specific product types.

In Table 1, additional time was added for finished products entering the marketplace in compliance with the IFRA QRA-based Standards and natural clearance of the shelves of existing non-compliant products. Based on exchange of data with Cosmetics Europe and manufacturers of finished cosmetic products it can be reasonably assumed that the time needed to reach the shelf in a store is about 12 to 18 months. This time would, for example, cover consumer-product testing for safety, stability, consumer acceptance and performance as well as industrial scale-up and placing on the market. An additional time period to consider is that of products remaining on the shelf when no longer compliant with the most recent version of the Standards. The shelf-life of products is variable but the minimum durability of the majority of cosmetic products may be as long as 36 months. How long a cosmetic product might remain in the hands of the final consumers cannot be assessed, despite recommendations on the product package on the life of the product after opening.

The limited study also highlights the importance of continued, active monitoring of clinical patch-test data for fragrance ingredients. This point was reinforced at the IDEA workshops.

A prospective study is about to be instigated for the evaluation of the QRA (see Section 3.2.2).

Table 1: Identification of Confirmed Positive Patch Test Reactions to Fragrance Ingredients in FM I and FM II from the Patch Test Database (Contact Allergy Unit, University Hospital Leuven, Belgium)

Fragrance Ingredient	Fragrance Mix (FM) I or II	Standard Implementation Completed[1]	Potential Implementation for Product Shelf Life[2]	Total Confirmed Positive Patch Test Reactions to Product				
				2008	2009	2010	2011	2012
Amyl cinnamal	FM I	2009	2014	0	1	0	1	0
Cinnamyl alcohol	FM I	2009	2014	1	0	4*	0	2
Cinnamal	FM I	2009	2014	0	0	1	0	1
Geraniol	FM I	2009	2014	8	4	4	0	2
Hydroxycitronellal	FM I	2009	2014	1	4	2	0	0
Eugenol	FM I	2009	2014	0	0	2	3	0
Isoeugenol	FM I	2009	2014	1	0	0	0	0
Evernia prunastri Oakmoss absolute	FM I	2011	2016	0	2	2	0	0
Hydroxyisohexyl-3-cyclohexene carboxaldehyde (HICC)	FM II	2010[3]; 2011[4]	2015; 2016	12	12	13	5	5
Citronellol	FM II	2009	2014	1	3	2	0	2
Coumarin	FM II	2010	2015	0	0	0	1	1
Farnesol	FM II	2008	2013	1	2	1	0	1
α-Hexylcinnamal	FM II	2009	2014	0	10	5	0	4
Citral	FM II	2008	2013	2	0	1	0	9

[1]Standards were implemented first for new fragrance compounds and then for existing fragrance compounds. The date reflects when restrictions on all fragrance compounds would have been implemented.
[2]This includes 12-18 months to get the "new" products to the store shelves and up to 36 months for the shelf life of the "old" products. How long a cosmetic product in the end might remain in the hands of the final consumers is not possible to assess.
[3]Standard based on QRA.
[4]Standard incorporating elicitation information

2.2.4. Weight of Evidence Approach (WoE) for Determining the NESIL for Fragrance Ingredients

Historical data for determining the sensitisation potential of an ingredient may be of variable quality and robustness. Therefore, WoE is used, which takes account of all the available data for the identification of a no-expected sensitisation induction level (NESIL), to form the basis of an exposure-based quantitative risk assessment process. WoE approach will be reviewed in the next phase of the IDEA project.

2.2.4.1. Guidelines for Applying a Weight of Evidence Approach (WoE) to Induction Sensitisation Data on Fragrance Ingredients

A NESIL for the induction of skin sensitisation is determined for fragrance ingredients following a WoE based approach. The establishment of sound NESILs for the induction of skin sensitisation is critical to this QRA.

The NESIL can be established using data from "experimental"[1] animal studies, especially the murine LLNA, and taking existing (historical) human studies into account. Historical "experimental"[1] human data exist for both the HRIPT and Human Maximization Test (HMT). For ethical reasons, predictive, experimental tests to provide hazard identification for skin sensitisation are no longer conducted in humans. However, there may be instances where human volunteer tests, specifically HRIPTs, will be needed to confirm the lack of sensitising activity of a substance at a previously determined "safe" (i.e. non-sensitising) dose per unit area.

These guidelines for deriving the NESIL have been developed specifically for fragrance ingredients. The approach outlined by Api *et al.* (2008) has been applied to other cosmetic ingredients (e.g. Ezendam *et al*., 2013) but in these cases, adequate human confirmatory data were not available. However, the principles followed in establishing a NESIL may be applicable to skin sensitisation risk assessment for ingredients other than fragrance ingredients.

The following section has been developed to provide guidelines for use in establishing NESILs for fragrance ingredients; however, these are only guidelines. Scientific judgment must prevail when establishing NESILs for fragrance ingredients.

When deriving a NESIL, expressed as a dose per unit area, there may be cases where the level derived from a LLNA EC3 value is significantly higher or lower than the level derived

[1] The term "experimental" used in this technical dossier in the context of animal testing refers to previously performed animal sensitisation tests conducted to determine the skin sensitisation potential (hazard). LLNA data (expressed as EC3 values) are also used to correlate to human potency of dermal allergens. The term "experimental" used in this technical dossier in the context of human testing refers to human sensitisation tests conducted to confirm a NOAEL and not to determine hazard.

from the No Observed Effect Level (NOAEL) obtained in a previously conducted HRIPT or HMT or from read-across or QSAR data. In these cases, a WoE approach may be helpful in deriving a scientifically sound NESIL.

WoE guidelines have been developed to assist in resolving discrepancies between data generated

Guideline 1

From experimental investigations and on the grounds of basic immunological considerations, the quantity of chemical per unit area of the skin (e.g. µg/cm²) is considered as the most appropriate "dose metric" for skin sensitisation. This is currently judged the best scientific approach and is in line with the overwhelming majority of available historical data in both humans and experimental animals. Thus, NOAELs, LOAELs and EC3 values for sensitising chemicals will be expressed as dose per unit area in these WoE guidelines and for skin sensitisation QRA.

Guideline 2

A NOAEL from a well-run HRIPT will be given precedence over NOAELs from other tests that were conducted in human volunteers (e.g. HMT, earlier precursors to the HRIPT such as the Modified Draize Test), regardless of the NOAELs indicated from those other tests. It is important to evaluate the quality of the studies and to discriminate between the available data. A well run HRIPT is one which follows the protocol described by Politano and Api (2008) or which is more severe than this in accordance with the critical factors described by McNamee *et al.* (2008).

Guideline 3

Where a Lowest Observed Effect Level (LOAEL; i.e. the lowest dose per unit area which resulted in sensitisation) from other human tests exists (e.g. HMT), which is lower than the NOAEL from the HRIPT, *it will be considered* unless there is some reason to disregard such a LOAEL. In some instances, the conduct of a confirmatory HRIPT to substantiate a NESIL may be warranted.

Guideline 4

In the absence of a NOAEL from a HRIPT, a NOAEL from a different predictive human test (e.g. HMT) can be used to set the NESIL, provided that it is supported by an EC3 value from an LLNA conducted according to OECD Guideline TG 429 (OECD, 2002).

Guideline 5

Adjuvant tests in animals (GPMT, FCAT, MEST, etc.) and non-adjuvant tests in guinea pigs (e.g. Buehler, OET, CET) shall not be used as primary sources for defining NESILs in this context. They may be used to contribute information to determine the potency classification, according to the guidelines provided in the ECETOC, 2003 Technical report No. 87, and be incorporated in a WoE approach.

Guideline 6

When only LLNA data are available (i.e. no historical human data exist), then a confirmatory HRIPT should be considered. A cautious approach should be used for selection of the dose level of fragrance ingredient in the conduct of any such confirmatory HRIPTs including consideration of data on similar ingredients. Under exceptional circumstances (e.g. low volume of use, low use level) the EC3 value (or weighted average where more than one study exists; limited to two significant figures), can be used to define a NESIL or a default NESIL can be applied, based on potency considerations (Gerberick *et al*., 2001). This requires expert judgment.

Guideline 7

A NOAEL from a well-run HRIPT will (even if higher) take precedence over all other NOAELs (including LLNA EC3 values). When there is a significant discrepancy between a HRIPT NOAEL and a LLNA EC3 value (e.g. around an order of magnitude or more), further consideration in setting the NESIL will be required. A LLNA EC3 value that exceeds a NOAEL determined by a HRIPT will not be used to define the NESIL. If the HRIPT NOAEL is the lowest NOAEL available, it takes precedence in deriving the NESIL. Additional sources of data such as guinea pig studies, evaluated as described in ECETOC technical report No. 87, may provide additional evidence for the purposes of establishing a potency classification. In addition, data elucidating species differences, e.g. studies on metabolism (in the skin), skin penetration and vehicle effects should be considered.

Guideline 8

Data from diagnostic patch test studies cannot be used directly in a WoE approach for the determination of NESILs for the induction of contact allergy to fragrance ingredients. These studies are useful in helping to determine the need for additional data, for example indicating where current exposures to a fragrance ingredient may be a source of clinically relevant positive reactions. The absence of relevant positive reactions following testing in dermatology clinics could be interpreted as evidence that current exposures to the fragrance ingredient are safe.

2.2.4.2. NESILs for Selected Fragrance Ingredients

Animal (guinea pig and LLNA), human (HMT and HRIPT) and diagnostic patch test data for a group of 11 fragrance ingredients were collated for the fragrance allergens identified as the most important under the SCCS Opinion on Fragrance Allergens in Cosmetic Products (SCCS, 2012a). The guidelines detailed above were applied to all the data and a NESIL was identified. These NESILs are provided in Table 2.

Table 2: Fragrance Ingredients WoE NESILs

Fragrance Ingredient	CAS No.	LLNA weighted mean EC3 values(µg/cm^2) [no. studies]	Human Data			Potency Classification[2]	WoE NESIL[3] (µg/cm^2)
			NOAEL – HRIPT (induction) (µg/cm^2)	NOAEL – MAX (induction) (µg/cm^2)	LOAEL[1] (induction) (µg/cm^2)		
p-t-Butyl-α-methylhydro-cinnamic aldehyde (BMHCA)	80-54-6	2372 [6]	4125	NA	29,528	Weak	4100
Cinnamyl alcohol	104-54-1	5250[1][4]	3000	2759	4724	Weak	3000
Cinnamal	104-55-2	262 [23]	591	NA	775	Moderate	590
Citral	5392-40-5	1414 [11]	1400	NA	3876	Weak	1400
Coumarin	91-64-5	>12,500 [2]	3543	5517	8858	Weak	3500
Eugenol	97-53-0	2703 [6]	5906	NA	NA	Weak	5900
Farnesol	4602-84-0	1200 [2]	2755	NA	6897[5]	Weak	2700
Geraniol	106-24-1	3525 [5]	11,811	NA	NA	Weak	11,800
Hydroxycitronellal	107-75-5	5612 [9]	5000	NA	5906	Weak	5000
Isoeugenol	97-54-1	498 [18]	250	NA	775	Moderate	250

All data in this Table are available from RIFM.
NOAEL = No Observed Effect Level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximisation Test;
LOAEL = Lowest Observed Effect Level; NA = Not Available

[1]Data derived from HRIPT or Human Maximisation tests.
[2]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[3]WoE NESIL limited to two significant figures.
[4]EC3 value from one LLNA, not the mean.
[5]LOAEL from human maximisation test, not a human repeated insult patch test.

2.2.5. Sensitisation Assessment Factors for Fragrance Ingredients

Sensitisation Assessment Factors (SAFs), which are uncertainty factors used in the quantitative risk assessment process, are supported by published peer-reviewed scientific data (ECHA, 2012). A detailed explanation of the SAFs originally used in QRA1 and the scientific literature used to support the decisions assigning the SAFs was provided in the paper by Api *et al*. (2008). Api *et al*. (2008) provides a summary of QRA2 SAF values. A review of current data supporting the SAFs was conducted by Basketter and Safford (2015a).

Uncertainty factors are necessary to extrapolate from experimental to real-life exposure scenarios. The SAFs used for fragrance ingredients are intended to bridge this gap. Of course, when applying the QRA skin sensitisation methodology for other types of ingredients, the SAFs may need to be changed depending on details of the experimental conditions and how close those conditions are to the real-life scenario.

In the 2008 publication the SAFs were defined for certain product types and use conditions. Product categories were further defined according to similar combinations of SAFs and exposures that will lead to similar acceptable use levels of a fragrance ingredient. These

acceptable use levels are used to set industry standards for fragrance allergens.

At the initial multi-stakeholder IDEA workshop, it was considered important to undertake a comprehensive review of the evidence to support each SAF. In the following sections, the rationale for the application of a SAF and the numerical values, based on work carried out is discussed. In keeping with convention, values of 1, 10, and also the half log of 10 and 0.1 are used; the last two being indicated hereafter as 3 and 0.3 for the sake of brevity. The authors of this report recognise that certain elements of quantitative risk assessment are a matter of judgement. Accordingly, where numerical safety factors are multiplied together, the final values are always rounded to the nearest value in the sequence 1, 3, 10, 30, 100 and so forth, for simplicity and to avoid the illusion of excessive precision.

2.2.5.1. Inter-Individual Variability

As indicated above, a confirmatory HRIPT is a major contributor to the WoE for quantifying the NESIL. This test is carried out on 100 or more healthy volunteers of both sexes and spanning a wide range of ages (18-70). Therefore, the result of the HRIPT and, thus, also the NESIL already implicitly covers a good deal of the variability between individuals. However, these are healthy volunteers that do not "exhibit any physical or dermatological condition which would preclude application of the test articles" (Politano and Api, 2008). Therefore, an additional SAF value may be needed. The uncertainty factor or SAF for inter-individual variability, allows for possible variations in the sensitivity of individuals within the human population compared to this small sample of subjects in the HRIPT (Basketter and Safford, 2015a). From general toxicology it is known that for various reasons there can be large differences between individuals in response to a chemical. In fact, "some individuals readily become allergic to many chemicals, and others remain clinically tolerant of everything that they come into contact with" (Friedmann *et al*., 2015). There is infinite variability. These factors include genetic effects, sensitive subpopulations, existing disease states, age, sex and ethnicity. While all of these parameters are potentially important, some have more influence than others with respect to the endpoint of skin sensitisation. For example, genetic effects, sensitive subpopulations (including polysensitised individuals) and inherent skin condition are more influential than age, sex, ethnicity and most pre-existing disease states (Basketter and Safford, 2015a; Api *et al*., 2008; Felter *et al*., 2002; Robinson, 1999). There is little evidence to suggest that subjects with diseased skin (e.g. atopic eczema, psoriasis) have more intrinsic sensitivity to skin sensitisers.

The conclusion from the IDEA Workshops is that to account for differences in sensitivity of individuals within the human population, not accommodated in the NESIL, a SAF of 10 should be applied. (Note: Uncertainty relating to skin state – e.g. presence of irritant dermatitis – is addressed in the section on skin condition 2.2.5.5).

2.2.5.2. Products

The consumer can be exposed to fragrance ingredients in many different product forms (e.g.

lotion, shower gel, eau de toilette). These product formulations are of varying complexity ranging from aqueous media, simple ethanolic media to multi-phase creams. Under the experimental conditions of a confirmatory HRIPT, exposure to the fragrance ingredient is typically in a simple vehicle (ethanol, diethyl phthalate (DEP)). In addition, some of the consumer product formulations may contain ingredients that are irritants (e.g. in depilatories) or enhance penetration. It is noted however that new and previously overlooked data indicate that enhancement of penetration through the epidermis does not necessarily enhance sensitisation. This is reviewed by Basketter and Safford (2015a).

The product SAF should take into consideration the role of vehicle or matrix – predicted effect of product formulation versus the experimental conditions. Experimental evidence suggests that the matrix in which the sensitiser is presented to the skin may influence the degree of sensitisation (Basketter and Safford, 2015a). In considering the appropriate Matrix SAF it must be remembered that the most common solvents used in the HRIPTs for fragrance ingredients are DEP/ethanol. These solvents are considered to be optimal for the induction of sensitisation in an experimental situation (Lalko *et al*., 2004). That said, the experimental data in both animals and humans which supports this is, at best, limited. Thus, for products based on these or similar solvents, a factor of 1 is considered appropriate to account for the matrix. For aqueous based products, (although it is considered possible that the sensitisation potential will be reduced based on observations in the LLNA), it is proposed to maintain a factor of 1 for these products since they are rarely purely aqueous, and will contain other ingredients such as surfactants, that help the product wet the skin.

