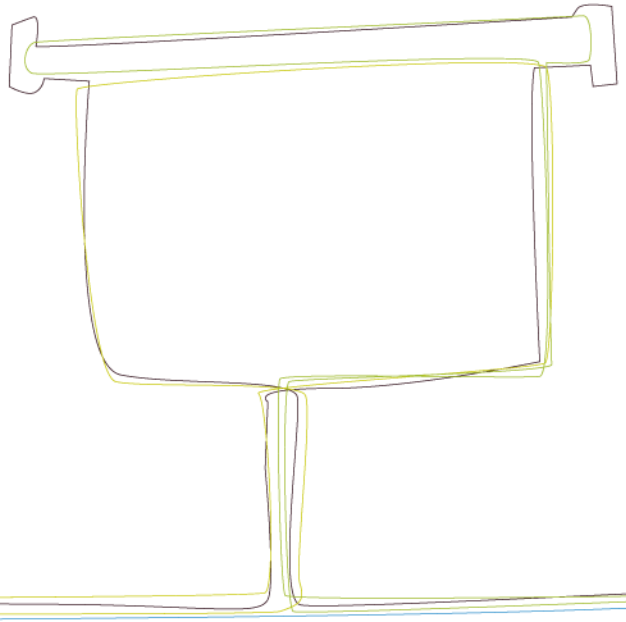
IDEA
International Dialogue for the Evaluation of Allergens

Rapporteur's Progress Report on the IDEA Workshop on

Validity of the QRA Methodology & Possibilities of Further Refinement

March 19-20, 2013



IDEA Annual Review – December 13th, 2013

Prof. Jim Bridges
Chairman of the IDEA Supervisory Group

Principles of Allergic Contact Dermatitis

- ACD arises as the result of two essential stages:
  - an induction phase: primes and sensitizes the immune system (CA).
  - an elicitation phase: an immune response is triggered (ACD).
- Both stages appear to involve a thresholded mechanism and thus safe use levels could be derived from an appropriate risk assessment.
- Effective primary prevention (induction) would ultimately minimize the secondary issues (elicitation).
- QRA can be utilised to prevent induction.
- QRA uses the tools available for general RA.

Outline of the QRA methodology

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Identify consumer exposure to a given fragrance material

Determine the NESIL (concentration which should not cause skin sensitization induction)

Apply safety factors for:
- Inter-individual variability
- Matrix effects
- Use considerations

Quantitative Risk assessment

Determine the maximum safe use level for the fragrance material

Regulatory Toxicology and Pharmacology, vol. 52, issue 1 (October 2008)

Issues: Hazard identification / characterization

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- Relevance of tests and quality of studies determines the reliability and utility of the NESIL for establishing maximum safe use levels.

- Ban of animal testing is challenging for hazard assessment. New tools show promise. These should be included in the procedure for NESIL determination when properly validated.

Risk Assessment related issues

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- Need for a “buffer zone” - technically termed the “Sensitization Assessment Factors” (SAFs) – to account for variability in individuals, differences in testing and using ingredients (matrix effects) and how finished products are used by consumers.

- While the QRA procedure is generally acceptable the SAFs need to be further substantiated.

SAF #1: Inter-individual variability factor

- The current QRA is **intended to protect the general population**.
- It uses a single factor of 10 to cover all sources of variability (age, gender, ethnicity, genetic effects, etc.). Additional allowance needs to be considered for people with compromised skin.
- *Understanding of inter-individual variability* should concentrate on (to be addressed at the next workshop):
  - The ability of skin to allow permeation to occur
  - The enzymatic / metabolic specificities
  - The genetic differences

Inter-individual variability: conclusion

- This SAF, while based on general toxicological principles, is arbitrary and should be substantiated / reconsidered based on scientific data.

- However the NESIL is usually confirmed by HRIPT (tolerance study on humans) which adds additional precaution. Therefore, the overall approach might be viewed as already sufficiently conservative.

SAF #2: Vehicle or product matrix effects

- The existing scale of 1, 3 and 10 was based on scientific data comparing experimental conditions and real-life scenarios.
- Product matrix and skin permeation are important but **bioavailability** is key to estimating the risk of induction.
- Better consideration needs to be given to potential vehicle effects. (NB the solvents used for LLNA and HRIPT may enhance or lower the observed response).
- Presence of irritants in the matrix require careful consideration.

Conclusion: This SAF needs to be supported by additional scientific data.

SAF #3: Use considerations

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- The existing scale was based on scientific data comparing experimental conditions and real-life scenarios.
- HRIPT is conducted under **full-occlusion**. This may result in an overly conservative safety factor depending on consumer product use.
- The assignment of use SAF should be reviewed in light of new scientific literature for potential update.

Refinement of exposure assessment

- **Professional** use of fragrance is currently not covered.
  - Include professional use of consumer products.
  - Give more emphasis to understand unregulated product types.

