

Report on the IDEA Workshop on

Validity of the QRA Methodology & Possibilities of Further Refinement

March 11-13, 2014

Dolce La Hulpe Brussels
Chaussée de Bruxelles, 135
B-1310 La Hulpe, Belgium

1. Background information regarding the International Dialogue for the Evaluation of Allergens (IDEA):

Fragrance Allergy is a topic of high interest for the fragrance industry, its customers and the Authorities as expressed through the 2012 SCCS Opinion on Fragrance Allergens. The fragrance industry is determined to address this issue and provide solutions supported by a broad, multi-stakeholder approach.

To fulfil this objective, a work plan (att.01) was developed in the course of 2012 and submitted to DG Sanco Risk Assessment Unit for scrutiny. All comments and suggestions were taken into consideration and the final document, having received the Commission's support, is a clear roadmap intended to deliver positive outcomes for the consumers, the Authorities and the industry. This work plan has now moved into its execution phase and the International Dialogue for the Evaluation of Allergens (IDEA) represents its transposition into concrete actions and investments. Through the organization of experts' workshops and the planning of scientific studies, IDEA aims at providing an agreed and transparent framework for assessing fragrance sensitizers in a prospective way and, ultimately, to find optimal solutions to the issue of fragrance induced skin allergies.

The objective of this workshop was to improve the current Dermal Sensitization Quantitative Risk Assessment methodology ('QRA) and to understand how far it can already be commonly agreed for application to fragrance allergens as a risk management tool. To reach this objective, the participants of this workshop were mandated to review the methodology as used today by the fragrance industry in view to identify the areas of further refinements. This event will be the opportunity to review and discuss the status of action items recommended by experts who participated in the first workshop on QRA, held on March 19-20, 2014.

IDEA Management Team

Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info



2. Summary agreed at the workshop:

The workshop participants identified a set of elements that should be taken into consideration for the development of a QRA 2.0.

The starting point of the QRA is the NESIL which is defined as the threshold known not to induce skin sensitization, considering all available hazard data in a weight of evidence approach, under the specific exposure conditions of a standard protocol HRIPT.

- Considerations related to Humans:
 - The variation in individual human susceptibility to skin sensitization is substantial. The biological basis of this variability is largely unknown, with ethnicity, gender, age (including infants), genetics each making only a minor contribution.
 - Regarding skin diseases / conditions:
 - Atopic dermatitis, psoriasis and dry skin have probably no impact on skin sensitization.
 - Irritant dermatitis is known to promote skin sensitization.
 - The inter-individual variability not accommodated in the NESIL is reflected by a SAF of 10.
- Considerations related to Products:
 - The impact of product use factors such as degree of occlusion, frequency / duration of product use and the product matrix itself are reflected in SAFs that range between 0.3 and 3.
 - The role of skin condition / site is determined by a stepwise consideration of pre-existing inflammation, irritation by product, and penetration / permeation of product and is reflected in SAFs each between 1 and 3.

In conclusion, the assumptions for the SAFs underpinning QRA 1.0 have been reviewed: QRA 2.0 represents a more detailed and transparent assessment with regard to aggregate exposure, skin condition, product type and site of application.

Factor	Consideration	Influence	New proposed SAF values
Occlusion	Some areas of skin are semi-occluded by clothing, or product with moisturising agents may lead to semi-occlusion.	Semi-occluded = Non-occluded ↓	1 0.5
Product matrix	Role of vehicle	Delivery	0.3 or 1 or 3
Frequency / duration of product use	Products may be used over extended periods of time resulting in bio-accumulation	↑	1 or 2
Skin condition / site	Pre-existing inflammation Irritation by product Penetration / permeation of product	Increase of induction susceptibility	1 or 3 1 or 3 1 or 3

3. Report of the Rapporteur :

A. The primary purposes of the workshop

The primary purposes of this workshop were to:

- Provide an update on progress in the development of the RIFM Quantitative Risk Assessment methodology for the identification and characterisation of allergenic fragrances since the previous workshop held in March 2013 and consider those aspects of the QRA that were not addressed previously.
- Identify how these developments can be incorporated in a revised methodology (QRA II) which is required to be submitted to the Commission Services (JRC) at the end of June 2014.
- Discuss ways in which QRA II might be advanced further in the future.