For solid matrices such as talc or residues on clothing, it is considered that the allergen itself would migrate from the solid substrate to sweat and sebum on the skin. It would then become the matrix from which skin penetration occurs. Given the oily nature of sebum it is proposed to use a factor of 1 for such exposures. A significant factor in the induction of sensitisation is the rate at which the allergen migrates into the sweat/sebum and this should be appropriately factored into the exposure calculation.

It was agreed at the IDEA Workshops that a SAF of either 0.3 or 1 or 3 could be used on a case by case basis (e.g. 0.3 (inert objects with no direct contact, e.g. candles or detergent pods or no vehicle/matrix) or 1 (most products) or 3 (penetration enhancers greater than anticipated from the experimental condition).

2.2.5.3. Occlusion

Occlusion of the skin (covering the area of application with a dressing) results in multiple effects, including increases in the hydration of the stratum corneum, skin temperature, microbial count, pH, and dermal irritation. The increase in hydration state, in particular, has been associated with increased dermal penetration. Although occlusion does not increase the absorption of all chemicals, the relative effect of occlusion is likely to be dependent on the lipophilicity of the chemical (Zhai and Maibach, 2001). The standard test conditions of the HRIPT used to confirm the NESIL employ a series of 24-hour exposures under full occlusion (Politano and Api, 2008). Typically, exposure to fragrance ingredients in consumer products involves a considerably lower degree and duration of occlusion than this.

Experimental data indicate that the sensitisation potential from partially occluded or non-occluded exposures may be lower than from full occlusion (Basketter and Safford, 2015a).

However, as *a conservative approach the worst case experimental conditions (full occlusion) were applied to all exposure situations and no correction (e.g. use of SAF smaller than 1) is introduced for non-occluded exposures/skin site*.

2.2.5.4. Frequency/Duration

With regard to the period/frequency of exposure, it is likely that many products will be used on a daily basis over extended periods of time (months, years). The experimental data from an HRIPT involves nine 24-hour exposures over a three-week period, and it has been questioned whether this is a valid simulation of for longer term use (Basketter and Safford, 2015a). There is limited experimental evidence to show that sensitisation may be increased when the normal dosing regimens of predictive tests are extended over longer periods.

It was agreed at the IDEA Workshops that frequency/duration SAF of 3 is sufficient.

2.2.5.5. Skin 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 sensitisation than others (Basketter and Safford, 2015a). However, the presence of compromised/inflamed skin may have an effect. The HRIPT is conducted on non-inflamed and intact skin, whilst consumers in the population at large may have compromised/inflamed skin due to a number of factors. In addition, there is little evidence that compromising the skin barrier by physical or chemical means increases the potential for the induction of sensitisation. However, the generation of inflammation in skin, particularly from contact with irritant chemicals (such as sodium lauryl sulfate or skin with active irritant contact dermatitis), may increase sensitivity to skin sensitisers (Basketter and Safford, 2015a). It is recognized that certain skin sites are more prone to inflammation than others, and that the SAFs may therefore vary between sites.

A SAF of 1, 3 or 10 should be assigned based on the susceptibility of the skin site to inflammation. Table 3 details SAFs used for each skin site, and Table 4 provides the rationale for applying skin condition SAFs to various products.

2.2.5.6. Defining SAF Numbers

The total SAF is calculated by multiplying the factors assigned to account for inter-individual variability, product effects, frequency of exposure and skin condition SAFs (see Table 5 for a summary of the SAFs based on the current proposals). As in other areas of toxicology, for each substance, careful consideration should be given to the appropriateness of applying a particular uncertainty factor (SAF).

Rationale for Fragrance Ingredients SAFs in Different Product Types:

Table 6 details the values assigned to each of the components of the total SAF for fragrance ingredients in a range of product types. These SAFs are specific for fragrance ingredients. SAFs for other categories of cosmetic ingredients may vary from these, based on the considerations discussed above.

2.2.5.7. Rationale to Define the Scope of Consumer Product Types Reviewed

The application of the QRA for fragrance ingredients required the identification of a range of product types. The list of product types is given in Table 6, Column 1. The list of product types is not intended to be exhaustive; it covers only the product types used in the aggregate exposure case studies.

Table 3: Summary of Skin Condition SAFs based on Body Site

Body Site	Additional definition for this study	Skin Condition SAF
Scalp		1
Face	Does not include: Eyes, Lips, Mouth, Behind Ears	3**
Peri-ocular	The eyelid and surrounding skin.	3**
Lips		3**
Intraoral	"Buccal" / "Inside Cheek"; Does not include: Lips	3**
Neck	Does not include: Behind Ears	3**
Behind Ears		1
Chest	Does not include: Axillae, Abdomen	1
Abdomen		1
Back	Does not include: Axillae	1
Axillae		10
Arms	Does include: Shoulder, Forearm, Upper arm; Does not include: Wrists, Hands, Palms, Axillae	1
Wrists		3**
Back of hand	Does not include: Palms, Wrists	3**
Palms		3**
Ano-genital		10
Legs	Does include: Buttocks, Thighs, Calves; Does not include: Feet	3**
Feet		3**

*In order to conduct the risk assessment considering aggregate exposure (see 0 and Appendix 4), the Skin Condition SAFs are aligned with the list of application sites from survey data.
**Note: for practical purposes the number 3 approximates 3.16 or the half log of 10.

Table 4: Rationale for Skin Condition SAF

Product Type	Rationale for Skin Condition SAF
Deodorants & Antiperspirants of all types including fragranced body sprays	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.
Hydroalcoholic Products (eau de toilette, parfum etc.)	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
Eye Products (Includes: eye shadow, mascara, eyeliner, eye make-up)	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
Body Creams, lotions	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
Hand cream	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
Facial Cream (Moisturizing)/Facial Balm	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
Women's Make up (Foundation)	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
Make-up remover	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
Lip Products	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
Hair styling aids (mousse, gels, leave in conditioners)	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
Hair sprays	The SAF is 1 because it is applied to the scalp. Products are not expected to be irritant and no additional contribution to skin condition is expected from product irritation
Shampoo	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
Body wash/shower gels	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
Conditioner (rinse-off)	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
Bar soap	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

Product Type	Rationale for Skin Condition SAF
Liquid soap	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
Face washes, gels, scrubs	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
Bath gels, foams, mousses	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
Toothpaste	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
Mouthwash	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

*Note: for practical purposes the number 3 approximates 3.16 or the half log of 10.

Table 5: Summary of SAF Values

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 (through using a mixed male/female HRIPT panel covering 18-70 years of age) is reflected by a SAF of 10.
Product	Role of vehicle/matrix	Delivery	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 (penetration enhancers greater than anticipated from the experimental condition)
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 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).

*Note: for practical purposes the number 3 approximates 3.16 or the half log of 10.

Table 6: SAFs for Fragrance Ingredients in Different Product Types

Product Type	Inter-individual SAF	Product SAF	Frequency/ Duration SAF	Skin Condition SAF	Total SAF	QRA1 SAF
Deodorants and Antiperspirant of all types	10	1	3*	10	300	300
Hydroalcoholic Products (Eau de Toilette, Parfum etc.)	10	1	3*	3**	100	100
Body Creams, lotions	10	1	3*	10	300	300
Hand Cream	10	1	3*	3*	100	100
Facial Cream/Facial Balm/Facial Make-up	10	1	3*	3*	100	100
Make-up remover	10	1	3*	3*	100	100
Lip Products	10	1	3*	3*	100	300
Hair styling aids (mousse, gels, leave in conditioners)	10	1	3*	3*	100	100
Hair sprays	10	1	3*	1	30	100
Shampoo	10	1	3*	10	300	100
Hair Conditioner (rinse off)	10	1	3*	3*	100	100
Bar soap	10	1	3*	10	300	100
Liquid soap	10	1	3*	3*	100	100
Body wash/shower gels, Bath gels, foams, mousses, Face washes, gels, scrubs	10	1	3*	10	300	100
Toothpaste	10	1	3*	3*	100	100
Mouthwash	10	1	3*	3*	100	100

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).
* Note: for practical purposes the number 3 approximates 3.16 or the half log of 10.

2.3. Exposure

2.3.1. Dose Metric

The measurement of exposure ("dose metric") recommended for use in skin sensitisation risk assessments for fragrance ingredients is dose/area (µg/cm^2). There is a difference between the applied versus the delivered dose since there are factors that can affect the effective amount of ingredient delivered to the viable epidermis such as evaporation, binding/sequestration in the skin, metabolism (inactivation and activation). For the purposes of QRA, the applied dose is used as a conservative estimate of actual consumer exposure.

Throughout the skin sensitisation literature, historical and current, allergen exposures are most commonly expressed in terms of percent (i.e. weight of allergen per volume of substance applied to the skin). This leads to the assumption that in any given test system an equal percentage exposure will lead to a similar incidence and/or severity of skin

sensitisation.

Based upon the understanding of the immunological mechanism involved, it is logical to assume that for an immune response to be initiated, a certain number of Langerhans cells (LC) are required to be activated in order to initiate the cascade of events leading to the threshold of induction for skin sensitisation being exceeded. This would suggest that for the induction of contact allergy, the application of an amount of allergen expressed as percent (weight/volume) is not as important as understanding both the dose applied and the surface area over which the allergen is applied. This has been thoroughly reviewed by Kimber *et al*. (2008) and has been established as an acceptable approach (Ter Burg, *et al*., 2010; ECHA, 2012).

2.3.2. Consumer Exposure Level (CEL)

Estimation of the Consumer Exposure Level (CEL) is an essential element of the QRA. Below we discuss the use for this purpose of Creme probabilistic aggregate exposure model to assess this. It is important to understand how consumers are likely to be exposed to fragrance ingredients from their use of the consumer products. Exposure levels occurring under intended and foreseeable conditions of use, but not deliberate misuse are addressed. The calculation of consumer exposure must include 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 and level of fragrance in product.

There are limited consumer habits and practices data for children, which are inadequate for probabilistic modelling. In addition, there are data to show that children are not more susceptible to skin sensitisation than adults (Cassimos *et al*., 1980; Epstein, 1961). Skin sensitisation is linked to exposure. In the application of the QRA (Api *et al.*, 2008), products designed for children (e.g. baby care consumer products, diapers) were considered in the SAF assignments.

The experimental evidence appears to show that young children are less easy to sensitise, so that a risk assessment for adults is conservative for children. A review on developmental immunotoxicology and risk assessment by Holsapple *et al*. (2004) concluded that current risk practices have been generally shown to be sufficient in protecting children (> 6 months old) and an additional safety factor is not needed to provide additional protection from that which is already achieved. Another review by Militello *et al.* (2006) finds that the risk of sensitisation appears to increase with age, which may be linked to an increase in exposure.

It should be noted that the CEL defined within this dossier addresses consumer products that are bought for personal use. Occupational/professional exposure is not included at this time because comprehensive habits and practices data are not available. It will be important to address occupational/professional exposure in the QRA approach when these exposure data become available. This is explored in recommendations for further refinement (see Section 3). Cross-reactivity appears to be an uncommon occurrence except with very closely related structures. When there are materials that cross-react, then the NESIL for the most potent material within the class is applied to all the materials. The levels of any such material

cannot exceed the limit dictated by the QRA (i.e. the IFRA Standard on Rose Ketones).

In the approach described here, dermal aggregate exposure is considered after the QRA-derived Upper Limit for acceptable consumer exposure level (AEL/CEL ratio = 1) for the fragrance ingredient is estimated. This is detailed in Section 2.3.3.

It is equally important to have accurate data on human parameters such as the body surface area over which the product is used. Skin penetration is not specifically addressed in measuring consumer exposure since the dose metric is unit weight applied per unit area of skin. As such, using a conservative approach, the applied dose is taken to be the delivered dose. In the case of reliable information on skin penetration rates the conservative approach can be modified.

Using these criteria, the data sources listed in Table 7 were used in the calculation of CEL. A hierarchy was established for selecting data based on quality and scope. When measured data for the same product type were available from more than one source, then the most conservative value (i.e. the highest value) was used unless there was a sound scientific rationale for using data from another source.

Examples:

1) For hydro-alcoholic fragrance products Cano and Rich (2001) data were selected for use in preference to the Loretz *et al*. (2008) data because the former reported distributions of amount, frequency and surface area in the same study while the latter did not identify frequency and surface in their study.
2) Hall *et al*. (2007) exposure study data were used in preference to the data published in Loretz *et al*. (2005) on the basis that the Hall *et al*. (2007) study participants used their own products rather than products supplied by the study investigator as in the CTFA study leading to more realistic use.
3) Cowan-Ellsberry *et al*. (2008) deodorant/antiperspirant data were used instead of those of Loretz *et al.* (2006) and Hall *et al.* (2007) because Cowan-Ellsberry *et al*. (2008) used measured 90th percentile exposure (amount) and surface area data and integrated them into a *per diem* exposure.

All of these sources of exposure data listed below use information of varying detail and completeness. This means that the robustness of the exposure data can also be different. For these reasons when evaluating a distribution of exposure data, the same percentile data point cannot be selected for each set of exposure data. For example, the 90th percentile was chosen from the Hall *et al.* (2007; 2011) and Loretz *et al.* (2006; 2008) exposure studies to define the most appropriate exposure level given the conservatism in the models. On the other hand, whilst the study conducted by Cano and Rich (2001), Tozer *et al*. (2004) and Cano (2006) measured distribution of amount, frequency of use and surface area was not overly conservative like the Hall *et al*. (2007; 2011) studies. On this basis it was more appropriate to choose a higher percentile from this study and therefore the 95th percentile was chosen. The individual references used to define the consumer exposure to different product types are detailed in Section 8 (Appendix 3) and Table 7.

