IDEA
International Dialogue for the Evaluation of Allergens

Report on the IDEA Workshop on

Validity of the QRA Methodology & Possibilities of Further Refinement

May 13-15, 2014

Martin's Klooster
Onze-Lieve-Vrouwstraat 18
3000 Leuven, 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 was the opportunity to review and discuss the status of action items recommended by experts who participated in the first two workshops on QRA, held on March 19-20, 2013 and March 11-13, 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. Report of the Rapporteur :

Aim of the workshop

The intention of this workshop was to build on the work carried out at, or following on from the two previous workshops on QRA.

Its main objective was to identify, in detail, the components necessary for a reliable, easy to use, consistent to apply and transparent methodology (termed QRA II), which is based on current scientific understanding and expectation to suggest a safe level of exposure for each fragrance material assessed. A safe use level is defined in this context as one that will not induce skin sensitisation (contact allergy) in consumers. Where this cannot be achieved fully at the workshop, to agree a work plan to complete QRA II, bearing in mind the deadline of the 20th of June 2014 for its submission via DG SANCO to the JRC.

Aspects identified for discussion

a) Form of the submission of the QRA

Two options for the submission were considered:

i) Provision of QRA I (see special issue of Regulatory Toxicology and Pharmacology (2008) Vol 52, no 1) along with documentation where changes have been made to it.

ii) A stand-alone document.

b) *Exposure assessment*

Reliable assessment of human exposure is commonly the weaker part of the risk assessment of chemicals. This has also been the case for fragrance substances. Consequently, a focus in the development of QRA II has been to develop an aggregate exposure model that enables the estimation of exposure to individual fragrance substances through the use of a wide range of cosmetic products.

c) Justification for data extrapolation

Various extrapolation factors (safety assessment factors, SAFs) were introduced in the RIFM QRA I method. It was agreed at the two previous workshops that the values assigned to these factors needed to be reconsidered in the light of the available scientific evidence.

d) *Hazard characterization*

Inevitably, because of the nature of the research required, substantial advances in the tests used for hazard characterisation (including reliable demonstration of thresholds relevant to human exposure) has been slow. The ban on animal testing makes this aspect of the development of the QRA a priority and a particularly challenging one. However, it was agreed at the previous workshop, that a revision of the guidance on animal testing was a very major task, and therefore couldn't be included in time for the submission of QRA II. It was agreed instead that it should be a central component of a subsequent development of QRA II (QRA III).

e) *Evaluation of the effectiveness of the QRA to protect consumer health*.

It was agreed that it was important to determine the effectiveness of the introduction of QRA I and QRA II in reducing contact allergy to fragrance substances.

IDEA
International Dialogue for the Evaluation of Allergens

A. PROPOSED CHANGES IN QRA I FOR QRA II

1. Form of the QRA II submission to JRC

This was discussed in a breakout group. The JRC submission date is 20th June. This means that a draft has to be available for internal evaluation by June 6th.

It was agreed that it would be a stand-alone document using a stick and paste of QRA I as the core. In terms of the SAFs these would need to be justified scientifically based on the recent commentary by Basketter and Safford (provided as a draft at the workshop).

The QRA dossier will be set out as follows:

i. Introduction

- A summary of key features developed in the last few years (and the reasons they have been prioritised i.e. SAFs, aggregate exposure).
- Explanation of the underlying science (induction *vs* elicitation and mode of action).

ii. The QRA methodology

- Hazard characterisation (deriving the NESIL, use of WoE)
- Aggregate exposure assessment (including exposure tables)
- Use of SAFs and modified SAFs for standard setting
- Plans for the Assessment of the effectiveness of the QRA (existing and new chemicals)

iii. Priorities for future development of QRA II

- An outline of the potential for alternative hazard characterisation models.
- Approach for the assessment of pre- and pro- haptens.
- Occupational/professional exposures.

iv. Case histories to demonstrate the use of the QRA.

v. Appendices

- References Including EU references.
- Background to the development of QRA II (workshops etc).
- An updated version of Basketter and Safford providing the scientific rationale for each SAF value.