In the light of the above, aspects of the QRA that were given particular attention at the workshop were:

- i) factors responsible for human variability,
- ii) exposure assessment,
- iii) the scientific basis for the use of sensitization assessment factors or SAFs, which are safety/default/uncertainty factors
- iv) the content, validation and application of QRA II.

NB. The replacement of laboratory animal studies to identify thresholds for induction by *in vitro* and *in silico* studies was regarded as a priority for further work. However, in view of the short time scale for the submission of QRA II it was agreed that this topic should be left to a future workshop(s)

B. Quantitative Risk Assessment (QRA)

B.1. The purpose of the QRA

QRA should provide a reliable, easy to use, consistent to apply and transparent methodology, based on current scientific understanding, that will identify a safe level of exposure to each fragrance material assessed. A safe use level is defined in this context as one that will not induce skin sensitisation in consumers.

The most relevant expression of exposure is a critical consideration for risk assessment purposes. It is not certain whether it is the currently used metric, the total dose applied to the body (mg applied per cm² skin), or the dose applied to a particular area that drains to a particular lymph node(s) that is the more critical factor in initiating induction. Based on current understanding of modes of action it might be expected to be the latter. However, for QRA II, the current metric needs to be retained. There is also uncertainty as to whether exposure per day is the best metric in all cases.

B.1.a. Relationship between induction and elicitation of sensitisation

The underlying premise of the QRA is that if induction can be prevented subsequent allergic elicitation reactions will not occur. The QRA relies primarily on animals tests, in particular the local lymph node assay and/or guinea pig maximisation test, to estimate the induction threshold. Safety assessment factors (SAF's) are then used to allow for differences between animals and humans in responsiveness, for possible differences in responsiveness between humans (human variability or inter-individual differences) and for potential differences between experimental and real-life conditions (matrix effects / use considerations).



Human data on fragrance allergy relates primarily to sensitisation. Clinical examination of patients by experienced dermatologists, using diagnostic patch testing, is the gold standard to determine the prevalence of skin sensitisation to allergens in the general population). The relationship between induction of contact allergy and the development of an allergic elicitation reaction is complex. The threshold level for induction is considered to be higher than the threshold for allergic elicitation reactions. However this has only been evaluated for moderate to strong sensitizers. Whether this relationship is the same for weak and extremely weak sensitizers remains uncertain. There is considerable uncertainty too on whether the biological variables that have been identified in humans for elicitation reactions are identical, and of comparable magnitude, for the induction of contact allergy in humans.

B.2. Short summary of QRA 1

Details of RIFM QRA I were published in a series of articles in 2008 (See reference section below). The aim of QRA I is to identify a safe (acceptable) dose for each fragrance application (product type) and compare this with the current/potential exposure of consumers to it. The safe /acceptable level (AEL) is derived from the equation:

$$\text{AEL} = \text{NESIL} / \text{SAF}'\text{s}$$

Where NESIL is the no expected sensitisation induction level and SAF's are default/safety/uncertainty assessment factors used to extrapolate from the experimental (defined and controlled exposure conditions) to real life consumer exposure (variable exposure controlled by the consumer).

If the calculated consumer exposure level (CEL) is below the safe dose then contact allergy is very unlikely to arise in the vast majority of consumers. In other words:

$\text{AEL}/\text{CEL} \geq 1$ is deemed a safe value.

QRA I is based on the same principles that are generally used in the risk assessment of chemicals for many other spheres of use. Namely identify an acceptable exposure level based primarily on animal testing, and estimate consumer exposure based on use and other relevant considerations.

- *Hazard identification and characterisation.* In principle this is more straightforward than in other areas of toxicology in that the endpoint of interest is pre-defined. Nonetheless the identification of a soundly based threshold (NESIL) is crucial. The NESIL should be based on a weight of evidence approach in which all sensitisation data are considered (animal and human). The primary methods for identifying the NESIL are currently animal based; the guinea pig tests and the local lymph node assay. Characterisation of the dose response relationship may also draw on human data (on sensitisation) and/or structure based predictions. The NESIL derived from the above may be supported by HRIPT data.
- *Exposure assessment.* Professional exposure groups who may receive considerably higher levels and durations of exposure to some fragranced products and the ingredients they contain) are not considered in QRA I for exposure assessment purposes. For consumer exposure a deterministic approach is used. Currently QRA I is applied to the assessment of the risk from the application of one fragrance ingredient at a time in one product only. Use patterns, areas of skin exposed etc. are based on 11 product categories. Frequency of use for a particular product is based on the estimate of the upper (97.5th) percentile of use by consumers for that type of product. The assessment also includes consideration of dermal retention based on the nature of the product.