Table 7: Summary of Available Habits and Practices and Human Parameters Data Used in the Calculation of Consumer Exposure to Different Product Types

(Exposures used in the QRA methodology are shown in bold-face and highlighted)

Product Type	Surface Area cm^2	Surface Area Reference	Retention Factor [1]	SCCS Notes of Guidance, 8th Revision, 2012		Loretz *et al*., 2005; 2006; 2008		Cano & Rich, 2001; Tozer *et al*., 2004; Cano, 2006	Hall *et al*., 2007; 2011; Steiling *et al*., 2012		HERA [1]	Api *et al*., 2007	Cowan-Ellsberry *et al*., 2008	RIFM [2]
				mg/d	$mg/cm^2/d$	90th Percentile		95th Percentile	90th Percentile		$mg/cm^2/d$	$mg/cm^2/d$	$mg/cm^2/d$	$mg/cm^2/d$
						mg/d	$mg/cm^2/d$	$mg/cm^2/d$	mg/d	$mg/cm^2/d$				
Deo non-spray	100	Bremmer, 2003, per axillae	1	1500	7.5				1500	7.5				
Deo aerosol Spray	100	Bremmer, 2003, per axillae	1	1430	7.2				1430	7.2				
Deo Spray (not ethanol based)	100	Bremmer, 2003, per axillae	1	690	3.5				6910	3.5				
Solid AP	96.8	Cowan- Ellsberry *et al.,* 2008, per axillae	1			1700	8.50						9.1**	
Shaving Cream/ Depilatory [3]	305	Bremmer, 2003 (1/4 area head, male)	0.01	2000	0.07									
Lip Products	4.8	Ferrario *et al.*,2000	1	57	11.9	55	11.46		56.53	11.8				
Eye Products [5]	24	Bremmer, 2003	1	20	0.83	52	2.17							
Body Cream/Lotion [6]	12895	EPA, 1997 (area body - head and ½ trunk, female) [10]	1	7820	0.6	14400	1.12		7800	0.60				
Men's Facial Cream	775	Bremmer, 2003 (1/4 area head + 1/2 area hands, male)	1	1540	2.0									

Product Type	Surface Area cm^2	Surface Area Reference	Retention Factor[1]	SCCS Notes of Guidance, 8th Revision, 2012		Loretz *et al*., 2005; 2006; 2008		Cano & Rich, 2001; Tozer *et al*., 2004; Cano, 2006	Hall *et al*., 2007; 2011; Steiling *et al*., 2012		HERA[1]	Api *et al*., 2007	Cowan-Ellsberry *et al*., 2008	RIFM[2]
				mg/d	$mg/cm^2/d$	90th Percentile		95th Percentile	90th Percentile		$mg/cm^2/d$	$mg/cm^2/d$	$mg/cm^2/d$	$mg/cm^2/d$
						mg/d	$mg/cm^2/d$	$mg/cm^2/d$	mg/d	$mg/cm^2/d$				
Toothpaste	216.8	Collins et al., 1987; Ferrario et al., 2000 (buccal + lips)	0.1[11]	2750	1.27				2750	1.27				
Mouthwash	216.8	Collins *et al*., 1987; Ferrario *et al*., 2000 (buccal + lips)	0.01[11]	21600	1.0				21620	1.0				
Hydroalcoholic Products for Shaved Skin	775	Bremmer, 2003 (1/4 area head + 1/2 area hands, male)	1					2.21						
Hydroalcoholic Products for Unshaved Skin	100	Bremmer, 2003, perfume spray	1			1770	17.70	2.21						
Women's Facial Cream	555	EPA, 1997 (1/2 area head, female)	1	1540	2.8	3500	6.31		1540	2.8				
Women's Facial Liquid Make-up	555	EPA[3] (1/2 area head, female)	1	510	0.92	1760	3.17		513	0.92				
Hair Sprays – Aerosol[8]	555	EPA, 1997(1/2 area head, female)	0.1			7730	1.39							
Hair Sprays - Pump Spray[8]	555	EPA, 1997(1/2 area head, female)	0.1			12220	2.20***							
Hair Styling Aids	1010	Bremmer, 2003 & EPA, 1997 (1/2 area hands +1/2 head)	0.1	4000	0.4				4000	0.4				
Shampoo	1430	EPA, 1997 (area hands + 1/2 head)	0.01	10460	0.07	23630	0.17		10460	0.07				
Conditioners, Rinse-off	1430	EPA,1997 (area hands +1/2 head)	0.01	3920	0.03	28200	0.20							
Make-up Remover	555	EPA, 1997 (1/2 area head, female)	0.1	5000	0.90									

Product Type	Surface Area cm^2	Surface Area Reference	Retention Factor [1]	SCCS Notes of Guidance, 8th Revision, 2012		Loretz *et al*., 2005; 2006; 2008		Cano & Rich, 2001; Tozer *et al*., 2004; Cano, 2006	Hall *et al*., 2007; 2011; Steiling *et al*., 2012		HERA [1]	Api *et al*., 2007	Cowan-Ellsberry *et al*., 2008	RIFM [2]
				mg/d	$mg/cm^2/d$	90th Percentile		95th Percentile	90th Percentile		$mg/cm^2/d$	$mg/cm^2/d$	$mg/cm^2/d$	$mg/cm^2/d$
						mg/d	$mg/cm^2/d$	$mg/cm^2/d$	mg/d	$mg/cm^2/d$				
Nail care	11	RIVM[2]	0.1	107.5	0.97									
Bar Soaps	840	EPA, 1997 (area hands)	0.01	20000	0.2									
Liquid Soap	840	EPA, 1997 (area hands)	0.01	20000	0.2									
Hand Cream	840	EPA, 1997 (area hands	1	2160	2.6				2160	2.6				
Face Washes, Gels, Scrubs	555	EPA, 1997 (1/2 area head, female)	0.01			8300	0.15							
Body WashGels, Foams, Mousses	16900	EPA, 1997 (body area, female)	0.01			25500	0.015							
Bath Foams, Gels, Mousses	16900	EPA, 1997 (body area, female)	0.01	18670	0.010				18670	0.010				
Feminine Hygiene - Tampons														2.9
Feminine Hygiene - Pads														0.14
Feminine Hygiene - Liners														0.14
Baby Diapers														0.0006
Baby Wipes														4.0
Intimate Wipes														4.4
Aerosol Air Freshener	3425	EPA, 1997 (1/2 area head + upper extremities, female)	1											0.025

Product Type	Sur-face Area cm^2	Surface Area Reference	Reten-tion Factor [1]	SCCS Notes of Guidance, 8th Revision, 2012		Loretz *et al*., 2005; 2006; 2008		Cano & Rich, 2001; Tozer *et al*., 2004; Cano, 2006	Hall *et al*., 2007; 2011; Steiling *et al*., 2012		HERA [1]	Api *et al*., 2007	Cowan-Ellsberry *et al*., 2008	RIFM [2]
				mg/d	$mg/cm^2/d$	90th Percentile		95th Percentile	90th Percentile		$mg/cm^2/d$	$mg/cm^2/d$	$mg/cm^2/d$	$mg/cm^2/d$
						mg/d	$mg/cm^2/d$	$mg/cm^2/d$	mg/d	$mg/cm^2/d$				
Hand wash Laundry											0.1			
Laundry Tablets & Powder												Insigni-ficant		
Hand Dishwashing												0.01		
Fabric Clothing												Insigni-ficant		
Hard Surface Cleaner												0.12		
Candles												0.00033		

**This exposure value is used in the QRA for fragrance ingredients for all types of deodorants and antiperspirants.

***This exposure value is used in the QRA for fragrance ingredients for all types of hair sprays.

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

1) HERA, Technical Guidance Document, 2003.
2) RIFM, 2005, AM Api, Internal memo December 12, 2005, on dermal exposure to pressurised aerosol air fresheners. RIFM, 2006, Memo to AM Api from RIFM Member Company, May 2006 on exposure to feminine hygiene products and baby wipes.
3) Shaving cream/depilatory cream products – the amount used was derived from the EC, 1996 Technical Guidance Document in support of Commission Directive 93/67/EEC on risk assessment for new notified substances and Commission Regulation (EC) No 1488/94 on risk assessment for existing substances. This reference did not distinguish between shaving the face or shaving the leg. As such, the dose/unit area for shaving the face was calculated and the same value was applied to shaving or depilating the legs. In the absence of more robust data, this was assumed to be a reasonable and conservative approach.
4) For frequency of use less than once per day, the default of once per day was used with the exception of nail care products where a frequency of 0.43 was used.
5) Eye products – This is based on the Loretz *et al*. 2008 measured data for all types of eye shadows from a specifically designed exposure study for eye products. The SCCS, 2012 exposure data on mascara product types were not used for the eye product category because there is little if any skin contact from this product type.
6) Body cream/lotion – The surface area comprises the total body surface area for a female minus the area of the head and half the trunk. This is based on habits and practices data for adults that indicate that body lotion is not applied to the head or the back.
7) These are product dilution factors. Different dilution factors are used for mouthwashes and toothpastes. The dilution factor used for mouthwashes is 1% or 0.01 and that used for toothpastes is 10% or 0.1. These values are different from the values used in the SCCS 2012 Guidelines, but considered to be more relevant since it takes into account the amount remaining in the oral cavity and perioral area rather than that ingested. It also takes into account salivation and distribution across the oral cavity surface (Muhlemann and Rudolf, 1975; Zero *et al*., 1988; Issa and Toumba, 2004). The difference in the dilution factors used for mouthwashes and toothpastes is based on the fact that while very different volumes of each product are applied (i.e. 30 g/day of mouthwash vs. 2.7 g of toothpaste), it is reasonable to expect that similar amounts of product would be in contact with the mouth (buccal cavity and lips) at any one time since the same surface area is involved. The exposure to oral care products (toothpastes and mouthwashes) is impacted by salivation, product dilution and distribution across the oral surfaces and the focus for sensitisation reactions is the perioral area. As such, in order to benchmark against the exposure approach used here, a worst case exposure scenario was evaluated using the principles of HERA. In HERA, it was assumed that a 0.01 cm film thickness was left on the skin (Vermeire *et al*., 1993) from a 10% aqueous product solution. This would result in a worst case exposure of $1 mg/cm^2$, assuming 100% retention of the fragrance ingredient from the product solution. This is consistent with the value identified by the primary exposure approach.
8) Hair Spray – exposure for the pump spray is recommended for all hair sprays since this figure was the most conservative (e.g. highest) value.

When introducing dermal aggregate exposure in the QRA, single point values for the habits and practices data are not used. The full distribution of exposure data were built in to the Creme RIFM Aggregate Exposure Model (see Executive Summary and section 2.3.3).

2.3.3. Consideration of Dermal Aggregate Exposure

Consumers generally use several products each day, and some of these will be applied to the same skin site. If these products contain the same fragrance ingredients, then it becomes important to consider aggregate exposure when conducting the risk assessment for skin sensitisation. In order to incorporate dermal aggregate exposure in the QRA for ingredients, it is necessary to account for the products applied to each body site. The methodology reported here is focussed on assessment of exposure in cosmetics. It does not include aromatherapy, drugs and topical treatments, massage and spa therapies, occupational exposure, natural exposure, foods as the necessary data base is lacking still.

Since 2010, the Research Institute for Fragrance Materials has been developing a model to estimate the aggregate exposure to fragrance ingredients resulting from the use of consumer products. This model has now been modified for use in dermal QRA2 for sensitisation. Creme Global (www.cremeglobal.com) is their well-established partner in modelling exposure to cosmetics and foods, and their exposure methodologies are used by regulatory bodies such as SCCS (SCCS, 2014) and EFSA (Vilone *et al*., 2014) and a trade association (Cosmetics Europe, previously COLIPA; Hall *et al*. 2007, 2011; McNamara *et al*., 2007).

The Creme RIFM Aggregate Exposure Model is based on declared habits and practices data from 36,446 panellists across Europe and The United States of America (Kantar Database, 2011), also described in Comiskey *et al*. (2015) and Safford *et al*. (2015). Each panellist 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 allow full distributions of data sets, providing a more realistic estimate of aggregate exposure to individuals across a population (Comiskey *et al*., 2015; Safford *et al*., 2015) compared to a deterministic aggregate approach. An overview of the Creme RIFM aggregate exposure model is provided in the Appendix 4 (Section 9). Output from the model provides dermal exposure as amount of product and/or fragrance per skin surface area (µg/cm^2) for different body areas for the highest use day for each consumer and also assumes a fragrance material is always present in every product, these assumptions are considered conservative. In order to select an appropriate percentile to use for risk assessment purposes, the probabilistic aggregate exposure model design is considered. The 95th percentile of exposure is used as 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 model.

An example of such conservatism in the model is that dermal aggregate exposure is calculated using the assumption that the fragrance ingredient is present in all products at the QRA2 upper use level (concentrations). This leads to an aggregate Consumer Exposure Level (CEL_{Agg}) that exceeds the Acceptable Exposure Level (AEL) i.e. $AEL/CEL_{Agg} < 1$ in some instances.

As such, this section of the dossier is intended to explain the proposed methods of reducing the QRA derived upper use levels so that when aggregate exposure is considered, the AEL is not exceeded. The proceeding sections describe a method to reduce the fragrance concentrations in product types and categories based on their relative contribution to aggregate exposure.

2.3.3.1. Deriving QRA2 Upper Use Levels

Initially the QRA upper use levels were calculated deterministically, based on the NESIL for the fragrance material, the total SAF for each product and application site (explained in the accompanying document) and the high percentile product exposure to each application site (Api *et al*., 2008). In the present proposal an example of such reverse calculations of the upper use levels were made for the fragrance Citral (Table 8), using the following formula:

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

Table 8: Derived QRA2 Upper Use Levels for Citral by Product Type

	Citral NESIL = 1400 µg/cm²		
Product Type	**Proposed Total SAF for QRA2**	**Exposure mg/cm²/day**	**QRA2 product type upper use levels**
Deodorants and antiperspirants of all types including fragranced body sprays	300	9.10	0.05%
Hydroalcoholic products (eau de toilette, parfum etc.)	100	2.21	0.63%
Body creams, lotions	300	0.60	0.78%
Hand cream	100	2.60	0.54%
Facial cream (moisturizing)/facial balm	100	2.80	0.50%
Eye products (Includes: eye shadow, mascara, eyeliner, eye make-up)	100	2.17	0.65%
Women's make up (foundation)	100	0.92	1.52%
Make-up remover	100	0.90	1.56%
Lip products	100	11.80	0.12%
Hair styling aids (mousse, gels, leave in conditioners)	100	0.4	3.50%
Hair sprays	30	2.20	2.12%
Shampoo	300	0.17	2.75%
Body wash/shower gels	300	0.015	31.10%
Conditioner (rinse-off)	100	0.2	7%
Bar soap	300	0.2	2.33%
Liquid soap	100	0.2	7.00%
Face washes, gels, scrubs	300	0.15	3.11%
Bath gels, foams, mousses	300	0.01	46.67%
Toothpaste	100	1.27	1.10%
Mouthwash	100	1.00	1.40%

Based on these calculations, it was found that in many cases the upper use levels far exceeded realistic industry use levels (e.g. body wash/shower gel, 31.10%; Table 8) due to the assumption that some products are used evenly all over the body leading to a reduced exposure per unit surface area which affords them a greater QRA2 upper use level. On the other hand, products that are assumed to be used on specific parts of the body (e.g. deodorants used on axillae, 0.05%; Table 8) their calculated QRA2 upper use levels are lower due to the reduced surface area with which they are applied. When the QRA2 upper use levels were input into the Creme RIFM Aggregate Exposure Model, it was found that many of the product types produced a CEL_{Agg} that exceeded the AEL for specific applications sites. This was due to product co-use and the fact that subjects in the habits and practices survey applied products in a way that is contrary to the QRA2 upper use levels assumptions e.g. shower gel used on palms and face only.

Moreover, the disparity in upper use levels between products (*cf*. bath gels and deodorants; Table 8) in the Creme RIFM aggregate exposure model resulted in all product types requiring a large reduction in upper use levels for specific application sites, despite the fact that only some products were driving the aggregate exposure. To rectify this issue it was decided that the product type with the lowest upper use level from their designated product categories would be used in the aggregate exposure model for all products in their category, where products with similar exposure and SAF were grouped together (Table 9). ***Note that product categorization was introduced in the implementation of the IFRA Standards based on QRA1 where it is anticipated that IFRA will also introduce product categorization in QRA2. It should be noted that the categorization shown here is for illustrative purposes and is subject to change, where other products and categories may need to be introduced.***

Importantly, these categorized (lowest) upper use levels were considered to be more realistic in terms of proximity with industry use levels, based on expert judgment. Thus, each of the product types in their categories had the same (lowest) upper use level, and the exposure results from each individual product type were aggregated by product category. It should be noted that not all the product types are available in the Creme RIFM model, for example, eye products, make-up remover and bath gels. Using the conservative assumption that, for a given category, the upper use level is acceptable then for a given category the product types not in the model can be assumed to have the same low concentration.

Table 9: Upper Use Levels for Citral in Product Types and Product Categories

Product Type	QRA2 product type upper use levels	Product Categorization	QRA2 categorized upper use levels
Deodorants and antiperspirants of all types including fragranced body sprays	0.05%	A	0.05%
Hydroalcoholic products (eau de toilette, parfum etc.)	0.63%	B	0.63%
Body creams, lotions	0.78%	C	0.50%
Hand cream	0.54%		
Facial cream (moisturizing)/facial balm	0.50%		
Eye products (Includes: eye shadow, mascara, eyeliner, eye make-up)	0.65%	D	0.12%
Women's make up (foundation)	1.52%		
Make-up remover	1.56%		
Lip products	0.12%		
Hair styling aids (mousse, gels, leave in conditioners)	3.50%		
Hair sprays	2.12%		
Shampoo	2.75%	E	2.33%
Body wash/shower gels	31.10%		
Conditioner (rinse-off)	7%		
Bar soap	2.33%		
Liquid soap	7.00%		
Face washes, gels, scrubs	3.11%		
Bath gels, foams, mousses	46.67%		
Toothpaste	1.10%	F	1.10%
Mouthwash	1.40%		

2.3.3.2. Aggregate Exposure Risk Assessment with Upper Limit Use Levels

The categorized upper use levels were input into the Creme RIFM aggregate exposure model to estimate the 95th percentile CEL_{Agg} for each of body 18 application sites (Table 10:). The AEL for Citral was calculated for each body application site. This first required the calculation of the total SAF, which is the summation of four SAFs: 1) inter-individual, 2) matrix, 3) frequency and 4) skin condition. The ratio of the total SAF to the NESIL for Citral was calculated to give the AEL (AEL = NESIL/Total SAF). Finally, the AEL/CEL_{Agg} could be calculated to determine if the ratio was above or below 1, where a value greater than 1 indicated that the CEL_{Agg} did not exceed the threshold set by the AEL.