2. Specific aspects of exposure assessment

i. Features

The major new aspect, in terms of exposure, is the introduction of the RIFM/Creme aggregate exposure assessment model. This enables the total exposure of consumers to a fragrance material from all product sources to be estimated instead of estimates of exposure to individual products. The model is proposed to be used for both retrospective and prospective use. Particular feature are:

- It is based on extensive database of consumer responses to questionnaires on their use of products containing fragrance materials and information on quantity of each fragrance material in each product type.
- The 95th percentile of worst case and worst day use for each product is assumed. This was described as extreme worst case.
- It is assumed that each product incorporates the maximum RIFM level.
- Body site SAFs are integrated.

ii. Case histories to support the introduction of the Creme model

Two products were considered: Benzaldehyde and BMHCA. Using the proposed QRA II model in conjunction with RIFM/Creme aggregate exposure model it was found that, in contrast to the QRA II without the aggregate exposure consideration, the RIFM/Creme model gave CEL/AEL values above 1 for certain exposure sites. In such circumstances the product use at such sites needs to be reduced. This indicates a useful application of the model however the calculation relies on the appropriateness of the SAF values.

iii. Current exclusions from QRA II for exposure

The following aspects are not proposed to be covered in QRA II:

- Occupational/professional exposures.
- Co-exposure to other chemicals with a common mode of action (showing cross reactivity and/or combination effects ie cumulative exposure).
- Consumer exposure to so called natural products (ie consumer exposure outside the control of the fragrance industry eg aromatherapy).
- A number of other consumer products that are also not considered in terms of consumer exposure (food, drugs etc.).

3. Specific aspects of the application of SAF values

i. The application of SAFs

In addition to the SAF for inter-individual variability (to allow for age, genetic differences, gender etc) for which a standard factor of 10 is used SAFs relating to exposure were introduced in QRA I to address uncertainties and inherent variability in the following:

- Product formulation.
- Consumer use (nature of application and frequency).
- The state of the skin e.g. inflammation
- Differences between skin sites.

ii. Proposed SAFs (See Table below)

The following values[1] were proposed):

Factor	Consideration	Influence	New proposed SAFs	Comments (comparison of the experimental condition with the product use condition)
Inter-Individual	There can be large inter-individual differences in response to a chemical exposure due to several different parameters.	Increase of induction susceptibility	10	The inter-individual variability not accommodated in the NESIL 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)
	Irritation by product	Increase of induction susceptibility	0.3 or 1 or 3	Can the product cause irritation related to repeated normal conditions of use? Ingredients that are added to mitigate any types of irritation
Frequency / duration of product use	Products may be used over extended periods resulting in bio-accumulation	↑	1 or 2	Products may be used frequently over extended periods of time resulting in accumulation (chemical or biological accumulation) or reservoir effect
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	To assure consistency, it was concluded that the occlusion factor should be 1 for all consumer products since at some time all body parts could be covered by

[1] Nota bene:
(1) Each value needs to be cross-references to the key statement in Basketter and Safford or elsewhere and to the publications supporting it.
(2) It is noted that QRA II appears to be largely in line with other methodologies for the risk assessment of chemicals.