- *Use of SAF's.* Uncertainties that are intended to be taken into account through the application of SAF's are: human inter-individual variability (SAF = 10), product matrix effects (SAF = 1, 3 or 10) and use patterns (SAF = 1, 3 or 10). Selection of the most appropriate SAF is a matter of judgement, and, may result in a total SAF in the range 10-1000.

B.3. Description of QRA II

QRA II should be based on experience in the use of QRA I and advances in scientific understanding since 2007/8. Experience can be drawn on from three main sources:

- Experience of company scientists and others using or reviewing the outputs from the QRA of a particular fragrance;
- Feedback from clinicians in the dermatological community of their findings in patients with established contact allergy to fragrance substances that had been through the QRA and ' safe use levels applied (IFRA Standards)
- Information on exposure to fragrance chemicals

There is considerable information on frequencies of contact allergy to those fragrance substances that are required to be identified on cosmetic ingredient labels, but not to other fragrance substances.

Proposed improvements to QRA should be justified and be compatible with accepted regulatory frameworks for the risk assessment of cosmetic ingredients as set out in the SCCS's guidelines (SCCP 19th December 2008, Notes of Guidance for the Testing of Cosmetics Ingredients and their Safety Evaluation).

C. Human variability in response

C.1. Issues that need to be taken into account

Langerhans cells are fairly evenly distributed between areas of skin. It was argued that this implies that the responsiveness of different areas of skin to a directly acting allergen is likely to be comparable.

It has been shown that following sufficient exposure to allergenic substances, T lymphocytes may become activated but that the expression of sensitisation is suppressed in many people (tolerance). Atopic individuals may be more difficult to sensitise through the skin (delayed hypersensitivity) although the mechanism behind this is different.

In our present state of knowledge is not possible to pick out an at risk group of the population (save for anatomical sites of application). There may be an inverse relationship between the potency of a sensitiser (ie the threshold for sensitisation) and the range of consumer responsiveness. Thus, for a strong allergen, there may be far less variability in human response than is the case for a much weaker sensitiser. If this hypothesis is accepted then it is reasonable to argue that to understand the extent and causes of human variability in sensitisation the focus should be on weak sensitisers rather than on strong ones.

In regard to the threshold for induction of sensitisation in the human population, it is much less clear, than for elicitation of contact allergy, what the range and causes of variability are or whether weak sensitisers should be focussed on in order to understand human variability in the induction of contact allergy. Key factors contributing to variations in induction thresholds between individuals are considered to be:

- Dermal penetration and dermal bioavailability,
- Chemical and/or biological (metabolism) and clearance processes and,

- Interaction of the fragrance chemical (or pre-hapten, pro-hapten products) with Langerhans cells and subsequent steps in the induction process.

C.2. Estimate of the magnitude of variability

An important question is the extent to which variability in the threshold for induction in animals and variability in human sensitization can provide valuable information on the principal causes of variations in induction initiation in humans.

D. Exposure assessment

D.1. Context

There is some ambiguity in risk assessment methodology in general as to which topics should be included as components of exposure assessment. Some regard exposure assessment as being restricted to the level/concentration of a chemical and/or its contaminants/breakdown products at the external surfaces of the body (skin, gut, lungs), others include absorption. Distribution, metabolism and excretion (toxicokinetics) are also sometimes included as additional elements of exposure assessment. This ambiguity was also apparent at the workshop and was not resolved.

The most widely used metric for assessing exposure *via* the dermal route is currently mg per cm² skin per day. However exposure per day is unlikely in every case to be the most appropriate metric. For instance the question was raised as to whether 0.1 mg applied 10 times during 24 hours would have potentially similar consequences to 1mg applied as a single dose.

