IDEA
International Dialogue for the Evaluation of Allergens

Report on the IDEA Workshop on

Validity of the QRA Methodology & Possibilities of Further Refinement

March 19-20, 2013

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.

IFRA Operations
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 60
Fax: +32-2 214 20 69

www.ifraorg.org

2. Summary agreed at the workshop:

The moderator identified a number of key conclusions on the work to date and identified a range of specific action steps: These were accepted at the workshop by the participants.

A. On risk assessment:

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

- Prospective and retrospective evaluation of its effectiveness by clinical and epidemiology data using sensitization as the relevant endpoint.
- Review of underlying methodologies and assumptions:
  - SAFs (Safety Assessment Factors).
  - NESILs (No Expected Sensitization Induction Levels).
  - Exposure (accumulation, aggregate exposure, chemical analysis, usage, retention and professional exposure).
- Adaptation for people with compromised skin.

B. On risk management:

- Commitment to act promptly on new insights.
- Labelling and provision of information on ingredients as an important complement to QRA and in-market validation.

C. On prospective and retrospective evaluation:

- For retrospective work, the group strongly encouraged to consider all available historical data. Data on preservatives might also contribute to validation of QRA for fragrances.
- For prospective work, focus should be on compliance with IFRA Standards, sensitization trends in the general population confirmed by clinical epidemiology data.
- For prospective work, clinical monitoring of new chemicals could provide important confirmation.

D. On refinement of QRA for the general population:

- SAFs are seen as being set appropriately with current state of knowledge. Re-evaluation of the inter-individual variability factor with scientific rationale is considered essential. Seen as controversial and not in keeping with the report
- An estimate of expected new induction when following QRA is encouraged.
- There could be value in developing 'QRA 2.0', based on latest data and including aggregate / occupational exposure.

IDEA
International Dialogue for the Evaluation of Allergens

3. Report of the Rapporteur :

Issues discussed at the workshop:

The following issues were discussed in detail:

A. Primary and secondary prevention:

Both the induction and the elicitation steps are likely to involve a threshold exposure level below which adverse effects will not occur. Thus safe use levels should be able to be derived using an appropriate risk assessment methodology. Induction and elicitation are different effects; the thresholds for which need to be determined by different methodologies. QRA in its present form is only applicable to prevent induction (primary prevention).

It is evident that a parallel procedure is needed to estimate the risks of elicitation. According to some epidemiologic studies, up to 25% of the population could be sensitized (not necessarily to fragrances). However, this estimate does not indicate the clinical relevance: i.e. skin sensitization is not necessarily accompanied by clinical effects. Nonetheless, an effective primary prevention would ultimately minimize the secondary issue(s).

B. The QRA procedure for allergens:

The intention of QRA is to replace the former risk assessment methodologies. Practical considerations have led to the setting of a default maximum pragmatic level (MPL) of the fragrance ingredients identified as dermal sensitizers for some product types. This MPL is defined as that "not exceeding the usual concentration of the fragrance compound in the finished product". The concept of MPL is deemed doubtful and not desirable. In addition to the methodological concerns, the MPL complicates the assessment of the effectiveness of the QRA.

The QRA follows traditional toxicological methodology lines. Dermal QRA has been used extensively on fragrances but there have also been attempts to work on other materials than fragrances (e.g. preservatives).

The QRA uses the classical risk assessment framework comprising:

- Exposure assessments based on dose per unit area of exposed skin, site of exposure and duration of exposure and frequency of exposure. Exposure assessment is done by assessing an individual chemical in an individual product. Other sources of exposure to the same chemical, such as an occupational exposure, from other domestic products are not generally considered.
- Risk assessment uses default (safety assessment factors) to arrive at an '*acceptable exposure level* (AEL)'.
- Hazard identification (NOAEL/NESIL) and hazard characterization (main tools are a combination of HRIPT, PT in humans. In animals the GP maximization test was widely used, more recently , the local lymph node assay (LLNA) has come to prominence

Safety factors are used to allow for uncertainties in various parts of the risk assessment, in particular:

- Identification of the threshold (NESIL) for induction.
- Inter-individual variability.

- Vehicle and/ or product matrix effects.
- Variation in exposures due to differences in use.

i) Identification of the No- Expected Sensitization Induction Level (NESIL):

Different views were expressed regarding the methodologies and assumptions leading to the NESIL calculation. Some felt that they were generally well acceptable some details needed refinement that only. For instance, the use of a dose per unit area was regarded as adequate but the reference to DNCB[1] maybe not appropriate to depict a methodology for fragrance ingredients. Others expressed the view that extensive improvements were needed. Concerns were expressed about guideline #6 (LLNA data only) due to the uncertainty of extrapolating animal testing results to humans. It was clarified that the NESIL, even based on LLNA data only, never equals the EC3. An additional safety factor is used to convert the test result into the NESIL. It was argued that more transparency could be provided on this additional safety factor.

