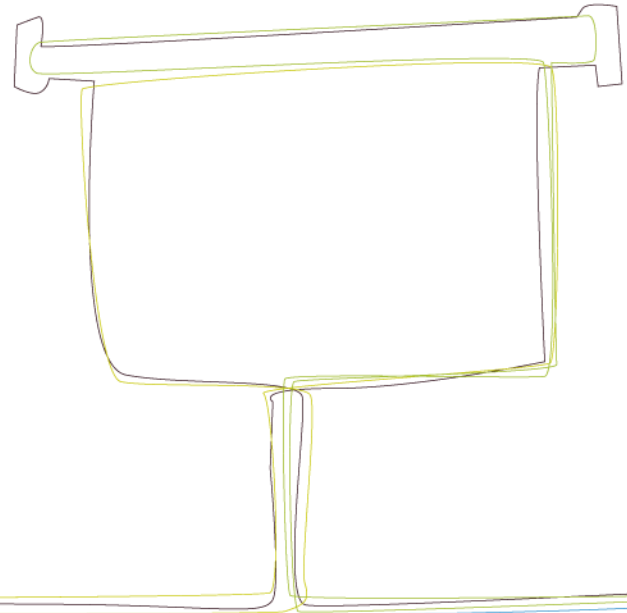




Completion of work on the dermal sensitisation QRA (QRA 2)

Prof Jim Bridges

Emeritus Professor of Toxicology and
Environmental Health and Chair of the IDEA
Supervisory Group



Background to QRA1



- In **2008**, RIFM for the fragrance industry published a detailed, exposure-based approach which was termed the Quantitative Risk Assessment (QRA) methodology (Api *et al.*, 2008).
- This methodology has been used to set IFRA Standards for some 100 fragrance ingredients.
- However, in 2008 the SCCS published its concerns about this QRA methodology.

Framework for QRA 1



External exposure
(individual products only)

Hazard assessment
(LLNA)

(NOEL confirmed with HRIPT)



SAF's

NESIL

→ **CEL** → → ↓ **AEL** ← ← ← ←



Risk assessment

Background to development of QRA2 through the IDEA project



- In **2008** also, the SCCP provided constructive criticism on the then proposed QRA1 (e.g. basis for SAF's, validation).
- In **2012**, the Scientific Committee on Consumer Safety (SCCS, 2012a) published an opinion which expressed its serious concerns about the number and nature of fragrance substances on the market capable of causing allergenic reactions on skin.
- IDEA project started in late **2012** to respond to these concerns.

Priorities for development of QRA 2



- To consider the general appropriateness of the QRA1 methodology;
- To review two key areas, where completion to meet the DG SANCO time requirements was considered achievable:
 - a) Review of each of the **uncertainty factors** (SAFs);
 - b) Introduce **dermal aggregate exposure** to replace the original individual product exposure assessment.

Framework for QRA 2

External exposure

(aggregated for a
fragrance ingredient)

Hazard assessment

(LLNA)

(NOEL confirmed using HRIPT)



Revised SAF's

NESIL

→ **CEL** → ↓ ← **AEL** ← ←

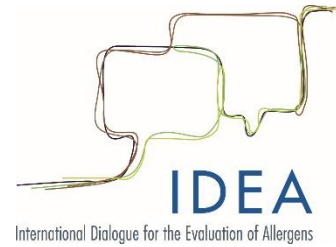


Risk assessment

Review of

SAFETY ASSESSMENT FACTORS (SAF'S)

SAF's – products effects- vehicle



The vehicle/matrix SAF is applied in consideration of its 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). This SAF is likely to be 1 for most product types.

SAFs -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.

SAF's: skin condition

The skin condition SAF considers the state of the skin at each body site 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.

SAF's- Inter-individual variability



It is concluded that inherent dermal condition is more influential than age, sex and ethnicity.

A SAF of 10 was concluded to be sufficient to account for this.

Conclusion in QRA 2 on the SAFs



- The scientific basis for the individual SAFs has been thoroughly reviewed (Basketter and Safford 2015).
- Following the SCCS WG /JRC discussion further consideration is being given to the use of fragranced products by consumers with chronically irritated skin.

Basketter and Safford, 2015. Skin sensitization quantitative risk assessment: a review of underlying assumptions. *Regul. Toxicol. Pharmacol.*
doi:10.1026/j.yrtph.2015.11.013

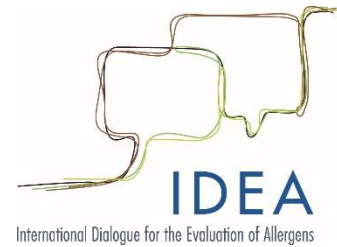
The RIFM Creme Model

AGGREGATE EXPOSURE TO INDIVIDUAL FRAGRANCE INGREDIENTS

Aggregate exposure model: inputs

- Use practices (e.g. distributions of how a consumer uses the product per application, including the area of application and frequency of use).
- Amount of each product used per application.
- The concentrations of the fragrance ingredient in each type of product.
- The QRA2 SAF values.

Use practices



- Based on real habits and practices collected from 36,446 panelists across Europe and the USA. Each panelist supplied diary data on which products they used during the day for seven consecutive days, as well as the application sites of most products.
- This data has been used to create a statistical representation of the population whose product usage habits are as close as possible to the real population.

Product use



- Uses the worst day of exposure (e.g. the day with the highest use) for each panelist in the database.
- Aggregate exposure for each body part is calculated by summing all exposures to each individual body part over a 24 hour period (even though washing or other factors may remove some earlier product).
- The above approach is conservative and therefore the selection of the 95th percentile for each body part as the value to be used is justified.

The dermal aggregate exposure model



Uses a custom built software system to enable probabilistic exposure calculations:

- It determines exposure per unit area of skin for a defined body site to a fragrance ingredient.
- It estimates the exposure from each fragrance ingredient in a variety of products and aggregates these across all body sites.

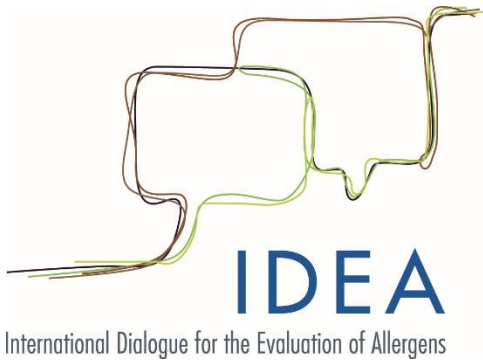
Current status of QRA 2



- Carrying out final revisions based on important inputs from meeting with SCCS WG /JRC.
- Conducting further work on the wider application of the aggregate exposure model.
- Studying the feasibility and identifying the most appropriate protocol to assess the effectiveness of the QRA in preventing sensitisation of consumers.

If we want things to stay as they are,
things will have to change

Di Lampedusa in The Leopard 1957



Thank you for
your attention