	Includes occlusion by body part, clothing or product.			clothing.
Skin condition/ site	Pre-existing inflammation	Increase of induction susceptibility	1 or 3	Pre-existing inflammation for body site: body areas that are specifically prone to increased level of inflammation – hands, underarms, any shaved area, under a diaper, peri-anal and peri-ocular regions

Body Site	**Additional definition for this study**	**Skin Site**		**Total Body Site SAF**
		Occlusion	**Inflammation**	
Scalp		1	1	1
Face*	Does not include: Eyes, Lips, Mouth, Behind Ears	1	3	3
Peri-ocular	The eyelid and surrounding skin.	1	3	3
Lips		1	3	3
Peri-oral	"Buccal" / "Inside Cheek" Does not include: Lips	1	3	3
Neck	Does not include: BehindEars	1	3	3
Behind Ears		1	1	1
Chest	Does not include: Underarms, Stomach	1	1	1
Abdomen		1	1	1
Back	Does not include: Underarms	1	1	1
Axillae		1	3	3
Arms	Does include: Shoulder, Forearm, Upper arm Does not include: Wrists, Hands, Palms, Underarms	1	1	1
Wrists		1	3	3
Back of Hand	Does not include: Palms, Wrists	1	3	3
Palms		1	3	3
Ano-genital		1	3	3
Legs	Does include: Bottom, Thighs, Calves Does not include: Feet	1	3	3
Feet		1	3	3

4. Evaluation of the QRA

Assuming that adequate interventions have arisen as a consequence of QRA I it should be expected that there would be a reduction in the levels of sensitisation, albeit these changes might not be major as skin sensitisation involves a life-long change in immune response. The importance of high quality patch testing in providing this relevant data was emphasised. There is a rich source of information from regularly recording baseline studies in

various academic publications. The academic support from such studies may not last beyond a few years and this is a very strong reason to use these databases now. This was agreed. A breakout group examined this aspect in more depth and arrived at the following conclusions.

i. *Retrospective studies*

First step is to check the quality of the data. In principle, since the QRA was implemented for a fragrance substance there should be a reduction in incidence of sensitisation to the specific substance. Preference should be for data from initial patch tests and for the results of consecutive testing. Expertise is required in the interpretation of data. In principle the analysis of the available data and its interpretation could be available in half a year.

ii. *Prospective studies*

- Using standards

Involve clinics across Europe and the USA with a minimum contribution per centre pre-identified (say, a minimum of 500 consecutive tests per clinic per year. Below this may cause selection and other bias) Questionnaire used to gain relevant information about patient behavior and exposure. Patch test methods have to be standardised using selected standard test materials (FMI and FMII and their 14 individual ingredients). Location of sensitisation and age and sex of patients should be recorded.

- New fragrance substances

Early information for the dermatological community regarding consumer exposure to new fragrance substances is needed. Each new substance needs to be available to the clinics.

B. NO CHANGE PROPOSED FOR QRA II

1. Degree of public protection

In QRA I the extent, if any, of public protection is not defined further although the aim is clear, namely to reduce the burden of contact allergy. The extent of the reduction that can be achieved through the application of QRA II is to be determined.

2. Hazard characterisation and threshold setting

i. *Use of animal testing*

Identification of an appropriate NESIL is the critical decision in the QRA. It is derived from a weight of evidence approach including animal tests (LLNA in mice, maximisation test in guinea pigs, historic human data and typically a confirmatory HRIPT). Although, as a result of an EU regulatory decision these tests will not be available for use in Europe, it was decided at an earlier workshop that there was insufficient time to include it as a central part of QRA II.

In regard to the use of the animal tests, the favoured current approach in QRA is to use the LLNA to identify an EC3 value which is equivalent to a NOEL in humans. It is stated that the LLNA provides a reliable assessment of the potency likely to be experienced in man. However, and although there are a number of studies to show that this is the case, this critical assumption has not been justified fully in QRA I. It is very important for QRA II that this assumption is backed by appropriate published literature.

ii. Use of HRIPT

The EC3 value for each fragrance in the LLNA is converted to a human exposure concentration per cm^2 of skin. Based on this value a likely lower (safe) dose is estimated and this is usually applied as the sole dose level in the HRIPT test in human volunteers. The assumption is made that this is the 'gold standard' for identifying a safe level in man (NB It is very important for QRA II that this assumption is backed by appropriate published literature).