The participants agreed that the capacity of the QRA to mitigate the risk of sensitization depends very much on the quality of testing data. Participants recommended that the Weight of Evidence (WoE) NESIL guidelines should be applied where robust data is available. The question was raised for the HRIPTs, as no clear guidance seems to exist for the dose selection. Another concern about HRIPT was the ethical aspect of this testing.

QRA 2. The question of the future absence of animal testing data was raised. Some new tools are already showing promise as a replacement for the skin sensitization data in animals. These should be introduced when properly validated as part of the development of the QRA.

ii) Consideration of Inter-individual variability:

The current QRA is intended to protect the general population. Currently, no particular attention is paid to people with compromised skin (e.g. atopic skin).

The current QRA considers a single safety factor of 10 to cover all sources of variability between individuals such as the age, the gender, the ethnicity, the inherent dermal barrier and the genetic effects. Main criticism was the arbitrary aspect of this value, as there is no scientific basis to set this safety factor at 10. This number should be substantiated, based on scientific data and potentially reconsidered at the light of sensitive population's specific problems. Indeed, it was argued that up to 10 % of the population (and even more if children are included) have a compromised skin. This safety factor should have to take this subgroup into account.

Regarding the safety aspect, pros and cons were raised for the single factor of 10. On the hand, the NESIL is confirmed by an HRIPT which adds an additional layer of precaution to this safety factor and the overall approach was viewed as conservative. On the other hand, there are experimental data linking the state of the skin and the risk of skin sensitization and showing that people with compromised skin might develop skin sensitization much more easily than the normal population (up to 100 or even 1000 times more easily). For this reason, the extrapolation of clinical observations to the general population should be treated with caution as this sensitive subgroup differs

significantly from the general population. This greater sensitivity could be partly explained by the enhanced skin penetration of compromised skins although this parameter is not sufficient to explain all cases.

QRA 2. It was agreed that further studies on the inter-individual variability should concentrate on three points:

- The ability of skin to allow permeation to occur.
- The enzymatic / metabolic specificities.
- The genetic differences.

One case of induction per million exposed people was seen as a reasonable target for consumer protection.

iii) Vehicle or product matrix effects:

The participants agreed that product matrix effects come just after the inter-individual variability in terms of importance and should also be the object of a special attention. The scale of 1, 3 and 10 was regarded as somehow arbitrary and additional scientific data should be collected to substantiate these safety factors. Furthermore, the same matrix effect of 3 was assigned to product types with very variable matrices (e.g. deodorants, hand washing detergents, baby creams). The rationale behind this categorization is not easy to follow and the participants recommended the implementation of a transparent and properly justified categorization procedure.

All participants agreed that the product matrix can indeed influence the immune reaction by virtue of an enhanced skin permeation. However, more important than the skin permeation is the bioavailability which is the true indicator of the Langerhans cells' capacity to capture a hapten and trigger the immune reaction.

Furthermore, it was agreed that the vehicle affects the outcome of LLNAs and HRIPTs although no clear consensus was reached concerning the magnitude of this impact. It was reported that DMSO and ethanol tend to increase the actual response, while DEP tends to lower it. For this reason, the safety factor should not focus solely on the intrinsic properties of the product matrix but also consider the differences existing between the experimental and the real-life conditions. This logic could lead to a safety factor under 1, as some matrices are likely to limit the allergens potency observed in laboratory.

The presence of irritants was also regarded as important for careful consideration. This variable is relatively difficult to evaluate, as it implies a sound examination of all ingredients of each consumer product. A recommendation was to develop a statistical model taking all the matrix parameters into account.

These various elements contribute to rationalization of a product matrix effect. Several studies going in this direction were reported, such a ROAT conducted on HICC-containing cosmetics and for which the observed elicitation rates in ethanol-based products were 5 to 7 times higher than in cream-based products.

QRA 2. Further work on matrix effects is needed to provide a better basis for incorporation of matrix effects in the QRA.

iv) Use considerations:

Likewise, the scale of this safety factor (1, 3 and 10) was regarded as rather arbitrary and additional scientific data should be collected to substantiate it. The small difference between the safety factor of a shampoo and the one of a deodorant was questioned and further studies requested to bring clarity to this aspect.

Occlusion was regarded as an important parameter as it has an important impact on the risk of induction. It was mentioned that both HRIPTs and LLNAs are conducted with fully-occlusive chambers while the fragrance allergens present in consumer products partly evaporate in normal conditions.