It was found that four body application sites had an AEL/CEL_{Agg} below 1, which suggests that the Citral concentration (upper use level) should be lowered; lips, intra-oral region, palms and the axillae (Table 10:). Lips had the lowest AEL/CEL_{Agg} (0.45), intra-oral region had the second lowest (0.48), followed by palms (0.63) and axillae (0.65). All other products had an AEL/CEL_{Agg} greater than 1. Therefore, the upper use level of Citral in the products applied to these application sites needed to be reduced such that their AEL/CEL_{Agg} were above 1.

Table 10: AEL/CEL$_{Agg}$ for Application Sites, Ordered from Lowest to Highest

Application site	Inter-individual SAF	Matrix SAF	Frequency SAF	Skin Condition SAF	Total SAF	NESIL	AEL (NESIL/ Total SAF)	CEL$_{Agg}$	AEL/CEL$_{Agg}$
Lips	10	1	3	3	100	1400	14	31.1	0.45
Intra-oral	10	1	3	3	100	1400	14	29	0.48
Palms	10	1	3	3	100	1400	14	22.3	0.63
Axillae	10	1	3	10	300	1400	4.7	7.22	0.65
Back of Hand	10	1	3	3	100	1400	14	8.93	1.57
Face	10	1	3	3	100	1400	14	8.37	1.67
Neck	10	1	3	3	100	1400	14	6.35	2.2
Ano-genital	10	1	3	10	300	1400	4.7	1.61	2.9
Scalp	10	1	3	1	30	1400	46.7	9.77	4.78
Wrists	10	1	3	3	100	1400	14	2.8	5
Feet	10	1	3	3	100	1400	14	2.65	5.28
Peri-ocular	10	1	3	3	100	1400	14	2.36	5.93
Behind ears	10	1	3	1	30	1400	46.7	4.16	11.22
Legs	10	1	3	1	30	1400	46.7	2.15	21.72
Arms	10	1	3	1	30	1400	46.7	1.71	27.29
Chest	10	1	3	1	30	1400	46.7	1.52	30.7
Abdomen	10	1	3	1	30	1400	46.7	1.52	30.7
Back	10	1	3	1	30	1400	46.7	1.51	30.91

2.3.3.3. Use of Aggregate Exposure Assessment for Adjusting Upper Use Levels

In this section, the method of reducing the upper use levels in the product types that were applied to the four applications sites, whose AEL/CEL$_{Agg}$ was less than 1 (lips, intra-oral, palms and axillae) is described.

2.3.3.4. Adjust Upper Use Levels in Products Applied to the Lips

For the case of adjusting the upper use level in products applied to the lips, there were four product categories to adjust (F, D, C, E), and therefore only four upper use level values (1.10%, 0.12%, 0.5%, 2.33%, respectively) to adjust. To adjust the upper use level in products applied to the lips, one must consider the contribution from those individual products categories to the overall aggregated exposure (Figure 4). Since not all product categories will

have an equal contribution to aggregate dermal exposure it was necessary to approximate what their individual contributions were to total exposure. This allowed the upper use level concentration to be reduced by way of deriving weighting factors.

The approximate percentage contribution that each individual product category has on the aggregate exposure to an application site was calculated from their individual 95th percentile product category exposure. The 95th percentile exposure for each individual product category was divided by the sum of all 95th percentile product category exposures to an application site (see Table 11). It should be noted that the total sum of the individual product category exposures do not equate to the CEL_{Agg} but are used to approximate their relative contribution to the CEL_{Agg}. Importantly, sensitivity analyses have shown that individual product exposures are a good approximation of their contribution to aggregate exposure.

Finally, based on the relative contribution each product category has on the aggregate exposure, it was possible to calculate a weighting factor. In the example below, Category F products had a contribution of 84.7%, therefore the upper use level of Citral in this product category was reduced by 84.7%, by multiplying the upper use level of Citral in Category F products by a weighting factor of 0.15 (1 – 0.847). For Category E product types, whose contribution to CEL_{Agg} was 0.6%, the upper use level was reduced by 0.6% using an upper use level weighting factor of 0.99 (1 – 0.006).

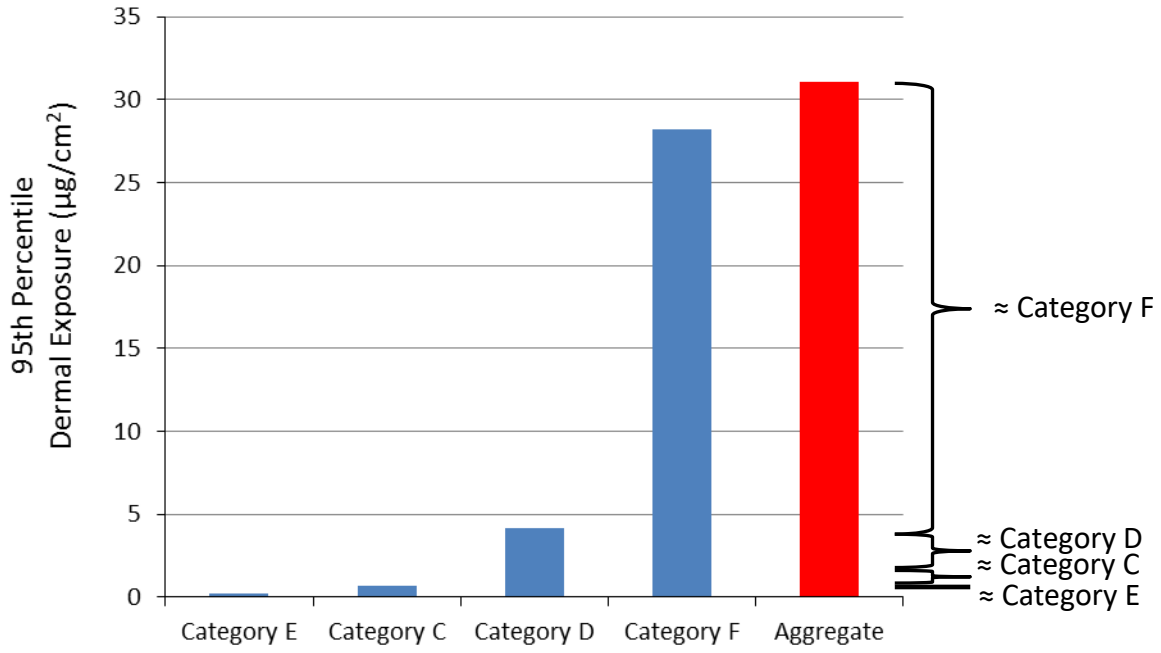

Figure 4: Illustration of Approximate Contribution of Product Categories to the CEL_{Agg} to the Lips

Table 11: Calculation of Approximate Percentage Relative Contribution to Aggregate Exposure Form Individual Product Categories Applied to the Lips to Produce Upper Use Level Weighting Factors

Product Category	95th Percentile Dermal Exposure (µg/cm²)	Relative Contribution	Percentage Relative Contribution	Upper Use Level Weighting Factor
F	28.2	28.2/33.3 = 0.847	84.7	1 - 0.847 = 0.15
D	4.2	4.2/33.3 = 0.126	12.6	1 - 0.126 = 0.87
C	0.7	0.7/33.3 = 0.021	2.1	1 - 0.021 = 0.98
E	0.2	0.2/33.3 = 0.006	0.6	1 - 0.006 = 0.99
Total	33.3	**1**	**100%**	**-**

When the weighted upper use levels were input into the Creme RIFM aggregate exposure model, it was found that the AEL/CEL_{Agg} was 1.9, which suggests that the upper use levels were reduced by more than was necessary. The AEL/CEL_{Agg} overshoot by a factor of almost 2 was caused by the high weighting factors, especially from Product Category F. In this instance it was necessary to incorporate a multiplication factor to appropriately reduce the individual product category weighting factors to produce an AEL/CEL_{Agg} that is closer to 1, thus:

Upper Use Level Weighting Factor = 1 – (Contribution × Multiplication Factor)

Using this method, it was found after several iterations that a multiplication factor of 0.776 (Table 12) provided appropriate upper use level weighting factors, which led to an AEL/CEL_{Agg} of 1.13 (Table 13). It should be noted that the adjustment factors produced an AEL/CEL_{Agg} that were in all cases above 1 (not equal to 1). The reason for this was that the probabilistic nature of the Creme RIFM model allows for standard error in the aggregate exposure estimates, thus an AEL/CEL_{Agg} that is slightly above 1 compensates for this.

Interestingly, the re-calculation of the AEL/CEL_{Agg} for all application sites with the adjusted upper use levels showed that the AEL/ CEL_{Agg} for the intra-oral region was found to be above 1 due to the reduced upper use level of Citral in product Category F. The AEL/CEL_{Agg} increased for all application sites, however the AEL/CEL_{Agg} for palms and axillae were still below 1 and thus required the upper use levels to be reduced in the products that contributed to their aggregate exposure.

Table 12: Calculation of Upper Use Level Weighting Factors Based on Product Category Contribution and Adjustment Factor

Product Category	Relative Contribution	Multiplication Factor	Upper Use Level Weighting Factor
F	0.847	0.776	1 – (0.847*0.776) =0.34
D	0.126	0.776	1 – (0.126*0.776) = 0.9
C	0.021	0.776	1 – (0.021*0.776) = 0.98
E	0.006	0.776	1 – (0.006*0.776) = 1

Table 13: Re-Calculation of AEL/CEL$_{Agg}$ where CEL$_{Agg}$ to Lips has been Adjusted. The AEL/CEL$_{Agg}$ for Axillae and Palms Remain Less than 1.

Application site	Inter-individual SAF	Matrix SAF	Frequency SAF	Skin Condition SAF	Total SAF	NESIL	AEL (NESIL/ Total SAF)	CEL$_{Agg}$	AEL/CEL$_{Agg}$
Palms	10	1	3	3	100	1400	14.0	21.7	0.65
Axillae	10	1	3	10	300	1400	4.7	7.06	0.66
Lips	10	1	3	3	100	1400	14.0	12.4	1.13
Intra-oral	10	1	3	3	100	1400	14.0	9.67	1.45
Back of hand	10	1	3	3	100	1400	14.0	8.66	1.62
Face	10	1	3	3	100	1400	14.0	8.4	1.67
Neck	10	1	3	3	100	1400	14.0	6.3	2.22
Ano-genital	10	1	3	10	300	1400	4.7	1.72	2.71
Scalp	10	1	3	1	30	1400	46.7	9.39	4.97
Wrists	10	1	3	3	100	1400	14.0	2.79	5.02
Feet	10	1	3	3	100	1400	14.0	2.45	5.71
Peri-ocular	10	1	3	3	100	1400	14.0	2.29	6.11
Behind ears	10	1	3	1	30	1400	46.7	3.89	12.00
Legs	10	1	3	1	30	1400	46.7	2.06	22.65
Arms	10	1	3	1	30	1400	46.7	1.71	27.29
Chest	10	1	3	1	30	1400	46.7	1.48	31.53
Abdomen	10	1	3	1	30	1400	46.7	1.44	32.41
Back	10	1	3	1	30	1400	46.7	1.43	32.63

2.3.3.5. Adjust Upper Use Levels in Products Applied to the Palms

An analysis of the aggregate exposure to the palms revealed that four product categories influenced dermal exposure with Product Category C having the highest contribution with 50.9%, and a weighting factor of 0.49 (Table 14). When the weighted upper use levels were input into the Creme RIFM aggregate exposure model, it was found that the AEL/CEL$_{Agg}$ was 1.18 and thus no further adjustments were required. The AEL/CEL$_{Agg}$ had increased for many other application sites, however, the axillae had an AEL/CEL$_{Agg}$ ratio of 0.68 (Table 15), and thus required further adjustment.

Table 14: Calculation of Approximate Percentage Relative Contribution to Aggregate Exposure Form Individual Product Categories Applied to the Palms to Produce Upper Use Level Weighting Factors

Product Category	95th Percentile Dermal Exposure (µg/cm²)	Relative Contribution	Percentage Relative Contribution	Upper Use Level Weighting Factor
C	14.1	14.1/27.7 = 0.509	50.9%	1 - 0.509 = 0.49
E	11.7	11.7/27.7 = 0.422	42.2%	1 - 0.422 = 0.58
B	1.4	1.4/27.7 = 0.051	5.1%	1 - 0.051 = 0.95
D	0.5	0.5/27.7 = 0.018	1.8%	1 - 0.018 = 0.98
Total	**27.7**	**1**	**100%**	**-**

Table 15: Re-calculation of AEL/CEL$_{Agg}$ where CEL$_{Agg}$ to Palms has been adjusted. The AEL/CEL$_{Agg}$ for Axillae Remains Less than 1

Application site	Inter-individual SAF	Matrix SAF	Frequency SAF	Skin Condition SAF	Total SAF	NESIL	AEL (NESIL/ Total SAF)	CEL$_{Agg}$	AEL/CEL$_{Agg}$
Axillae	10	1	3	10	300	1400	4.7	6.9	0.68
Lips	10	1	3	3	100	1400	14.0	12.2	1.15
Palms	10	1	3	3	100	1400	14.0	11.9	1.18
Intra-oral	10	1	3	3	100	1400	14.0	9.69	1.44
Back of hand	10	1	3	3	100	1400	14.0	4.8	2.92
Face	10	1	3	3	100	1400	14.0	4.69	2.99
Neck	10	1	3	3	100	1400	14.0	3.99	3.51
Ano-genital	10	1	3	10	300	1400	4.7	0.942	4.95
Wrists	10	1	3	3	100	1400	14.0	1.9	7.37
Scalp	10	1	3	1	30	1400	46.7	5.7	8.19
Feet	10	1	3	3	100	1400	14.0	1.32	10.61
Peri-ocular	10	1	3	3	100	1400	14.0	1.3	10.77
Behind ears	10	1	3	1	30	1400	46.7	2.82	16.55
Legs	10	1	3	1	30	1400	46.7	1.04	44.87
Chest	10	1	3	1	30	1400	46.7	1.01	46.20
Arms	10	1	3	1	30	1400	46.7	0.941	49.59
Abdomen	10	1	3	1	30	1400	46.7	0.833	56.02
Back	10	1	3	1	30	1400	46.7	0.776	60.14

2.3.3.6. Adjust Upper Use Levels in Products Applied to the Axillae

An analysis of the aggregate exposure to the axillae revealed that Product Category A had the highest contribution with 88.6%, and a weighting factor of 0.11 (Table 16). However, when the weighted upper use levels were input into the Creme RIFM aggregate exposure model, it was found that the AEL/CEL_{Agg} was 3.78, which suggest that the upper use levels were reduced by more than was necessary.

Table 16: Calculation of Approximate Percentage Relative Contribution to Aggregate Exposure from Individual Product Categories Applied to the Axillae to Produce Upper Use Level Weighting Factors

Product Category	95th Percentile Dermal Exposure (µg/cm²)	Relative Contribution	Percentage Relative Contribution	Upper Use Level Weighting Factor
A	6.64	6.64/7.49 = 0.886	88.6%	1 – 0.886 = 0.11
C	0.62	0.62/7.49 = 0.083	8.3%	1 – 0.083 = 0.92
E	0.23	0.23/7.49 = 0.031	3.1%	1 – 0.031 = 0.97
Total	7.49	**1**	**100%**	**-**

The AEL/CEL_{Agg} which had overshot by a factor of four was caused by the high weighting factors, especially from Product Category A. In this instance it was necessary to incorporate a multiplication factor to appropriately reduce the individual product category weighting factor of 0.414 (Table 17) to produce an AEL/CEL_{Agg} of 1.07 (Table 18).

