IDEA Annual Review

Refinement and validation of the dermal sensitisation QRA

December 17th, 2014

Prof. Jim Bridges

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

Background to the QRA

In 2008, 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 since been used to set worldwide limits (IFRA Standards) for fragrance ingredients which are potentially capable of sensitization to protect consumers.

Theoretical basis for QRA

Two stages in the development of skin sensitization:

a) *induction* during which contact allergy to the substance develops

b) *elicitation* leading to allergic contact dermatitis, following subsequent exposure to the substance in sensitized individuals.

Premise : Both stages have a threshold assigned. By prevention of induction, elicitation can be avoided (primary prevention).
The QRA aims at preventing the induction step from occurring.

QRA 1.

External exposure

(single product only)

↓

↓

↓

Hazard assessment

(LLNA)

(checked using HRIPT)

↓

NESIL

→ **CEL** → ↓ **AEL** ← ← ←

↓

SAFs

Risk assessment

Priorities for development of QRA 2

IDEA
International Dialogue for the Evaluation of Allergens

- To consider the general appropriateness of the methodology;
- To carry out specific reviews of two important areas where completion within the initial two year time frame 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.

Aim for July 2014: QRA 2 as applied to fragrance ingredients

IDEA
International Dialogue for the Evaluation of Allergens

External exposure

(aggregate for an ingredient)

↓

↓

Revised **CEL** → ↓

Hazard assessment

(LLNA)

(checked using HRIPT)

↓

NESIL

← **AEL** ←

↓ Revised **SAFs**

Risk assessment

IDEA
International Dialogue for the Evaluation of Allergens

Review of

SENSITISATION ASSESSMENT FACTORS (SAFs)

SAF - **Inter-individual variability**

- **General**: The Human Repeated Insult Patch Test (HRIPT) uses 100 or more healthy subjects of both sexes and a wide age range. It is uncertain whether this is sufficient to allow for possible variations in consumer sensitivity.

- **Skin condition:** May be more important than age, sex and ethnicity. Subjects with diseased skin not necessarily more prone to the induction of skin sensitization. However, the generation of inflammation in skin (particularly from contact with irritant substances) may increase sensitivity to skin sensitisers.

SAFs - Product effects

- **Vehicle / matrix**- The most common solvents used in the HRIPTs are diethyl phthalate/ethanol or petrolatum as they are considered to be optimal for the induction of sensitisation. Unclear whether enhancement of penetration promotes the induction of skin sensitisation.

- **Irritation by product**- Irritation caused by the product itself, during or following use, may increase susceptibility to the induction of skin sensitisation.

SAFs -Application conditions

- **Occlusion-** May result in multiple effects, for instance changes in the hydration of the stratum corneum and dermal irritation. The HRIPT employs occlusion.

- **Frequency/Duration-** Products may be used daily over periods of months or years. Frequent use and long term use increase the probability of sensitisation.

Conclusion in QRA 2 on the SAFs

- **Current status**. The SAF values still require additional examination and evaluation for assignment by product type.

- **Application**. The SAF for each individual consumer product is calculated by multiplying the inter-individual variability, product effects (frequency and occlusion) and skin considerations/site SAFs.

IDEA
International Dialogue for the Evaluation of Allergens

THE RIFM/Creme Model

AGGREGATE EXPOSURE TO INDIVIDUAL FRAGRANCE INGREDIENTS

Data needed to assess dermal aggregate exposure for consumers

- Frequency of product use (consumer habits)
- Skin sites of application of the products
- Amount per use of each product
- Chemical concentration of fragrance ingredient in the product
- Retention factor
- Subject bodyweight and height
- Surface area of product application body sites

Exposure assessment

- The measurement of exposure ('dose metric') is dose/area (µg/cm^2).
- Applied dose and delivered dose can differ due to losses from evaporation, binding/sequestration in the skin (particularly in the stratum corneum with subsequent loss through exfoliation) and metabolism (inactivation and activation).

NB The applied dose is used as a conservative estimate of actual consumer exposure.

The Dermal Aggregate Exposure Model

- Based on real habits and practices 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.

Conservative aspects of the model

- 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).
- Selection of 95th percentile for each body part as the value to be used.

.

The aggregate exposure model

Uses custom built software system to enable probabilistic exposure calculations.

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

NB In order to consider dermal aggregate exposure in the QRA, the body site SAFs need to be aligned with the list of application sites from survey data.

Current status of QRA 2

- Report sent to DG-SANCO/JRC in July 2014. It comprise 120 pages, 21 tables and 13 figures.
- In addition to setting out the methodology and using worked examples of its application, it also proposes next steps in optimising risk assessment.
- The product specific SAFs will be finalized by May 2015.

Current status of QRA 2

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

Di Lampedusa in The Leopard 1957

NEXT STEPS FOR QRA

IDEA
International Dialogue for the Evaluation of Allergens

- Other sources of exposure should be considered for a number of fragrance ingredients.
- Evidence of the effectiveness of the QRA in preventing sensitisation among consumers is needed.
- Suitable methodologies for non-animal risk assessment are urgently required.

Conclusions on QRA 2

- Good progress has been made in developing the methodology due to excellent collaboration.
- The methodology for QRA is comparable with that used for the risk assessment of other effects of human exposure to chemicals.
- Areas for further work have been identified.

IDEA

International Dialogue for the Evaluation of Allergens

Thank you very much for your attention