The review of the three safety assessment factors led to the conclusion that a scientific rationale should be identified for all safety factors

QRA 2. Data needs to be collected (retrospective evaluation) and produced (prospective evaluation) in view to re-evaluate the SAF in a transparent and systematic way using a more biological approach. Thus, use and matrix factors address basically the same thing, namely the skin penetration and the presentation of the hapten to the immune system. These two factors could be replaced with a safety factor on the body areas and another linked to the consumer product.

C. <u>Exposure assessment:</u>

Professional (occupational), pharmaceutical and alternative medicine (e.g. aromatherapy) use of fragrances does not fall under the scope of the QRA currently applied by the fragrance industry.

i) Aggregate exposure assessment:

The state of development of the RIFM aggregate exposure model was presented.
Particular issues discussed were:

- Household care products and detergents have been excluded because they do not represent a significant exposure for the consumer. On the other hand, it becomes evident that specific product types can drive the aggregate exposure. The model gives accurate predictions of this exposure.
- The need to identify the uncertainties in the assessment. Several elements of variability are already captured in the sensitivity analysis (e.g. natural variability across people's habits, bodyweights, etc. / level of the fragrance ingredient in the fragrance compound / level of the fragrance compound in the finished product) and the model provides exposure data with a standard deviation. However, the presentation of the uncertainty needs to be more transparent.
- Assumptions on retention. A retention factor of 1 % for a rinse-off product is used based on empirical observations but should be investigated further.
- The problems of how to aggregate exposure at different body areas. It was agreed that these cannot be summed as different lymph nodes are implied. Thus, the aggregate exposure model can only be used to sum the contributions of product types applied to the same site. (NB In the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, aggregate exposure to cosmetics products is calculated to be

17.4g/day based on addition of deterministic values for a range of products. The products used in this model account for 96.7% of this figure but it was mentioned that the remaining 3.3 % might deliver at very small locations the most significant dose per unit area).

- The current form of the model assumes that the fragrance allergens accumulate over 24 hours (then the clock is reset and the aggregate exposure restarts from zero). This parameter was not regarded as substantiated.

QRA 2 It was recommended that precise data be collected on the product types driving the exposure. The exposure evaluation needs to be global rather than limited to the product categories of interest to the fragrance industry. Emphasis should be given to understand the consumer exposure to unregulated product types like aromatherapy and OTC products. Occupational exposure also needs to be considered. Attention should be paid to cocktail effects and cross-reacting sensitizers for the calculation of the exposure. For instance, cinnamyl alcohol could quickly get metabolized in the skin into cinnamal therefore cinnamyl alcohol should also be considered when evaluating the consumer exposure to cinnamal.

In respect of occupational exposure for example, the following topics were regarded as important:

- Definition of the scope of professional products to consider (e.g. occupations to include in the model). The participants agreed that non-cosmetic uses of fragrance should be excluded from the model. Furthermore, there as a consensus that this is not possible to examine all professional uses and the work should focus on one or two occupations.
- Definition of the data requirement (e.g. product types, fragrance use levels, exposure scenarios).
- Identification and collection of the relevant data sources (in the literature and in the industry).
- Production of the missing data (via surveys in the industry or at the workplace).

Studies conducted on nurses or hairdressers could be of interest to initiate an occupational exposure assessment.

D. <u>Data sources for developing the QRA:</u>

The participants strongly encouraged the industry to carefully monitor the effectiveness of the QRA via the collection of literature / clinical data and the establishment of a broad dialogue between the industry and the dermatologists.

Relevant clinical data is readily available in the literature and needs to be compiled. The value of clinical data was discussed as it usually gives an indication of the elicitation rate. The participants agreed that this information is, nonetheless, an excellent way of determining whether induction took place. In that sense, data on sensitized people is useful and the evolution of these figures over time can be a marker of the QRA effectiveness. An effective means of data validation is an essential prerequisite for its use.

Several data centres such as ESSCA (European Surveillance System of Contact Allergies) hold important datasets that might be used as basis for a retrospective analysis. The data sources utilized should include information on non-fragrance ingredients. Beyond its application to fragrance materials, it was mentioned that the QRA was used for the risk assessment of transition metals (nickel, chromium) and 5 preservatives, but it remained unclear how the outcome impacted on the market.