Table 17: Calculation of Upper Use Level Weighting Factors Based on Product Category Contribution and Adjustment Factor

Product Category	Relative Contribution	Multiplication Factor	Upper Use Level Weighting Factor
A	0.886	0.414	1 – (0.886*0.414) =0.63
C	0.083	0.414	1 – (0.083*0.414) = 0.97
E	0.031	0.414	1 – (0.031*0.414) = 0.99

Table 18: AEL/CEL_{Agg} Calculations where CEL_{Agg} to Axillae has been Adjusted. All Applications Sites have an AEL/CEL_{Agg} Greater than 1

Application site	Inter-individual SAF	Matrix SAF	Frequency SAF	Skin Condition SAF	Total SAF	NESIL	AEL (NESIL/ Total SAF)	CEL_{Agg}	AEL/CEL_{Agg}
Axillae	10	1	3	10	300	1400	4.7	4.36	1.07
Lips	10	1	3	3	100	1400	14.0	12.2	1.15
Palms	10	1	3	3	100	1400	14.0	11.7	1.20
Intra-oral	10	1	3	3	100	1400	14.0	9.65	1.45
Back of Hand	10	1	3	3	100	1400	14.0	4.6	3.04
Face	10	1	3	3	100	1400	14.0	4.31	3.25
Neck	10	1	3	3	100	1400	14.0	3.74	3.74
Ano-genital	10	1	3	10	300	1400	4.7	0.907	5.15
Wrists	10	1	3	3	100	1400	14.0	1.87	7.49
Scalp	10	1	3	1	30	1400	46.7	5.7	8.19
Peri-ocular	10	1	3	3	100	1400	14.0	1.3	10.77
Feet	10	1	3	3	100	1400	14.0	1.29	10.85
Behind ears	10	1	3	1	30	1400	46.7	2.81	16.61
Legs	10	1	3	1	30	1400	46.7	1.01	46.20
Chest	10	1	3	1	30	1400	46.7	0.952	49.02
Arms	10	1	3	1	30	1400	46.7	0.901	51.79
Abdomen	10	1	3	1	30	1400	46.7	0.802	58.19
Back	10	1	3	1	30	1400	46.7	0.756	61.73

The upper use level weighting factors for the product categories used on each application site were calculated and were used to adjust the Citral upper use levels (Table 19), collectively called the 'QRA2 aggregate adjustment factor'. It should be noted that in the present study, the adjustment factors were calculated based on the fragrance Citral. However, the same NESIL value was used to calculate the upper use levels for each product type and the AEL for each application site. Therefore, the adjustment factors calculated for Citral could also be used to adjust the upper use levels for all fragrances whose NESIL is known.

Table 19: Upper Use Levels for Citral in Product Types and Product Categories with Adjustment Factors

Product Type	Citral NESIL =1400 µg/cm^2				
	QRA2 Upper use limit	**Product Categorization**	**QRA2 category**	**QRA2 aggregate adjustment factor**	**QRA2 aggregate exposure adjusted upper use level**
Deodorants & Antiperspirants of all types including fragranced body sprays	0.05%	A	0.05%	0.63	0.03%
Hydroalcoholic Products (eau de toilette, parfum etc.)	0.63%	B	0.63%	0.95	0.60%
Body Creams, lotions	0.78%	C	0.50%	0.47	0.23%
Hand cream	0.54%				
Facial Cream (Moisturizing)/Facial Balm	0.50%				
Eye Products (Includes: eye shadow, mascara, eyeliner, eye make-up)	0.65%	D	0.12%	0.88	0.11%
Women's Make up (Foundation)	1.52%				
Make-up remover	1.56%				
Lip Products	0.12%				
Hair styling aids (mousse, gels, leave in conditioners)	3.50%				
Hair sprays	2.12%				
Shampoo	2.75%	E	2.33%	0.57	1.33%
Body wash/shower gels	31.10%				
Conditioner (rinse-off)	7%				
Bar soap	2.33%				
Liquid soap	7.00%				
Face washes, gels, scrubs	3.11%				
Bath gels, foams, mousses	46.67%				
Toothpaste	1.10%	F	1.10%	0.34	0.37%
Mouthwash	1.40%				

3. Planned Work to Further Refine the QRA

QRA2 is an advance in the development of a robust and transparent risk assessment methodology for skin sensitisers compared to the original QRA procedure but further work is necessary in several key areas. The immediate priorities are:

- To complete the ongoing work to incorporate consideration of pro- and particularly pre-haptens into QRA2.
- Agreeing a protocol and conducting a critical evaluation of the effectiveness of QRA2 in minimising consumer sensitisation.

The IDEA project is also committed to identify and characterise non-animal tests as basis for conducting risk assessment in line with the requirements of the Cosmetics Directive.

3.1. Pre- and pro-haptens

A pre-hapten is a chemical that has been chemically (abiotically) activated. This may occur before it gets into contact with the skin. A pro-hapten is a chemical that must penetrate into the epidermis and gain access to the so-called “drug metabolising enzymes” to be activated and form a hapten. The number of fragrance ingredients in general use that can act as pre- or pro-haptens is unknown.

In order to complete the exposure aspects of the QRA highest priority has been assigned to the topic of pro- and particularly pre-haptens. Two IDEA workshops in 2015 have been devoted to this topic. The June 2015 Expert workshop focused on improved mechanistic understanding of pre- and pro-hapten formation as well as on analytical developments. The second workshop in October 2015 helped to bridge this knowledge with clinical findings. A third workshop will be held in December 2016 with the focus on establishing a framework to be added to QRA2 that would allow the identification and assessment of pre- and pro-haptens.

Pre- and pro-haptens are by definition hapten precursors. To be a hapten a chemical needs to:

- Gain access in sufficient concentration to the target protein(s) in the skin that are responsible for the initiation of sensitisation.
- Be sufficiently reactive with the critical target sites of the protein(s). It should be noted that the most common pathways for hapten formation from precursors are oxidation and hydrolysis.
- Have limited reactivity with other cellular targets that would result in cytotoxicity or other substantial cell damage.

Such activation of a pre-hapten can in principle arise during processing or storage of a raw ingredient/formulation or on the surface of the skin as a result of application or within the skin.

For materials where *in vivo* tests are available, then biotic transformations that take place in human skin are, at least in part, taken into account, particularly in the HRIPT. In addition, inter-individual variability is taken into account in the SAFs.

The role of abiotic transformations, in particular autoxidation, is not completely understood and this is a topic that is under review in the IDEA project (see for example Natsch *et al*., 2015), A task force is working on the measurement of hydroperoxides as one important oxidation product. It is recognised that an effective feedback loop from clinical experience is needed to verify that relevant pre- and pro-haptens have not been missed.

3.2. Assessment of the Effectiveness of the QRA2 for Fragrance Allergens

It is a priority for the IDEA project following the completion of QRA2 to assess its effectiveness for the primary prevention of contact sensitisation to fragrance ingredients identified as potential sensitisers. An indication of the reduction in the prevalence of positive clinical patch tests to a fragrance ingredient that has been subjected to QRA-based restrictions is considered as an indication of its effectiveness.

However, there are many confounding factors and as recently shown (Fall *et al*., 2015), the rate of prevalence of clinical patch test reactions to nickel remains largely unchanged despite strong risk management measures. Particular concerns include:

- The number of consecutive patients needed for testing individual fragrance ingredients.
- The difficulty in determining the age of the consumer product. This knowledge is also critical because although there is a shelf life in stores the consumer may keep a product in the home for extended periods of time. As such perfumes in the product may not be in compliance with current IFRA Standards.
- The clinical relevance of the positive patch test.
- The exact exposure source that may have induced the contact allergy.

It may not be known exactly when the patients acquired the allergy because many fragrance ingredients have been in use for some time, with no restriction for sensitisation. This presents a challenge with both retrospective and prospective clinical studies. Both retrospective and prospective studies will need expert interpretation, due to the difficulty in determining when a patient became induced.

The designing of a prospective study was further discussed in a workshop dedicated to the topic of ‘definition of allergens’ taking place after the submission of the QRA2 interim report September 23 – 25, 2014. At this workshop the advantages and disadvantages of various approaches were further elaborated but no final conclusion was reached. Nevertheless, it was recommended that a prospective study should be considered rather than a retrospective study. A working group is nearing the completion of its task of identifying the protocol and participants for such a study. A workshop will be held to discuss the outcome in January 2017. It has been concluded that basic requirements for a prospective study on existing fragrance ingredients include:

- An accurate baseline data for prevalence;
- A broad collection of baseline data from clinics that will participate in the prospective study but acknowledge the pitfalls that can occur by linking the new with the existing data;
- The generation of a common protocol with a high degree of standardization and calibration for the preparation, application, reading and interpretation as the basis for establishment of baseline data from consistent and comparable clinics;
- Harmonisation of patch testing technique and ingredients is expected to reduce the variability of patch testing results;
- A broad coverage of regions when selecting the participating centres.

While there is agreement that the most relevant information on effectiveness would result from a new ingredient introduced into the market for the first time, it has to be recognized such an approach is extremely challenging because it might take a significant amount of time before the exposure to the material in the market can be regarded as relevant.

3.3. Introduction of Robust Non-Animal Test as Replacement for Hazard and Potency Identification

The further development of the hazard identification and characterization aspects of the QRA is critically dependent on the development of non-animal tests. There is already a major industry and academic effort in developing *in silico, in chemico* and *in vitro* sensitisation methods to determine sensitisation potential. The analysis, based on a very recent IDEA workshop, is that thus far, these methods seem to be quite good at evaluating the hazard potential of a chemical, but they lack the ability to reliably determine the potency or identify the NESIL of a material. In the future, it is foreseen that the NESIL will be determined using a combination of non-animal based methodologies, chosen and integrated based on consideration of the adverse outcome pathway (AOP) (OECD, 2012). The IDEA team are already actively involved in the development and utilization of non-animal tests through active collaboration with others.

3.4. Weight of Evidence to Evaluate all the Data for Each Fragrance Ingredient

It is likely that hazard identification in the future will require a number of different types of information: structure and physicochemical properties, vulnerability to form, either abiotically or biotically, reactive forms, several different in vitro tests (possibly involving a tiered approach), historic data on related chemicals (QSAR/read across) and in some cases human data. It is essential that a transparent consistent scientifically justified weighing of evidence protocol is in place to enable this. Progress on this WoE protocol depends on the identification of the types and nature of the studies that may need to be incorporated in completing the risk assessment.

3.5. Exposure to other sources of fragrance ingredients

Some consumer products are used in an occupational setting e.g. shampoos in hair salons or liquid hand soaps in hospitals. The most relevant difference compared with normal consumer use will be the frequency of use. Occupational/professional exposure is not included in this report to date, as data is not available for either hair salon or hospital workers. The raw data from the report by Geier *et al*. (2002) (a research project on early detection of occupational and non-occupational contact allergens. On behalf of the German liability insurance associations. Final report 2002. "Frühzeitige Erkennung allergener Stoffe bei beruflicher und nichtberuflicher Exposition“. Im Auftrag der DGUV. Abschlußbericht) is not available and the limited data available will only allow an estimate of the 90^{th} – 95^{th} percentile values and not an accurate value. Collecting information in hair salons and hospitals would require different studies. The topic has been discussed at several IDEA Workshops and it was agreed that occupational use of consumer products should be considered as a separate activity from consumer exposure.

4. References

The full publications are included with the technical dossier and are available at RIFM. The numbers that appear after the reference are the unique location identifiers.

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5. Glossary of Terms

Term	Definition
ACD	Allergic Contact Dermatitis
AEL	Acceptable Exposure Level
AOP	Adverse Outcome Pathway
CEL	Consumer Exposure Level
CEL_{agg}	Aggregated Consumer Exposure Level
CET	Closed Epicutaneous Test (guinea pigs)
DDE	Daily Dermal Exposure
DDEi	Daily Dermal Exposure to Individual
DDEPS	Daily Dermal Exposure with Product Sensitisation Assessment Factor
DE	Dermal Exposure
DPRA	Direct Peptide Reactivity Assay
DST	Dermal Sensitisation Threshold
EC3	Estimated Concentration required to result in a threshold positive response; i.e. a Stimulation Index = 3
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
EPA	(US) Environmental Protection Agency
EPAA	European Partnership for Alternative Approaches to Animal Testing
EURL ECVAM	European Union Reference Laboratory for Alternatives To Animal Testing (EURL-ECVAM)
FCAT	Freund's Complete Adjuvant Test
FM	Fragrance Mix
GCP	Good Clinical Practices
GPMT	Guinea Pig Maximisation Test
h-CLAT	human Cell Line Activation Test
HERA	Human and Environmental Risk Assessment
HICC	Hydroxyisohexyl-3- cyclohexene carboxaldehyde
HMT	Human Maximisation Test
HRIPT	Human Repeat Insult Patch Test
IATA	Integrated Approaches to Testing and Assessment
ICD	Irritant Contact Dermatitis
IDEA	International Dialogue for the Evaluation of Allergens
IFRA	International Fragrance Association
ITS	Integrated Testing Strategy
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
MEST	Mouse Ear Swelling Test
NESIL	No Expected Sensitisation Induction Level
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Cooperation and Development
OET	Open epicutaneous test (guinea pigs)
PDDE	Population Daily Dermal Exposure
PDDEAGG	Aggregate Population Daily Dermal Exposure

Term	Definition
QRA	Quantitative Risk Assessment
QSAR	Quantitative Structure-Activity Relationship
RfD	Reference Dose
RIFM	Research Institute for Fragrance Materials, Inc.
SA	Surface Area
SAF	Sensitisation Assessment Factor
SCCP	Scientific Committee on Consumer Products
SCCS	Scientific Committee on Consumer Safety
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHER	Scientific Committee on Health and Environmental risks
TIMES	TImes MEtabolism Simulator
TTC	Threshold of Toxicological Concern
W_i	Individual Weighting
WoE	Weight of Evidence
WPDDE	Weighted Population Daily Dermal Exposure

6. Appendix 1: IDEA Project Overview

6.1. Introduction

The IDEA project (International Dialogue for the Evaluation of Allergens, http://www.ideaproject.info) is designed to provide a broadly agreed and transparent framework for assessing fragrance sensitisers globally. It is an opportunity to build partnerships between the international fragrance industry and its stakeholders to improve the risk assessment of those fragrance ingredients identified as allergens. The objective is to improve consumer protection.

The IDEA work plan, endorsed by Commissioner Tonio Borg, is a clear roadmap designed to achieve the goals outlined above.

IDEA consists of a series of workshops bringing together leading international scientists to reach a consensus on improving existing assessment methods. Recommendations made at the workshop are then followed up in industry or research projects. Every year a public Annual Review takes place under the auspices of DG SANCO.

6.2. A Work Plan Developed by the Industry and the EU Commission to Address the Issue of Fragrance Allergens

In December 2011, the SCCS (Scientific Committee on Consumer Safety) advising the European Commission, released its draft Opinion on fragrance allergens in cosmetic products (SCCS/1459/11). The recommendations made in this Opinion were eye-opening for the industry which became even more aware of the communication gap existing between all parties and, as a consequence, the knowledge gaps concerning fragrance allergens and, more specifically, the methods to characterize, assess and diagnose them.

On this basis, a work plan was developed that outlined steps that could be taken to improve the risk assessment of fragrance allergens and make even safer the use of scented-products. Industry's scientists at the origin met several times in Nyon (Switzerland) and, because the work plan was born at the second meeting, this advisory group is called the "Nyon II" group. The intent of this initiative was strategic: a consumer adequately protected and safely enjoying fragrance products is the best way for the industry to secure its business and preserve its competitiveness.

Once fully drafted, the work plan was handed over to the European Commission (DG SANCO, Risk Assessment Unit) for review and critical comments. It is noteworthy that this project has been designed from the outset to be conducted in partnership with the European Commission and its Scientific Committees on consumer safety – the active involvement of these stakeholders being essential for success. On March 14th, 2013, after a thorough review process involving IFRA and the Commission, the project was fully endorsed by Commissioner Tonio Borg.

The final work plan, consisting of four tasks, has meanwhile moved into its implementation phase: the IDEA project. Both IFRA and the European Commission assumed that this project can be completed in three to seven years.