D.2. Topics discussed

Relevant topics discussed at the workshop were:

- Variables affecting bioavailability;
- Comparison of exposure conditions for human repeat insult patch test (HRIPT) with those of typical consumer exposure;
- Aggregate exposure, including frequency and nature of use and other sources of exposure to the same fragrance.

D.2.a. Factors affecting bioavailability

Important considerations are fragrance chemical stability and nature and levels of pre- and pro hapten products and the level and duration of external exposure to a fragrance and related chemicals.

Other important variables to consider are:

- Influence of occlusion,
- Skin permeability (including variations due to damaged or inflamed skin),
- Site(s) of exposure,
- Matrix effects due to other components in a formulation,
- Potential for the build-up of a fragrance substance within the skin and,
- Extent to which QRAI / QRAII covers not only haptens but also pre- and pro-haptens. This issue was not considered further in any detail although in the guinea pig test and to a rather lesser extent in the LLNA assay the metabolic capacity to form haptens from pro-haptens was assumed to be largely present.

D.2.b. Comparison of exposure conditions for HRIPT and typical human exposure

The fragrance industry uses HRIPT data on human sensitisation to fragrance materials (before consumer exposure) to assess effects of exposure and thresholds. It relies on a standard protocol to maximise the potential for reproducibility of results, which includes a standard population sample of +100 volunteers (excluding those with skin disease), application (usually to the arm or back) of the fragrance material in a simple solvent under full occlusion for 24 hours, three times a week for three weeks. It would be helpful to characterise the extent of human variability represented by such population samples.

Of necessity the HRIPT exposure scenario differs from that expected from the consumer population as a whole, where factors such as matrix effects exposure of other sites, different frequencies and duration of use, lack of occlusion and use by individuals with a variety of skin conditions may apply. This needs to be considered in the estimates of the consumer population exposure and in the appropriate selection of SAF values.

D.2.c. Aggregate exposure

One of the main advances, since the original QRA I methodology was published, is the development of a model for estimating aggregate exposure by Creme supported by RIFM. Compared to the simple way to derive the consumer exposure level (CEL) in QRA I, the aggregate exposure model is a substantial advance in many respects including the following:

- It is probabilistic not deterministic,
- It draws on a very large number of consumer diaries and therefore a much wider range of the population,
- It is based on actual consumer use habits and actual areas of application to the skin rather than the use of standard assumptions,
- It covers access to both acute and chronic exposure estimates,
- It takes into account multiple product use throughout the day,
- The dermal retention factor derived from both frequency and amount of use.

As a consequence of the above the RIFM / Creme aggregate exposure method is very likely to give a much more reliable measure of the total exposure to a fragrance in a day. As it allows to some extent for accumulation it will in many cases result in higher estimates of consumer exposure (CEL) to individual fragrances than is the case using the current QRA I methodology.

Not surprisingly there are a number of challenges in the application of the RIFM / Creme model to specific products that will need to be addressed including:

- Individual products containing the same fragrance material may be applied over multiple sites. This needs to be considered in the context that the critical concentration to initiate induction is the concentration reaching a particular lymph node;
- Different products containing the same fragrance material may be applied to the same site(s). This may entail that a site has a number of matrices applied concurrently to the same site which may compromise bioavailability.

As a result it is challenging to use, in the most appropriate manner, the aggregate exposure for each application site/product use and to define the most suitable SAF values in a simple QRA II.

The risk of induction and elicitation of sensitisation from a particular use of a fragrance is also increased if there is exposure to other chemicals with the same mode of induction and elicitation of sensitisation (cumulative exposure) however there is insufficient data yet to introduce a suitable cumulative exposure model.

E. Selection of suitable SAF's

E.1. Context

It was noted that safety /default/uncertainty factors are widely used for regulatory risk assessment purposes in the EU. They are intended to cover:

- Intrinsic variability in data
- Variability due to the methodology used
- Uncertainties due to either deficiencies in the quality, relevance and/or comprehensiveness of the data available.

Applications of safety factors include the risk assessment of food additives and contaminants (EFSA) and industrial chemicals (ECHA). It is important in selecting a SAF to ensure that some balance is achieved between ensuring protection of the exposed population and the unnecessary curtailment of the use of valuable products. A particular issue in this regard is the avoidance of double accounting through overlapping default factors.