C. BEYOND QRA II

In view of the short time to submission there are several areas that, while very important will not achieve significantly progressed in time for the submission of QRA II. The identification and prioritisation of these areas was given as a remit to a breakout group.

- **Chemical considerations.** It was discussed whether structural alerts. (Q) SAR for induction could be better developed. The use of (Q) SAR for the identification of potential pre-haptens and /or pro-haptens was also considered to be a viable approach. It was agreed to ask the IDEA pre-& pro-hapten group to develop this recommendation.

- **Kinetics of absorption and persistence in the skin.** Better use of physicochemical data, such as volatility, might aid in the understanding of the influence of concentration and retention on potency.

- **Modes of action studies** with particular focus on the main drivers of potency was recognised as very important in the development of non-animal tests.

- **Effects of combinations of fragrance substances.** This is generally considered under the topic of cumulative exposure. Development in this area is dependent on progress on SAR and mode(s) of action.

- **Replacement of animal tests**

Some data will continue to be developed for REACH purposes using LLNA. However although it is an important source of data for the NESIL determination the LLNA should not be regarded as a gold standard for the purpose of future research into non-animal tests.

The likelihood in the near future, for at least some materials is that animal tests will not be available. The available list of validated non–animal models is very limited and this situation is unlikely to change rapidly. It was proposed to map out the strengths and weakness/uncertainties of each.

One approach is to use regression analysis based on an existing LLNA data base and other relevant data. The Direct Peptide Reactivity Assay (DPRA) based on the peptide binding rate seems to be the strongest contributor to potency assessment. To date use of physical chemistry data such as log P not found to be useful for the potency estimation of skin sensitisers.

For the future, the development of a framework based on the use judiciously chosen combinations of tests (termed *integrated testing strategies. (ITS))* is likely to prove the best way forward.

Tests may be designed to represent parts of the adverse outcome pathway beginning with structural alerts. Tests for reactivity with proteins, irritancy metabolic fate etc. may also be included in the series. Data may be

presented as a probability of particular potency assignment computer software. It is an ongoing development with tests for other parts of the mode of action sequence being introduced progressively.

- **Occupational/professional exposure**

- This is a strong confounder of testing consumers for dermal sensitisation. However it falls under different legislation from that of consumer exposure. It can provide a valuable early warning of potential allergens.

D. CONCLUDING REMARK

Substantial progress was made at the Workshop. The next month will be a very challenging one and the help of the workshop participants will be needed at various stages in completing a strongly science based document. A time table will be drawn up and circulated to all *asap*. Everyone should identify how they can contribute.

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. Pieter-Jan Coenraads (University Medical Centre Groningen and member of the SCCS).

- 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), Prof. Jeanne Duus Johansen (University of Copenhagen), Dr. Janine Ezendam (RIVM), Prof. Margarida Goncàlo (University of Coimbra), Dr. Christine Lafforgue (Université Paris sud 11), Dr. Cronan McNamara (Crème Global), Prof. David Roberts (Liverpool John Moores University), Dr. Bob Safford (Consultant), Dr. Joanne Salverda (RIVM), Prof. Axel Schnuch (IVDK / University of Göttingen).

- Industry: Dr. Anne Marie Api (RIFM), Dr. Christophe Brault (LVMH), Dr. Dagmar Bury (L'Oréal), Dr. Peter Cadby (Chanel), Mr. Graham Ellis (Givaudan), Dr. Nicola Gilmour (Unilever), Dr. Peter Griem (Symrise), Dr. Etje Hulzebos (I.F.F.), Dr. Petra Kern (Procter & Gamble), Dr. Maya Krasteva (L'Oréal), Dr. Christeine Lally (Procter & Gamble), Dr. Florian Schellauf (Cosmetics Europe), Dr. Benjamin Smith (Firmenich).

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

- Supervisory Group members: Prof. Jim Bridges (Rapporteur), Dr. Ian White (Guy's & St Thomas' NHS Hospitals).