E. Further validation of the QRA:

i) Retrospective analysis:

This depends on the availability of comprehensive high quality data (see data sources above). Retrospective analysis of 5 preservatives was regarded as very promising. This is because preservatives are used at relatively constant levels for a given product category, which tends to facilitate the analysis and eliminate some biases.
The retrospective analysis of fragrance ingredients was regarded as more complex (due to the wide range of use levels) but nevertheless very important and the participants strongly encouraged the preparation of a retrospective analysis on individual fragrance ingredients.

ii) Prospective analysis:

This initiative should involve as many stakeholders as possible in the industry and the medical community. The QRA model is based on assumptions and its results inevitably involve some uncertainty. Clinical feedback via an enhanced dialogue with the dermatologists should be used to assess whether the QRA threshold values are adequate. This could be facilitated by developing a system in partnership with ESSCA, IVDK and/or KUL where patients experiencing allergic reactions would be followed up to first understand which consumer product may have caused the problem and secondly determine whether or not fragrance allergens are implied in this problem. Information would be gathered on the alleged product (use level, batch number, etc.) to fill a database linking the exposure and the clinical prevalence. Products reported by the patients (according to the above procedure) should be analysed for IFRA compliance in order to understand whether or not the induction (or the elicitation) reaction is due to the presence of an allergen above its QRA level. Market trends should be monitored to evaluate the risks of induction as early as possible. The industry should also inform the dermatologists as early as possible about new fragrance ingredients placed on the market.
New studies should focus on specific ingredients as it is probably the most robust approach to measure the effectiveness of the QRA. Indeed, the monitoring of fragrance mixes might lead to overlooking the effects of individual fragrance allergens.

Both for retrospective and prospective analyses, the prevalence data of a given allergen should be considered with regard to respective exposure data this should be before and after the application of the QRA. Relative potency in the form of a Sensitization Exposure Quotient (SEQ) was presented. This SEQ seems to provide a fair estimate of the allergens' potency and might be of help for the confirmation of hazard assessments and the adjustment of consumer exposure.

F. Development of IFRA Standards:

It was noted that the companies at the IFRA Board level are very attentive to participate in the development and the implementation of all scientific progresses leading to a better protection of the consumer. The IFRA compliance is important and more efforts should be done by the fragrance industry to ensure that the market effectively complies with the IFRA Standards.

The development of IFRA Standards is regarded as a lengthy and complicated process, as a consequence it may be unable to respond rapidly to new skin sensitization threats. It was mentioned that consumer products with corrected levels of a given fragrance allergen take years to appear on the marketplace. This delayed risk management can translate into the sensitization of a part of the population. As a consequence, secondary prevention measures have to be taken on top of the primary prevention (eg. HICC).

G. General recommendations:

i) Risk assessment:

- Characterize the mode of action of chemically induced allergens and how (and why) it varies between humans and between humans and animals. This includes the processes by which matrix factors influence uptake.
- Identify the potential hazard test replacements/ improvements and the implications for uncertainty of extrapolation.
- What is the suitability of the current data base to inform the process? Is it sufficient yet to enable SAR/QSAR?
- Improve the scientific basis for support of each of the adjustment/ default factors. This needs a better understanding of human variability in response and the elucidation of the reasons for this.
- Develop further the aggregate exposure model. Include co-exposure and cross reactivity of related chemicals.
- Characterize the influence of other factors in a product (eg. irritants) on the allergenicity of individual fragrances.
- Use clinical data to identify the success or not of the safe levels set based on the QRA.
- To facilitate progress on the work on safety factors in particular it was proposed that an ad hoc working group should be established.

ii) Communication:

Participants made several recommendations to the Industry in order to speed up the process and ensure a proactive management of the skin sensitization risks:

- Improve the dialogue with the dermatologists: the dermatologists are the frontline agents to diagnose new skin sensitization issues in the general population. Their feedback is precious and needs to be collected via appropriate channels in order to react immediately when new problems occur. The outcome of this surveillance should be integrated to the IFRA Standards development process.
- In line with this first recommendation, the dermatologists should be made aware as soon as possible about new fragrance ingredients coming on the market. For the time being, there is no way to understand how, when and where the patients have been exposed to a new fragrance allergen. An early understanding of the issue would significantly decrease the number of people sensitized to a new fragrance allergen. The participants agreed that the labelling of fragrance ingredients is likely the most appropriate solution.
- Organize web-based events with the dermatologists (e.g. webinars, forums) to involve them directly and effectively in IFRA Standards development process.

iii) Risk management:

Appropriate risk management measures need to be taken to better inform the consumer on the fragrance allergens content of cosmetic products. The labelling of fragrance allergens contained in all cosmetic products is therefore needed. It was noted that this concept might result in a requirement for the full disclosure of the fragrance formulae composition.

iv) Discussions with regulators:

It has to be recognized by the regulators that several markets (e.g. aromatherapy) are independent of the fragrance industry and it was recommended that the regulator ensures adequate consumer information on these product types.
Furthermore, and regarding products scented by the fragrance industry, the responsibility of the fragrance industry ends at the delivery of an IFRA compliant formula and this is up to the downstream users to ensure the safety of marketed consumer products.