The workshop provided an interesting debate on two contrasting approaches to setting SAF's:

- i) Select a larger SAF, and for companies that wish to reduce this value, putting the onus on them to generate extra data and to use weight of evidence to reduce the SAF for their product.
- ii) Set a lower generic set of SAF which Companies would use, unless there were greater data gaps or uncertainties to require higher SAF's.

The industry-associated participants opted for option ii).

In general toxicology, most commonly in the extrapolation of NO(A)EL (no observable effect adverse effect levels in laboratory animals) to a safe level for chronic exposure of consumers, a factor of 10 is used for extrapolation to man and a further factor of 10 is applied to allow for variations in inter-individual human responses. These factors may be varied for particular chemical according to the quality and comprehensiveness of the database available. The extent to which this approach may be relied upon for allergic sensitisation is unknown.

E.2. Considerations in selection of numerical SAF values

In the selection of appropriate SAF values the following overlapping issues are important:

- The variables that need to be considered and how many separate SAF's are therefore required. This aspect was discussed in some detail at the workshop.
- The percentage of consumers that the SAF's are designed to protect against fragrance chemical contact allergy. Should only consumers be considered or should professional exposures also be considered? Is the aim to protect 100% of consumers, or, as in other areas of risk assessment should it be accepted that it is impossible to guarantee the protection of every member of the population however sensitive they may be? It is noted that in terms of exposure in the RIFM / Creme model the 97.5th percentile exposure for consumer use was used.



- Other factors that affect the size of SAF's such as the degree of confidence needed in the achievement of this protection.

The main variables discussed considered were:

E.2.a. Exposure factors

In particular the following need to be considered:

- Influence of occlusion. It was queried whether a separate SAF was needed. -
- Site(s) of exposure. Some areas of skin are more permeable than others and appear to be more likely to develop an allergic reaction but this cannot necessarily be taken to imply that exposure at these sites is more likely to be the cause of induction. As Langerhans cells are fairly evenly distributed between areas of skin responsiveness of different areas of skin to a directly acting allergen might be assumed to be comparable. It was queried whether a SAF was needed.
- Matrix effects due to other components in a formulation. Solvent and other matrix effects were considered to be in general relatively small (1 or 3).
- Duration of exposure and potential for the build-up of a fragrance within the skin/ lymphocytes. As noted above it was questioned whether per day exposure was always the most appropriate metric however discussion of alternative approaches was rather limited.

It was not generally agreed whether these factors should be represented by one or more SAF values. Some factors for specific fragrances may justify a SAF of less than one.

Further discussion at the next workshop is necessary on both the number of SAFs and their magnitude.

E.2.b. Human variability in response

This arises from a combination of genetic and environmental contributors including:

- Skin permeability/bioavailability (including variations due to damaged or inflamed Skin). It was felt that variation was likely to be greatest for damaged/inflamed skin. The question was raised as to whether a factor of 10 was enough for severely inflamed skin.
- Metabolism, distribution and clearance. Variations in these parameters were not considered specifically at the workshop.
- Langerhans cell interaction(s) and subsequent interactions and responses. Variations in these parameters were not considered specifically at the workshop.

Older studies by Kligman et al, Maibach et Al, and others had identified that the scale of variability can be several orders of magnitude for specific fragrance chemicals.

How to use these data to identify a SAF for protection against induction in consumers' needs further discussion at the next QRA workshop.



F. Application of QRA II and related issues

QRA II methodology and the guidelines for its use need to obtain the formal approval from the Commission (through the JRC) and are likely to require approval as appropriate for risk assessment purposes by the SCCS.

Application of the findings from the use of QRA II needs to actively involve other stakeholders. In particular a meaningful dialogue is needed with the community of clinical dermatologists on the output of QRA II and its use to set IFRA standards for each fragrance material. This should cover both the selection of the IFRA standard, the anticipated uses of the fragrance (including uses other than as a fragrance) and necessary procedures for frequent feedback on experiences in the clinics with patients using products containing the fragrance material.

A further aspect is to ensure that member companies of IFRA apply QRA consistently and appropriately to their products and ensure compliance with the IFRA standards. It was proposed that an inter-company quality control scheme should be introduced to maximise the value and confidence in its use of QRA II.