6.3. IDEA is a Long-Term Project Conducted in Partnership with the EU Commission

IDEA consists of a series of two to three-day workshops bringing together leading international scientists to reach a consensus on improving existing methods. Each workshop focuses on a specific task of the work plan but the tasks are not necessarily addressed in the order outlined in the work plan (Figure 5). In 2013, three IDEA workshops were organised: the first was dedicated to the refinement and the validation of the QRA methodology (task IV), the second one focused on the risk assessment of pre- and pro-haptens (task III) and the last one aimed at characterising fragrance allergens (task I). The order in which the tasks have to be addressed is jointly defined by IFRA and the European Commission.

At the end of each year, an Annual Review is organised by the European Commission to monitor and validate the progress recorded over the past year, update the programme and priorities when needed and ensure that all stakeholders can express their views and get further clarification on the project.

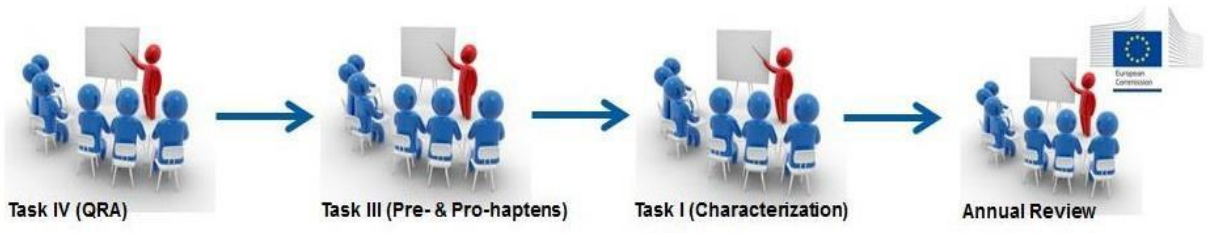

Figure 5: IDEA Working Plan

The workshop participants are identified by the IDEA Management Team ("Nyon II" group plus the IFRA staff) and by the European Commission. Scientific expertise is the sole criterion for being invited to an IDEA workshop and the number of observers (e.g. representatives of the EU Commission and trade associations) is strictly kept to a minimum. The required expertise can be general (e.g. dermatology, toxicology, chemistry, epidemiology, etc.) or specific (e.g. specialist on hydroperoxides, specialist on aggregate exposure, etc.). However, the IDEA Management Team tries, as much as possible, to keep a balance between Academia, industry experts and SCCS representation (Figure 6).

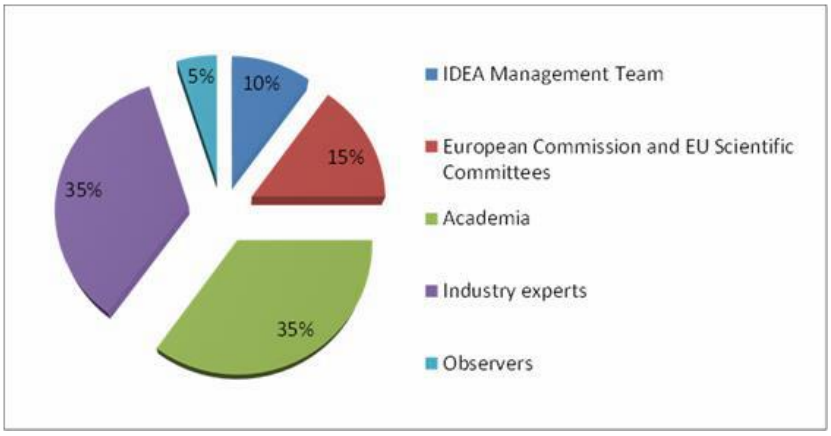

Figure 6: Distribution of Affiliations of the Participants to the IDEA Workshops.

A typical 2-day workshop starts with one day of formal lectures to set the scene of the task to address and to share background knowledge and positions among all participants. These presentations are given by academics, industry representatives and EU Scientific Committees' members. The first day finishes with a moderated discussion where the workshop Rapporteur presents his conclusions and the Moderator helps the participants to phrase consensus and common understanding. The second day starts with the formation of several working groups. A theme identified by the IDEA Management Team (the Rapporteur, the Moderator and the IFRA staff) is assigned to each working group. The working groups get half a day to work on the theme, draw conclusions and make recommendations. The Moderator of each working group presents these conclusions and recommendations in plenary session. Then, a moderated discussion takes place and the final workshop conclusions and recommendations are drawn.

Every workshop leads to the preparation and the publication (on the IDEA website) of three important documents:

- *Key Conclusions*

  This is a one to two-page document that represents the consensus, common understandings and conclusions recorded by the participants during the workshop. The document is prepared by all participants with the help of the Moderator. It is formatted by the IDEA Management Team and submitted to the workshop Rapporteur for approval in case essential editorial changes are needed.

- *Progress Report*

  This is a more detailed summary of the discussions and conclusions of the workshop, prepared by the Rapporteur, factually and transparently. The draft is reviewed by the

workshop participants who have three weeks to submit comments. Like the key conclusions, the final progress report is made available to the public through the IDEA website.

- *Recommendations*

Recommendations are drawn up in a short document, transposing the recommendations made by the workshop participants into action items. The industry is committed to address all these action items in a timely manner and via a suitable action plan. The required actions can be very diverse (toxicological studies, clinical studies, analytical developments, retrospective analyses, etc.). They also demand significant resources but all are conducted or initiated by the industry. Preliminary results of these studies and investigations are presented at the Annual Review and consolidated results are presented at the next IDEA workshop addressing the same task. Workshop participants are entitled to critically review the work done by industry.

6.4. IDEA is a Project Conducted in Full Transparency

The way the IDEA project works is set out in the diagram below. Precautions are taken to avoid conflicts of interest and biased opinions. Firstly, the IDEA project is controlled by a "Supervisory Group" of four to seven members with no vested interests in industry activities; they are jointly nominated by the European Commission and IFRA.

The role of the Supervisory Group is to scrutinize all aspects of the project to guarantee the neutrality of scientific debates and experts' selection procedures. The Group also reviews and approves the (draft) agenda of all IDEA workshops (Figure 7).

For each workshop, the Supervisory Group nominates a Rapporteur from its members. The Rapporteur attends the workshop and writes the report based on the outcome. The progress report is reviewed by the Supervisory Group which draws conclusions and sets recommendations for improving the overall process. Rapporteurs of the workshops held during the year present their progress reports at the Annual Review.

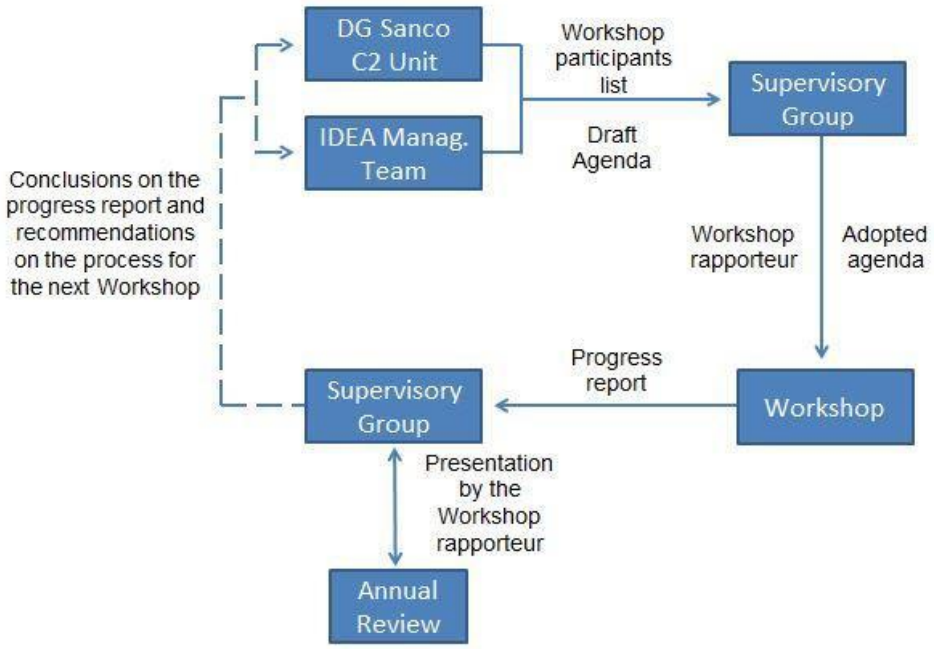

Figure 7: The Role of the Supervisory Group in the IDEA Workshops.

The current IDEA Supervisory Group members are:

- Prof. James Bridges (Chairman) – University of Surrey and former Chairman of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).
- Prof. Helmut Greim – Technical University of Munich and former Chairman of the Scientific Committee on Health and Environmental Risks (SCHER).
- Dr. Alain Khaiat – Consultant and former vice president to R&D for Johnson & Johnson.
- Dr. Christen Mowad – Geisinger Medical Center and President of the American Contact Dermatitis Society.
- Dr. Ian White – Guy's & St Thomas' NHS Hospitals and former Chairman of SCCS.

The IDEA Management Team and the IDEA Supervisory Group established a *modus operandi* that lays down the rules to be followed during the workshops and specifies those costs relating to the workshop which can be reimbursed and to whom.

Finally, all workshop documents (including presentations, key conclusions, progress reports, recommendations) are made publicly available on the IDEA website (http://www.ideaproject.info).

6.5. IDEA and the Revision of the Dermal Sensitisation QRA

Recently, efforts to review the existing methodology have been expanded via the IDEA

project. The group's remit was to review the QRA approach for skin sensitisation and the current scientific literature. All elements of the published risk assessment process for skin sensitisation were reviewed with respect to fragrance allergens. However, the main objective of the participants (see Table 20) was to complete a thorough review of uncertainty factors or sensitisation assessment factors to increase transparency and to apply dermal aggregate exposure to the reviewed QRA methodology for the purpose of setting IFRA Standards to restrict consumer exposure to fragrance allergens to levels which avoid the induction of skin sensitisation. The key conclusions from the Workshops are described below.

6.5.1. Workshop # 1, March 2013 (IDEA, 2013)

QRA is seen as a promising tool to prevent induction of contact sensitisation for people with normal skin. However, it requires further refinements for the general population as follows:

- Prospective and retrospective evaluation of its effectiveness by clinical and epidemiology data using sensitisation as the relevant endpoint.
- Review of underlying methodologies and assumptions.
- Development of SAFs (Sensitisation Assessment Factors).
- Identification of NESILs (No Expected Sensitisation Induction Levels).
- Examination of exposure (accumulation, aggregate exposure, chemical analysis, usage, retention and professional exposure).
- Adaptation for people with compromised skin.
- SAFs are set appropriately given the current state of knowledge but re- evaluation of the inter-individual variability factor (with a description of the underlying scientific rationale) is considered essential.
- Estimation of expected new induction when following QRA to be encouraged.
- There could be value in developing "QRA2", based on latest data and including aggregate/occupational exposure.

6.5.2. Workshop # 2, March 2014 (IDEA, 2014a)

The starting point of the QRA is the NESIL which is defined as the threshold level of a substance known not to induce skin sensitisation, considering all available hazard data in a weight of evidence approach, under the specific exposure conditions of a standard protocol HRIPT. The workshop participants reviewed the SAFs and supported SAFs for:

1) Inter-individual variability accommodated in the NESIL as reflected by a SAF of 10.
2) Impact of product use factors such as degree of occlusion, frequency/ duration of product use and the product matrix itself reflected in SAFs that range between 0.3 and 6. The role of skin condition/site, determined by a stepwise consideration of pre-existing inflammation, irritation by product, and penetration/ permeation of product, reflected in SAFs each of 1 or 3.

6.5.3. Workshop # 3, May 2014 (IDEA, 2014b)

During the third workshop, held on 14-15 May, 2014, examples were presented on how the interim SAFs were applied and how aggregate exposure was derived. The details for finalization of the SAFs and application of the Creme RIFM Aggregate Exposure Model are provided in this dossier.

Table 20: IDEA Workshop QRA Participants

Title	First name	Last name	Affiliation	QRA WS 2013	QRA WS 03-2014	QRA WS 05-2014
Dr.	Jay	Ansell	PCPC		X	
Dr.	Eric	Antignac	L'Oréal		X	
Dr.	Anne Marie	Api	RIFM	X	X	X
Dr.	David	Basketter	Consultant in toxicology	X	X	X
Prof.	Donald	Belsito	Columbia University Medical Center and industry Expert Panel Member	X	X	X
Dr.	Hans	Bender	Consultant (Moderator of the QRA Workshop)	X	X	X
Dr.	Christophe	Brault	LVMH	X		X
Prof.	James	Bridges	University of Surrey and SCENIHR Chair (Rapporteur of the QRA Workshop)	X	X	X
Prof.	Magnus	Bruze	Lunds Universiteit and industry Expert Panel Member	X	X	X
Dr.	Dagmar	Bury	L'Oréal		X	X
Dr.	Peter	Cadby	Chanel		X	X
Dr.	Gaetano	Castaldo	EU Commission – DG Sanco – Risk Management Unit		X	X
Prof.	Pieter-Jan	Coenraads	University Medical Centre Groningen, Member of European Destinations of Excellence (EDEN) and the SCCS	X		X
Dr.	Federica	de Gaetano	EU Commission – DG Sanco – Risk Management Unit	X	X	X
Prof.	Thomas	Diepgen	Ruprecht-Karls University, Member of EDEN	X	X	X
Prof.	Jeanne	Duus Johansen	University of Copenhagen and Member of the SCCS WG on Fragrance Allergens	X		X
Mr.	Graham	Ellis	Givaudan	X		X
Dr.	Janine	Ezendam	National Institute for Public Health and the Environment (RIVM)		X	X
Prof.	Peter	Friedmann	University of Southampton		X	
Prof.	David	Gawkrodger	Vice-chair of the SCCS		X	
Dr.	Nicola	Gilmour	Unilever	X	X	X
Dr.	Margarida	Goncàlo	University of Coimbra, Portugal, EDEN participant			X
Prof.	Helmut	Greim	Technical University of Munich	X		
Dr.	Peter	Griem	Symrise	X	X	X

Title	First name	Last name	Affiliation	QRA WS 2013	QRA WS 03-2014	QRA WS 05-2014
Dr.	Etje	Hulzebos	IFF		X	X
Dr.	Petra	Kern	Procter & Gamble	X	X	X
Dr.	Maya	Krasteva	L'Oréal			X
Dr.	Christine	Lafforgue	Université Paris sud 11	X	X	X
Dr.	Christeine	Lally	P&G, Brussels		X	X
Dr.	Fred	Lebreux	International Fragrance Association	X	X	X
Dr.	Sylvie	Lemoine	AISE		X	
Dr.	Cronan	McNamara	Creme Global	X	X	X
Prof.	Hans	Merk	Universitätsklinikum Aachen	X		
Dr.	Andreas	Natsch	Givaudan		X	
Prof.	David	Roberts	Liverpool John Moores University and Member of the SCCS WG on Fragrance Allergens	X	X	X
Prof.	Vera	Rogiers	Vrije Universiteit Brussel and SCCS Vice-chair	X	X	
Dr.	Bob	Safford	Consultant	X	X	X
Dr.	Joanne	Salverda	National Institute for Public Health and the Environment (RIVM)		X	X
Dr.	Florian	Schellauf	Cosmetics Europe	X	X	X
Dr.	Scott	Schneider	Firmenich		X	
Prof.	Axel	Schnuch	IVDK / University of Göttingen	X	X	X
Dr.	Ben	Smith	Firmenich			X
Ms.	Izabela	Taborska	EU Commission – DG Sanco – Risk Management Unit		X	X
Prof.	Wolfgang	Uter	University Erlangen and Member of the SCCS WG on Fragrance Allergens	X		
Dr.	Matthias	Vey	International Fragrance Association	X	X	X
Dr.	Ian	White	Guy's & St Thomas' NHS Hospitals, Member of the SCCS WG on Fragrance Allergens	X	X	X

7. Appendix 2: Use of Non-Animal Based Sensitisation Methods to Determine the NESIL

Currently there is a major industry and academic effort in developing *in silico, in chemico* and *in vitro* sensitisation methods to determine sensitisation potential. Thus far, these methods have shown good performance at evaluating the hazard potential of a chemical, but they lack the ability to determine the potency or identify the NESIL of a substance. In the future, it is foreseen that the NESIL will be determined using a combination of non-animal based methodologies, chosen and integrated based on consideration of the adverse outcome pathway (AOP) (OECD, 2012). However, this is not possible at present. It is likely that the confirmatory HRIPT will be maintained even if dose levels chosen for this will be derived by alternative methods.