- The aggregate exposure model developed by RIFM was regarded appropriate and will be incorporated into the QRA:
  - Fine-tune how exposure can be aggregated at **different body areas.**
  - Substantiate the choice of an accumulation period of 24 hours.

Exposure assessment: further work

- Investigate further the assumptions on **retention** (1% for rinse-off products) which are purely empirical.

- Consider potential **cross-reacting sensitizers** for the calculation of exposure.

- Evaluate the exposure at a global level (not limit to product categories of interest to the fragrance industry).

Documenting effectiveness of the QRA

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- Need to carefully **monitor the effectiveness** of the QRA via the collection of clinical data and a broad dialogue between industry and dermatologists.

- Two sources of clinical data were identified:
  - **Retrospective analysis**
  - **Prospective analysis**

  These data could be developed in partnership with networks like ESSCA and IVDK.

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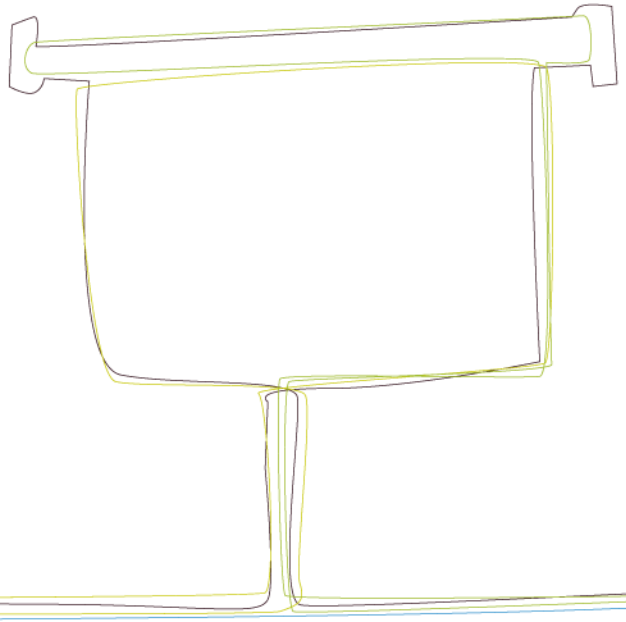
Progress report on actions taken

Validity of the QRA Methodology & Possibilities of Further Refinement



Process and timeframe

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- Recommendations from workshop:
  - pertaining to risk assessment will be addressed by RIFM.
  - pertaining to risk management and dialogue with trade associations / regulators will be addressed by IFRA.

- Preliminary results are already available and consolidated results will be presented at the next QRA workshop (March 2014).

General actions needed

- Skin sensitization is a general issue. QRA has limited value if not applied by everyone.
- Market trends and new fragrance ingredients need to be monitored to evaluate the risk of induction and dermatologists should be informed immediately.
- Ensure **compliance** with the IFRA Standards across the value chain.
- Other industries (OTC products, aromatherapy) should be sensitized to the problem of contact allergy.

Risk assessment

- RIFM reconvened its QRA Expert Group to:
  - **Substantiate the three SAFs.** (ONGOING)
  - Design **prospective studies** in collaboration with the dermatology community to measure the effectiveness of the QRA. (ONGOING)
  - Determine whether existing **retrospective data** can be used to build predictive models). (DONE)
  - Include **professional** exposure in the QRA methodology (ONGOING)
- With its Aggregate Exposure TF, RIFM continues to further develop the **aggregate exposure model** and incorporate it into the QRA methodology (ONGOING)

Improve the dialogue with the dermatologists

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- RIFM is expanding its formal interactions with the international dermatology community. (ONGOING)
- IFRA is working on the improvement of the communication procedure between the dermatology community and the Industry (upstream and downstream).
- IFRA amended its **IFRA Standards development process** to include the dermatology community. The draft IFRA Standards will be shared for consultation with ESCD, ASCD, EADV and other relevant groups. (DONE)

Risk Management (ONGOING)

- IFRA is committed to **implement the refined QRA methodology**. The currently 81 IFRA Standards based on QRA will be progressively updated from the next Amendment to the IFRA Code of Practice.
- Work on **better informing the consumer** on the presence of fragrance allergens in consumer products going beyond QRA and targeting secondary prevention.
- IFRA is revamping its **compliance program** to ensure that its members apply the QRA methodology.

Dialogue with regulators/trade associations

- Continue dialogue with regulators and explain that several markets are not properly regulated to prevent induction of skin sensitization to fragrance allergens. A dialogue has been established with **EMEA** (the European Medicines Agency). (ONGOING)

- Contact trade associations and strongly recommend the application of QRA to their industries. A dialogue has been established with **AESGP** (the Association of the European Self-Medication Industry) and CHPA in the USA. (ONGOING)

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Thank you for your attention

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