G. Follow-up and priorities for further work

The development of the RIFM / Creme aggregate exposure model represents the most significant advance since the RIFM QRA I was first published in 2008.

Additional challenge in the development of QRA II is to ensure that inter-individual differences among consumers in the potential for the initiation of induction by any fragrance material is taken into account but not unnecessarily over compensated for. Key requirements to achieve this are:

- the judicious selection and use of hazard characterisation tests;
- the selection of appropriate SAFs;
- a robust procedure(s) for the validation of the QRA process

The target of a revised QRA being available by the end of June 2014 for submission to the JRC requires prioritisation into short term (2 months only) and longer term tasks (deliverables).

G.1. The main short term tasks

These may be identified as:

- i) Guidance on how to apply the RIFM / Creme aggregate exposure model for the risk assessment of individual exposures;
- ii) Specification of the values to be assigned to allow for uncertainty and extrinsic and methodological uncertainty. Along with guidance on specific circumstances where difference SAFs ought to be applied;
- iii) Selected case histories to demonstrate the appropriate application of QRA II
- iv) Establish feedback mechanism so that clinical experience with a fragrance allergen results in evaluation of the assumptions within QRA.

G.2. Longer term tasks

Theses have been identified as:

- i) Further progress on databases to enable the development of (Q)SAR tools for inducers. Use of these SARs to develop cumulative exposure models.

- ii) A protocol to enable identification and testing of pre-haptens based on structural considerations for each fragrance (see pre and pro hapten workshop findings)
- iii) Laboratory studies to identify the ability of the hazard characterisation tests to convert pro-haptens to haptens;
- iv) Development of exposure assessment models for professional exposure to fragrances;
- v) Identification of how to phase the regulatory imposed shift from animal based hazard assessment to *in vitro* and *in silico* based hazard assessment;
- vi) Continuation of effective dialogue among the key stakeholders coupled with effective actions to improve the utility of the QRA in order to ensure protection of consumers and others.

H. References

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Professor Jim Bridges
Workshop Rapporteur

Appendix 1 – Workshop Participants:

- European Commission and European Scientific Committees: Dr. Gaetano Castaldo (EU Commission, DG Sanco B2 Unit), Dr. Federica De Gaetano (EU Commission, DG Sanco B2 Unit), Prof. David Gawkrödger (Royal Hallamshire Hospital and Vice-chairman of the SCCS), Ms. Izabela Taborska (EU Commission, DG Sanco B2 Unit).
- Academic community and national Authorities: Dr. David Basketter (Consultant), Prof. Donald Belsito (Columbia University Medical Center and RIFM Expert Panel Member), Prof. Magnus Bruze (Lunds Universiteit and RIFM Expert Panel Member), Prof. Thomas Diepgen (Ruprecht-Karls University), Dr. Janine Ezendam (RIVM), Dr. Peter Friedmann (University of Southampton), Dr. Christine Lafforgue (Université Paris sud 11), Dr. Cronan McNamara (Crème Global), Prof. David Roberts (Liverpool John Moores University), Prof. Vera Rogiers (Vrije Universiteit Brussel), Dr. Bob Safford (Consultant), Dr. Joanne Salverda (RIVM), Prof. Axel Schnuch (IVDK / University of Göttingen), Dr. Ian White (Guy's & St Thomas' NHS Hospitals).
- Industry: Dr. Jay Ansell (PCPC), Dr. Eric Antignac (L'Oréal), Dr. Anne Marie Api (RIFM), Dr. Dagmar Bury (L'Oréal), Dr. Peter Cadby (Chanel), Dr. Nicola Gilmour (Unilever), Dr. Peter Griem (Symrise), Dr. Etje Hulzebos (I.F.F.), Dr. Petra Kern (Procter & Gamble), Dr. Christeine Lally (Procter & Gamble), Dr. Sylvie Lemoine (A.I.S.E.), Dr. Andreas Natsch (Givaudan), Dr. Florian Schellauf (Cosmetics Europe), Dr. Scott Schneider (Firmenich), Mr. Pierre Sivac (IFRA).
- IDEA Staff: Dr. Hans-J. Bender (Moderator), Dr. Fred Lebreux (IFRA), Dr. Matthias Vey (IFRA).
- Supervisory Group members: Prof. Jim Bridges (Rapporteur).