With respect to non-animal alternatives, there have been significant advances in our understanding of the modes of action underlying allergic responses to chemicals. This has resulted in a variety of *in vitro/in silico* test methods designed to model key biological and chemical events. While there are clearly areas for refinement, on an individual basis the current non-animal alternatives for skin sensitisation all provide some degree of hazard identification. However, the science of potency estimation using non-animal test methods still requires work and is the focus of numerous research efforts.

In order to avoid duplication of effort and build on the significant work currently being done by the fragrance industry and the broader science community, a partnership with others is being developed. Two particular areas are:

1) Data generation, in the most promising assays, with the goal of broadening the chemical space of available datasets.
2) Collaboration on data assessment strategies to enhance hazard assessments and provide potency estimation that may be useful for the development of the QRA.

Specifically, data generation is being sponsored in the Direct Peptide Reactivity Assay (DPRA), KeratinoSens™ and human Cell Line Activation Test (h-CLAT). Each of these assays models a key event along the adverse outcome pathway (AOP) in the skin sensitisation process; they are considered to be highly developed and are expected to be adopted as OECD test guidance in the near future (suggesting the potential for wide application). These data along with LLNA data as a reference test and suitable *in silico* data (e.g. TIMES, absorption models) will feed into integrated testing strategies being developed.

This expert group is currently working to support the OECD Secretariat in the development of *in vitro* test guidance and Integrated Approaches to Testing and Assessment (IATA) for skin sensitisation. There is also active contribution to the EPAA (European Partnership for Alternative Approaches to Animal Testing) initiative on the development of alternative approaches to animal testing for skin sensitisation. In consultation with EURL ECVAM, IDEA intends to regularly review progress to identify those tests that are ready to be incorporated into the QRA and take actions to ensure this.

7.1. Develop a Framework that Incorporates these Advances

A priority for the further development of the QRA is to replace the current use of animal studies with a combination of *in vitro* and *in silico* methods.

In order to attain this objective, as indicated above, the *first* requirement is to have methods that can reliably identify fragrance ingredients that have the potential (directly or through the aegis of abiotic or biotic transformations) to cause induction of sensitisation.

The *second* requirement is a combination of *in vitro* and *in silico* methods which can be used to determine the potency of individual fragrance ingredients that have been established to have the potential to cause the induction of sensitisation. This is anticipated to be the most challenging of the three requirements to fulfil.

It will require the establishment of effective collaboration with a number of key partners.

7.2. Summary of Review of Potential *In Vitro* Tests

Several *in vitro, in chemico* and *in silico* tests have been developed to predict the skin sensitisation hazard (Kimber *et al*., 2011; Roggen, 2013; Vandebriel and van Loveren, 2010). Three of these have undergone validation studies by the European Centre for the Validation of Alternatives to Animal Testing (ECVAM). Each of these assays model a key event and/or relevant cellular response along the adverse outcome pathway (AOP) in the skin sensitisation process (OECD, 2012).

The human cell line activation assay (h-CLAT) evaluates induction of the surface markers CD86 and CD54 on THP-1 cells, a human monocytic leukemia cell line (Sakaguchi *et al*., 2006). The KeratinoSens™ assay measures a dose-response analysis of Nrf2 induction in a transfected HaCaT keratinocyte cell line (Emter *et al*., 2010). Both of these assays also provide an estimate of the cytotoxicity of a chemical. The direct peptide reactivity assay (DPRA) measures peptide depletion of a cysteine- and a lysine- containing heptapeptide in the presence of the test chemical (Gerberick *et al*., 2004). An ECVAM statement and draft OECD guidelines on the latter two assays have been published.

Natsch *et al*. (2011) and Roberts and Natsch (2009) have described modifications to the DPRA in which peptide depletion is measured with a high-throughput fluorescent assay at multiple doses and multiple time points to determine rate constants. In another modification, a more reactive peptide which contains both lysine and cysteine residues is used and analysis is performed by liquid chromatography coupled to mass spectrometry (LC-MS) to determine adduct formation in addition to recording peptide depletion (Natsch and Gfeller, 2008). This later approach also contains a profiling based on the fluorescent test at an early time point for highly reactive chemicals. The DPRA, and its various modifications, are best used to detect chemicals that have the ability to interact and bind directly with cysteine- and lysine-based peptides. However, it is well known that some classes of chemical sensitisers may require a degree of activation by abiotic (a pre-hapten) or biotic (a pro-hapten) processes in order to become sufficiently reactive (Lepoittevin, 2006;

Smith & Hotchkiss, 2001). In some cases chemicals requiring abiotic activation are detected in the DPRA; however pro-haptens are not readily characterised (Gerberick *et al*., 2007). Among other improvements, the Peroxidase Peptide Reactivity Assay (PPRA) builds on the DPRA and incorporates a horseradish peroxidase and hydrogen peroxide system to assess the skin sensitisation potential of pre- and pro-haptens (Gerberick *et al*., 2009; Troutman *et al*. 2011). Similarly, modifications to the KeratinoSens™ assay have been described that incorporate rat liver S9 fractions to increase the ability to detect pro-haptens within this cell based system (Natsch and Haupt, 2013).

Next to the tests mentioned above, a number of other test systems have been proposed, focusing on gene expression of a wider set of pathways (Johansson *et al.*, 2011), other target genes (Lambrechts *et al.,* 2010; van der Veen *et al*., 2013) or on key sensitiser-specific inflammation markers (Gibbs *et al*., 2013). Test system development remains an active area of interest, and these assays highlight the broad spectrum of ongoing work (reviewed Goebel *et al*., 2012). However since these developments are typically newer, the number of chemicals tested is lower as compared to the tests which have already undergone validation.

The validation studies focused mainly on the binary classification of chemicals to predict sensitisation hazard, yet in order to replace animal testing fully, the alternative approaches should also be able to inform risk assessment and give an estimate of sensitiser potency and prediction of the NESIL. Ideally therefore, information from several different approaches should be combined to predict a dose-per area threshold (routinely expressed as µg/cm^2) for sensitisation induction, which can then be applied as point of departure in quantitative risk assessment (QRA).

Most *in vitro* and *in chemico* assays do give a quantitative read-out and thus analysing these quantitative data and comparing them against human and animal data is in principle possible. Quantitative data from multiple endpoints can be fed into such a potency assessment, ideally integrating data from different steps of the skin sensitisation adverse outcome pathway (OECD, 2012). Natsch *et al.* (2009) have performed such an early analysis with data on peptide binding and data on Nrf2 induction. By combining Nrf2 response and glutathione binding, an algorithm for sensitiser potency assessment was later reported (McKim *et al.,* 2010). Potency prediction based on cytotoxicity and gene expression in a single assay was shown for a very limited set of test chemicals (Lambrechts *et al*., 2010). Recently, a dataset on 145 chemicals from all three endpoints in the validation studies was analysed using a Bayesian network (Jaworska *et al*., 2013), with very promising results to predict four sensitiser potency classes, but not yet to predict a dose-per area or EC3 value. Good correlation to LLNA EC3 values for individual parameters from single assays was shown for very specific sets of chemicals (Delaine *et al*., 2011; Natsch *et al*., 2011; Roberts and Natsch, 2009).

ECVAM has issued recommendations on the DPRA and KeratinoSens™ assay suggesting further work to assess the potential for potency predictions. Specifically for the KeratinoSens™ assay it was considered a potential fruitful area to pursue how the dose-response information could contribute to potency assessment and quantitative risk assessment. For such an evaluation, the use of human reference data was considered particularly useful, and the potential of integrated approaches using Nrf2–dependent

luciferase induction combined with other information sources, in particular peptide reactivity assays, were highlighted in the relevant reports (ECVAM, 2013; 2014).

There is an ongoing active debate on how to best arrive at potency predictions. One proposal is to build "local" models within so called applicability domains of chemicals (those reacting by particular mechanisms) (Aptula *et al*., 2005). This approach contains the general principle of read-across, namely that toxicity of molecules acting by similar molecular mechanisms can be more accurately predicted from information on similarly acting molecules. This approach uses the chemical structure of the molecule as one key input. While purely *in silico* based approaches then rely fully on chemical structure and parameters predicted from the structure such as physicochemical information and predicted reactivity indices (Roberts *et al.,* 2006), it is also possible to use the *in vitro* and *in chemico* data for quantitative predictions within domains which are defined based on structural alerts or experimental information on reaction mechanism(s). The second approach is to build a "global" model not taking into account chemical domains. There is strong empirical support for read-across and local models, but they have downsides: (i) not all chemicals belong to domains with sufficient *in vivo* evidence to build local models and (ii) attribution to domains involves at least some expert judgment which may introduce bias. In the future, the two approaches may be combined (see Figure 8) – a concept not yet explored in the skin sensitisation area.

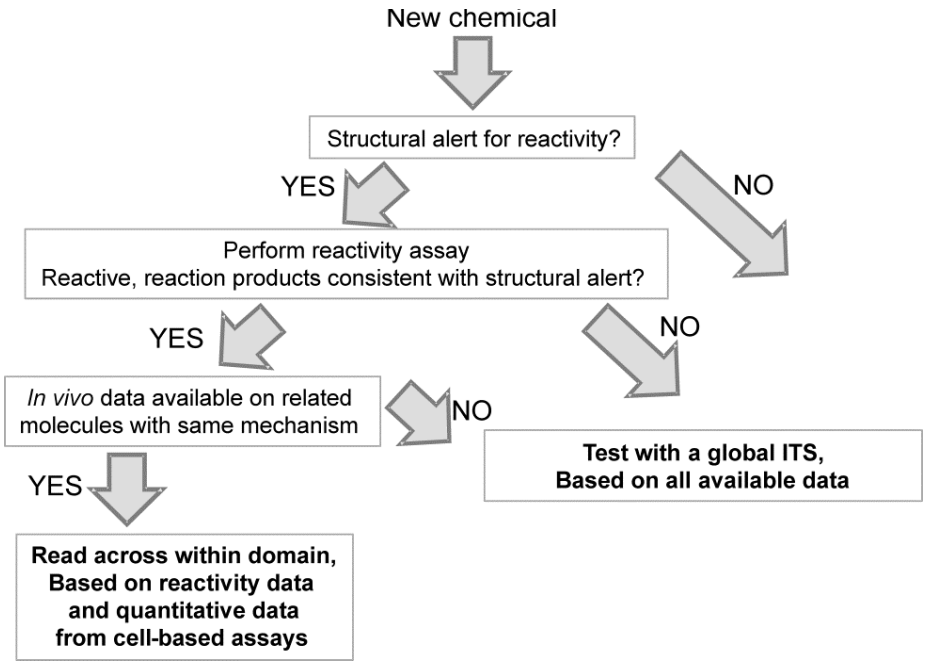

Figure 8: A Potential Paradigm of how a Holistic Integrated Testing Strategy (ITS) on all Available Data can be combined with Predictions in Specific Applicability Domains.

In conclusion, the approaches to predict NESILs for the use in QRA still require substantial further work in order to achieve a scheme using validated assays and a validated approach. This effort is expected to require several more years of research and collaboration; however several groups are actively working to achieve this goal to fully replace animal testing for sensitisation risk assessment. For many fragrance ingredients there are sufficient existing data from which a NESIL can be derived. Therefore the lack of an agreed scheme on deriving a NESIL from *in vitro* data would not present a real issue for risk assessment for these ingredients. However, for new ingredients the development of an agreed approach is very important.

8. Appendix 3: Habits and Practices and Human Parameters Data Sources

8.1. Habits and Practices Data Sources:

1) Cano and Rich (2001); Tozer *et al*. (2004) and Cano (2006) data on hydroalcoholic products – measured distribution of amount, frequency and surface area

   Status: data available from companies report(s) and reported in presentations, but unpublished in full

2) Hall *et al*. (2007) (Cosmetics Europe, formerly Colipa data) – measured frequency, duration and amount for seven different consumer products, analysis based on a probabilistic basis

   Status: published and noted in the SCCS Notes of Guidance, 8th Revision

3) Hall *et al*. (2011) (Cosmetics Europe, formerly Colipa data) – measured frequency, duration and amount for five different consumer products, analysis based on a probabilistic basis

   Status: published and noted in the SCCS Notes of Guidance, 8th Revision

4) Steiling *et al*. (2012) (Cosmetics Europe, formerly Colipa data) – measured frequency, duration and amount for deodorants/antiperspirants in aerosol form based on a probabilistic basis

   Status: published and noted in the SCCS Notes of Guidance, 8th Revision

5) Loretz *et al*. (2005) (Personal Care Products Council, formerly CTFA data) – measured frequency, duration and amount for three different consumer products analysis based on a probabilistic basis

   Status: published

6) Loretz *et al*. (2006) (Personal Care Products Council, formerly CTFA data) – measured frequency, duration and amount for six different consumer products analysis based on a probabilistic basis

   Status: published

7) Loretz *et al*. (2008) (Personal Care Products Council, formerly CTFA data) – measured frequency, duration and amount for three different consumer products analysis based on a probabilistic basis

Status: published

8) AISE/HERA (2002) and Technical Guidance Document, (2003)

   Status: data available on HERA website

9) Api *et al*. (2005) (FMA data) - measured skin contact transfer of three fragrance residues from candles to human hands

   Status: Published

10) RIFM data – measured frequency, duration and amount for different consumer product types, based on RIFM member company data

    Status: data available, but unpublished (RIFM 2005; 2006)

11) EC data (EC (1996). Technical guidance document in support of Commission Directive 93/67/EEC on risk assessment for new notified substances and Commission Regulation (EC) No 1488/94 on risk assessment for existing substances.)

    Status: published data and used only when measured data are not available

12) SCCS's Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation, 8th Revision

    Status: published data and used only when measured data are not available

8.2. Human Parameters Data

There are four sources of data. Again using a hierarchal approach, when data were available from all sources, a conservative approach was employed by using the smallest surface area. This resulted in a higher CEL.

1) EPA (EPA, 1997) – body surface area estimates based on direct measurement. For the purposes of this technical dossier, 50th percentile surface areas were chosen consistent with the approach used by SCCS in their Notes of Guidance (SCCS, 2012).
2) RIVM (Bremmer *et al*., 2003) – body surface area estimates based on a computer programme, CONSEXPO. CONSEXPO is used to calculate exposure in consumer products, using mathematical models.

   Default models and default values have been determined per product category for use in the assessment of consumer exposure to compounds in cosmetics.

3) Individual published data for oral care (Collins *et al*., 1987) – the surface area of

the adult human mouth was measured in ten adults/sex and expressed as the mean total surface area.

4) Individual published data for lip (Ferrario *et al*., 2000) - the surface area of the adult female human lip was measured in 96 women and expressed as the mean total surface area.

Within these data sources, the individual references used to define the consumer exposure to different product types are detailed in Section 2.3 and Table 7.

9. Appendix 4: Creme RIFM Dermal Aggregate Exposure Model

The methods employed in this study are based on the peer-reviewed methods used in the assessment of exposure to chemicals in food (McNamara *et al*. 2003), which have been applied also in the case of exposure assessment for cosmetics and personal care products (Hall *et al*., 2009; Hall *et al.,* 2005). The first phase of the Creme RIFM Aggregate Exposure Model has been published (Comiskey *et al*., 2015; Safford *et al*., 2015). The probabilistic exposure calculations were carried out using a custom-built software system in which these models have been implemented. In this article, the probabilistic exposure assessment models which are used in this study are described. The calculation of exposure to a chemical from a number of different products (Aggregate Exposure) requires suitable methods for both:

1) Calculating the exposure from a single product.
2) Aggregating the exposures from individual products.