Professor Jim Bridges
Workshop Rapporteur

Appendix 1 – Workshop Participants:

- European Commission and European Scientific Committees: Prof. Jeanne Duus Johansen (University of Copenhagen and Member of the SCCS WG on Fragrance Allergens), Dr. Federica De Gaetano (EU Commission – DG Sanco – Risk Management Unit), Prof. David Roberts (Liverpool John Moores University and Member of the SCCS WG on Fragrance Allergens), Prof. Vera Rogiers (Vrije Universiteit Brussel and SCCS Vice-chair), Prof. Wolfgang Uter (University Erlangen and Member of the SCCS WG on Fragrance Allergens), Dr. Ian White (Guy's & St Thomas' NHS Hospitals and SCCS Chair).

- Academic community: 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. Pieter-Jan Coenraads (University Medical Centre Groningen), Prof. Thomas Diepgen (Ruprecht-Karls University), Dr. Christine Lafforgue (Université Paris sud 11), Prof. Hans Merk (Universitätsklinikum Aachen), Dr. Cronan McNamara (Crème Global), Dr. Bob Safford (Consultant), Prof. Axel Schnuch (IVDK / University of Göttingen).

- Industry: Dr. Anne Marie Api (RIFM), Dr. Christophe Brault (LVMH), Mr. Graham Ellis (Givaudan), Dr. Nicola Gilmour (Unilever), Dr. Peter Griem (Symrise), Dr. Petra Kern (Procter & Gamble), Dr. Florian Schellauf (Cosmetics Europe).

- IDEA Staff: Dr. Hans-J. Bender (Consultant) Rapporteur, Dr. Fred Lebreux (IFRA), Dr. Matthias Vey (IFRA).

- Supervisory Group members: Professor Jim Bridges, Professor Helmut Greim.

Appendix 2 – Additional reading on QRA:

- Api, A.-M. *et al.* (2008). Special Issue: Dermal Sensitization Quantitative Risk Assessment for Fragrance Ingredients. Regulatory Toxicology and Pharmacology, **52**(1), 1-73.
- SCCP Opinion on Dermal Sensitisation QRA (SCCP-1153-08).
- Felter, S.P., Robinson, M.K., Basketter. D.A. and Gerberick, G.F. (2002). A review of the scientific basis for uncertainty factors for use in quantitative risk assessment for the induction of allergic contact dermatitis. Contact Dermatitis, **47**(5), 257-266.
- The IFRA-RIFM QRA Informational Booklet (att.10).
- Monika R. Upadhye, Howard I. Maibach (1992)' Influence of area of application of allergen on sensitization in contact dermatitis. *Contact dermatitis*. ***27*****:** 281-286.
- Kligman AM. (1966) 'The identification of contact allergens by human assay. II. Factors influencing the induction and measurement of allergic contact dermatitis. *J Invest Dermatol.* ***47***(5):375-92.

Appendix 3 – Glossary of abbreviations:

International Dialogue for the Evaluation of Allergens (IDEA)

AEL:	Acceptable Exposure Level
DEP:	Di**e**thyl Phthalate
DG-SANCO:	Directorate General for Health and Consumers
DMSO:	Dimethyl Sulfoxide
DNCB:	2,4-Dinitrochlorobenzene
EC3:	Effective Concentration for a SI of 3 in proliferation of lymph node cells
ESSCA:	European Surveillance System of Contact Allergies
GP:	Guinea Pig
HICC:	4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
HRIPT:	Human Repeat Insult Patch Testing
IFRA:	International Fragrance Research Association
IVDK:	Information Network of Department of Dermatology
KUL:	Katholieke Universiteit Leuven
LLNA:	Local Lymph Node Assay
MPL:	Maximum Pragmatic Level
NB:	Note Well
NESIL:	No Expected Sensitization Induction Level
NOAEL:	No Oserved Adeverse Effect Level
PT:	Patch Test

QRA:	Quantitative Risk Assessment
QSAR:	Quantitative Structure Activity Relationship
ROAT:	Repeated Open Application Test
SAF:	Safety Assessment Factor
SAR:	Structure Activity Relationship
SEQ:	Sensitization Exposure Quotient
SCCS:	Scientific Committee on Consumer Safety
SG:	Supervisory Group
RFIM:	Research Institute for Fragrance Materials
WoE:	Weight of Evidence