9.1. Dermal Exposure from a Single Product

If a product is applied to a particular part of the body, and the surface area, SA, of that body part is known, then exposure per unit area can be calculated. The exposure per unit surface area is called the dermal exposure, DE, and it is the relevant measurement for conducting risk assessments for dermal sensitisation (Api *et al*., 2008). As the DE is dependent on the surface area of the body part in question, a separate DE can be measured for each body part defined. There are 18 distinct body sites defined for this study and the DE will be calculated separately for each. The daily dermal exposure, DDE, from one product to a particular body part surface area (µg/cm^2/day) is given by:

$$Daily\ Dermal\ Exposure = \frac{Frequency \times Amount \times Concentration \times Retention}{Surface\ Area} \quad (1)$$

where:

frequency refers to the number of usage occasions of a product in one day,
amount is the amount (grams) of product applied in each application,
retention is a percentage of how much of the product stays on the body after application,
concentration is the percentage of the chemical in the product, and
surface area is the area of the site of application.

The equation above calculates the DDE from one product to one application site for one person. However, there are 36,446 subjects in the habits and practices survey. Therefore, the above equation is repeated for each product exposure to each application site for every subject. The *population daily dermal exposure*, PDDE, is usually reported as a statistic (typically a relatively high percentile, such as the 95th percentile), of the individual exposures.

Therefore we can write:

$$PDDE = Stat(DDE_1, DDE_2, \dots, DDE_M) \quad (2)$$

where DDE_i is the daily exposure to individual i, and the Stat() function is similar to the P95 (95th percentile).

9.2. Exposure from Multiple Products (Aggregate Exposure)

Where a subject uses a number of products, each of which may contain the fragrance ingredient/chemical of interest, the total chemical exposure can be calculated by summing the contributions from the individual products (for that subject). And so, the aggregate daily dermal exposure for an individual subject can be written as:

$$\begin{aligned} DDE_{AGG} &= DDE_{Product\ 1} DDE_{AggGG} \\ &= DDE_{Product\ 1} + DDE_{Product\ 2} + \cdots + DDE_{Product\ N} \end{aligned} \quad (3)$$

where the terms $DDE_{Product\,i}$ denote the daily dermal exposure from a single product, as defined in equation (1) above. Then, the aggregate population daily dermal exposure, $PDDE_{Agg}$, is again calculated as:

$$\begin{aligned} &PDDE_{AGG} PDDE_{AggGG} \\ &= Stat(DDE_{AGG\ 1},\ DDE_{AGG\ 1}, \dots, DDE_{AGG\ M})\left(DDE_{AggGG\ 1},\ DDE_{AggGG\ 1}, \dots, DDE_{AggGG\ M}\right) \end{aligned} \quad (4)$$

where the terms DDE_{Aggi} denote the aggregate exposure for an individual subject, as defined in equation (3) above.

In relation to the two required methods which were identified at the beginning of this section, the method of aggregation is simply to sum the individual contributions from the different products at the individual subject level, and then move from individual exposure to the population exposure, in the same way as for a single product.

9.3. Simulating the Population with Weighting Factors

As it is not practical to measure the usage habits for the entire population directly, the method used, following existing methodologies, is to create a simulated population based on a statistical representation of the population whose product usage habits were as close as possible to the real population. The exposure calculated for this simulated population can then be used as the estimate of the exposure to the real population. Statistical Weighting Factors are associated with the sample subjects to ensure that demographic groups are accurately represented in the calculation. For example, one particular subject in the frequency of product use survey may represent 10,000 people in their population based on their age, ethnicity and gender. This means that we can take account of each subject's weighting, W_i,

and following from the equation for PDDE, the weighted population daily dermal exposure, WPDDE, is:

$$WPDDE = StatWeighted(W_1, DDE_1, W_2, DDE_2, \dots, W_M, DDE_M) \quad (5)$$

9.4. Use of Aggregate Risk Assessment for Calculation of Adjusting Upper Use Levels

The estimated aggregate consumer exposure levels (CEL_{agg}) (Table 10 in the dossier) are the 95th percentiles of consumer exposure (µg/cm^2) estimated with the Creme RIFM model. Estimated exposures are presented for each of the 18 body sites and are found to be exceeding their corresponding AEL in 4 body sites. The body sites with lowest AEL/CEL ratio is lips, and therefore a first set of adjustments to concentration levels will target the product categories involved in exposure to the lips.

9.4.1. Lips

The product categories involved in exposure for lips are Oral Care, Cosmetics, Moisturizers, Cleansing, with categories contributing in various degrees to the overall exposure.

To take into account the relative contribution of product categories to overall exposure, the 95th percentiles of exposure of individual categories is considered. As a way of approximating the relative contribution of each category to the 95th percentile of exposure, we consider the contribution of a single product's 95th percentile to the sum of all categories' 95th percentiles. Note that the summation of individual percentiles is intended solely for the use of best estimating relative contributions to overall exposure.

By this method, the relative contribution of the 4 categories to exposure to the lips was estimated and is illustrated in Figure 9 and Table 21.

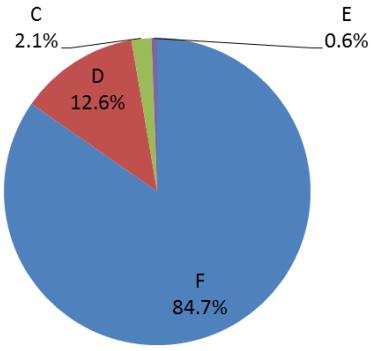

Figure 9: Relative Contribution of the 4 Categories to Exposure to the Lips

	Contribution
F - Oral Care	84.7%
D - Cosmetics	12.6%
C - Moisturizers	2.1%
E - Cleansing	0.6%

Table 21: Relative Contribution of the 4 Categories to Exposure to the Lips

As a first step in reducing upper use levels and take relative contributions into account, weighting factors were initially computed as:

$$w_g = 1 - contribution_g \quad (6)$$

where w_g is the weighting factor for category *G*, and depends on the contribution of category *G* expressed as a proportion (a number between 0 and 1, e.g. the relative contribution of 84.7% corresponds to the proportion value 0.847) (Table 22).

	Contribution	W_g
F - Oral Care	84.7% or 0.847	0.15
D - Cosmetics	12.6% or 0.126	0.87
C - Moisturizers	2.1% or 0.021	0.98
E - Cleansing	0.6% or 0.006	0.99

Table 22: Calculation of the Weighting Factors for Category G (w_g) for the 4 Categories Contributing to the Exposure to the Lips (Oral Care, Cosmetics, Moisturizers and Cleansing)

For each product in a category, the upper use level was reduced by applying the relevant weighting factor (Table 22). If for example category F contributes 84.7% to the exposure, then upper use levels for category F are reduced by 84.7%.

A second iteration of assessments using the Creme RIFM model with the reduced upper use levels for the four categories leads to an updated estimate of exposure levels.

The new AEL/CEL ratio for lips is 1.9 and indicates that the application of weighting factors still results in an excessive (or unnecessarily high) reduction in exposure level. With the aim of obtaining an AEL/CEL ratio that is equal to 1, a further multiplication factor is introduced to correct weighting factors.

A suitable multiplication factor was obtained through an iterative process with an initial value of 1. The factor 0.776, when applied to the relative contribution in each of the four categories, leads to a new set of weighting factors (Table 23), and in turn to an AEL/CEL ratio of 1.13.

The new weighting factor applied to initial upper use level for products in category *G* is then:

$$w_g = 1 - \left(contribution_g * 0.776\right) \quad (7)$$

	Contribution	w_g
F - Oral Care	0.847	1 – (0.847 * 0.776) = 0.34
D - Cosmetics	0.126	1 – (0.126 * 0.776) = 0.9
C - Moisturizers	0.021	1 – (0.021 * 0.776) = 0.98
E - Cleansing	0.006	1 – (0.006 * 0.776) = 1

Table 23: Application of the Corrective Factor Obtained by Iteration to the Calculation of the Weighting Factors for Category G (w_g) for the 4 Categories Contributing to the Exposure to the Lips (Oral Care, Cosmetics, Moisturizers and Cleansing).

The reductions thus applied to Oral Care products were also sufficient to produce an acceptable exposure level for the intra-oral body site (AEL/CEL = 1.45).

9.4.2. Palms

The body sites palms and axillae had still levels of exposure that exceeded their AEL (Table 13 in the dossier) and therefore the same approach to reducing upper use levels outlined above was attempted.

With regard to exposure to palms four product categories were found to be involved, and their relative contribution to overall exposure was estimated (Figure 10 and Table 24).

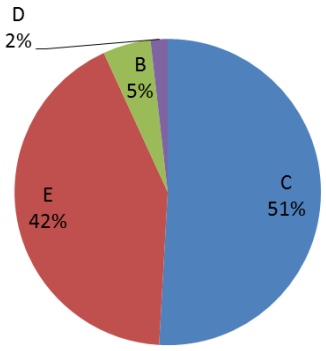

Figure 10: Relative Contribution of the 4 Categories to Exposure to the Palms.

	Contribution
C - Moisturizers	50.9%
E - Cleansing	42.2%
B - Hydro alcoholics	5.1%
D - Cosmetics	1.8%

Table 24: Relative Contribution of the 4 Categories to Exposure to the Palms.

Weighting factors were derived on the basis of relative contributions to overall exposure to the palms (Table 25) with the formula:

$$w_g = 1 - contribution_g \quad (6)$$

	Contribution	w_g
C - Moisturizers	0.509	0.49
E - Cleansing	0.422	0.58
B - Hydro alcoholics	0.051	0.95
D - Cosmetics	0.018	0.98

Table 25: Calculation of the Weighting Factors for Category G (w_g) for the 4 Categories Contributing to the Exposure to the Palms (Moisturizers, Cleansing, Hydro alcoholics and Cosmetics).

The updated AEL/CEL ratio for exposure to the palms was found to be 1.18, and no further adjustments were deemed to be required.

9.4.3. Axillae

Although the AEL/CEL ratio had increased for several body sites, the exposure to axillae was still exceeding its AEL (AEL/CEL = 0.68).

The relative contribution of the three product categories involved in exposure to axillae (Figure 11 and Table 26) was estimated and again used to derive weighting factors (Table 27).

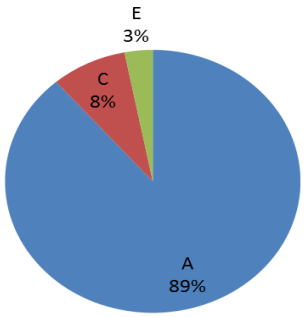

Figure 11: Relative Contribution of the 4 Categories to Exposure to the Axillae.

	Contribution
A - Deodorants	88.6%
C - Moisturizers	8.3%
E - Cleansing	3.1%

Table 26: Relative Contribution of the 4 Categories to Exposure to the Axillae.

	Contribution	W_g
A - Deodorants	0.886	0.11
C - Moisturizers	0.083	0.92
E - Cleansing	0.031	0.97

Table 27: Calculation of the Weighting Factors for Category G (w_g) for the 4 Categories Contributing to the Exposure to the Axillae (Deodorants, Moisturizers and Cleansing).

An assessment of aggregate exposure to the axillae with the above weighting factors resulted in AEL/CEL ratio of 3.78, suggesting that a multiplication factor should be introduced to appropriately reduce individual product categories weighting factors (Table 28).

By an iterative process it was found that a multiplication factor of 0.414 produces an AEL/CEL ratio of 1.07, which is deemed satisfactory.

	Contribution	W_g
A - Deodorants	0.886	1 – (0.886 * 0.414) = 0.63
C - Moisturizers	0.83	1 – (0.83 * 0.414) = 0.97
E - Cleansing	0.031	1 – (0.031 * 0.414) = 0.99

Table 28: Application of the Corrective Factor Obtained by Iteration to the Calculation of the Weighting Factors for Category G (w_g) for the 4 Categories Contributing to the Exposure to the Lips (Oral Care, Cosmetics, Moisturizers and Cleansing).

9.4.4. Summary of Final Weighting Factors Used

	Lips	Palms	Axillae	Final
A – Deodorants			0.63	0.63
B - Hydroalcoholics		0.95		0.95
C - Moisturizers	0.98	0.49	0.97	0.4658
D - Cosmetics	0.9	0.98		0.882
E - Cleansing	1	0.58	0.99	0.5742
F - Oral Care	0.34			0.34

Table 29: Summary of Final Weighting Factors Used.

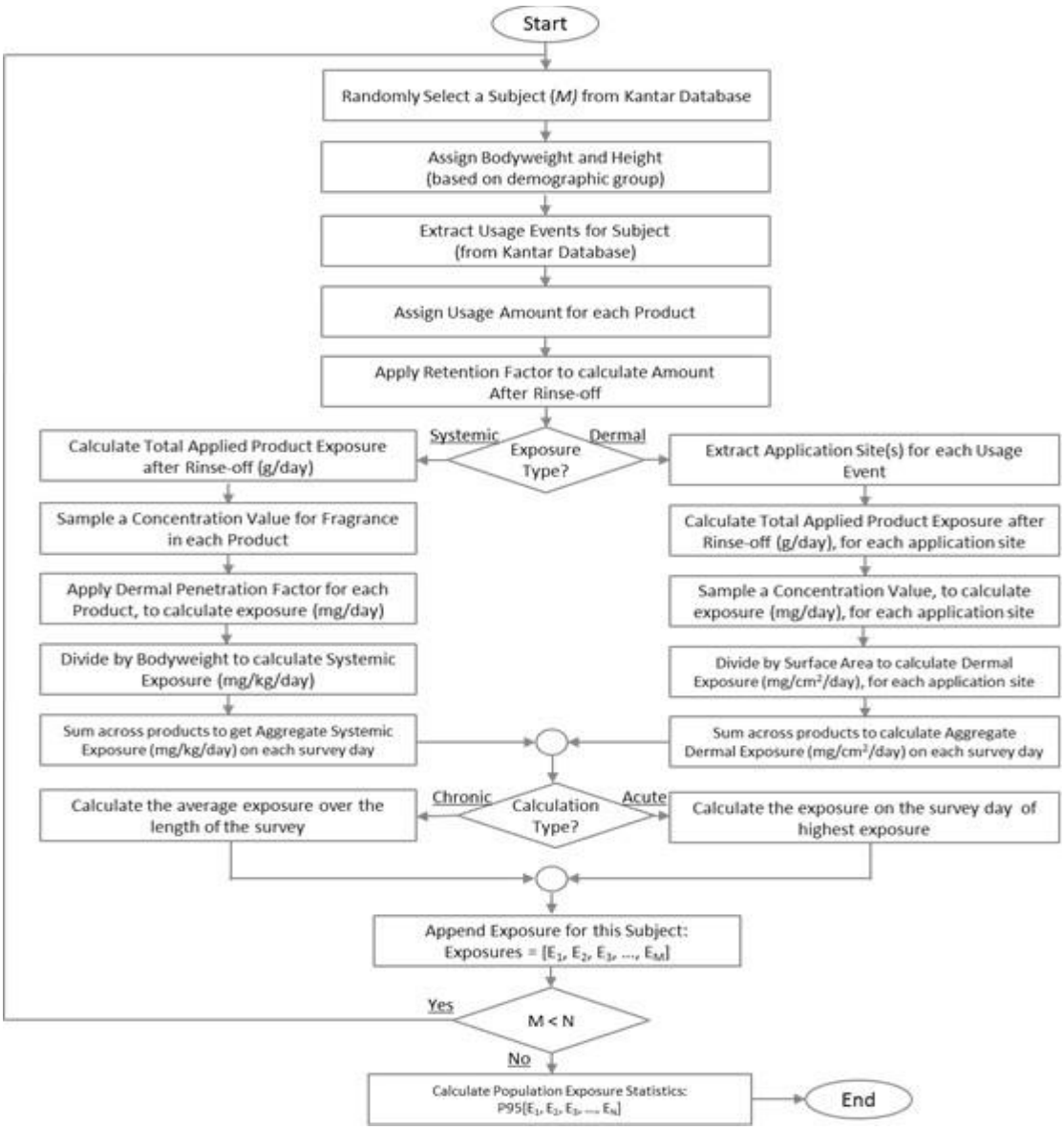

Figure 12: Overview of the Dermal Aggregate Exposure Model