**QRA: WHY?**

**Importance of the QRA Methodology for Fragrance Ingredients**
Significant developments have been incorporated in the way dermal sensitization risk assessments are conducted for fragrance ingredients. The goal or ideal state is to eliminate fragrance allergy in the general population. The core strategy used by the fragrance industry is primary prevention of dermal sensitization to fragrance ingredients in consumer products. It was recognized that preventing induction of sensitization to fragrance ingredients (primary prevention) needed to be accomplished more effectively than we have in the past. The Research Institute for Fragrance Materials, Inc. (RIFM) and the International Fragrance Association (IFRA) wanted to lead with a scientifically robust strategy. The QRA Methodology is a major improvement over previous risk assessment practices because it specifically addresses the elements of exposure-based risk assessment that are unique to the induction of dermal sensitization, while being consistent with the principles of general toxicology risk assessment. This exposure-based risk assessment approach for fragrance ingredients has been globally adopted by IFRA and RIFM.

**Key Points Identified by the Expert Panel**
1. A recommendation for the overall risk assessment approach to be used for evaluation of fragrance ingredients identified as potential dermal sensitzizers
2. Guidance on different elements of the recommended dermal sensitization risk assessment process (e.g. determination of known benchmarks for hazard identification; sensitization assessment factors or SAFs (known as uncertainty factors in general toxicology); calculation of consumer exposure and interpretation of these data for risk characterization and risk management.
3. **Key goal (2011):** To review all chemically defined fragrance ingredients with structural alerts for dermal sensitization that are used > 1 metric ton per year on a worldwide basis.

There are several critical developments in the refined methodology for dermal sensitization QRA of fragrance ingredients.

- QRA for dermal sensitization is now used for dermal sensitization exposure-based risk assessments for fragrance ingredients and support of the safety of fragrances in consumer products
- The QRA will be the core strategy for primary prevention of dermal sensitization to fragrance ingredients in consumer products.
- Based on the Expert Panel’s recommendation IFRA and RIFM will be using the QRA to set international Standards (IFRA Standards) for fragrance ingredients identified as potential dermal sensitzizers
- The global scientific, regulatory and academic communities should be aware of the changes and how the implementation of this new approach provides a significant improvement for dermal sensitization risk assessment of fragrance ingredients over the historical methodology that was more qualitatively based
Conclusions of the QRA Expert Group *Published in Regulatory Toxicology and Pharmacology, October 2008, Vol. 52, pp 3-23*

- The general principles of risk assessment can be applied to the induction of dermal sensitization as it is a threshold phenomenon. However, these general principles required tailoring to take into account unique elements of dermal sensitization as a toxicity endpoint.
- The principles of exposure-based QRA are appropriate for the evaluation of fragrance ingredients identified as potential dermal sensitizers.
- Following the identification of a fragrance ingredient as a potential dermal sensitizer, a Weight of Evidence (WoE) approach should be used to determine a No Expected Sensitization Induction Level (NESIL).
- Guidelines were established to determine the NESILs in the risk assessment process using the WoE approach.
- SAFs were predefined for certain product types within the exposure-based QRA process using published peer-reviewed scientific data.
- Product categories were defined according to similar combinations of SAFs and exposures which result in similar acceptable use levels of a fragrance ingredient.
- The dose metric used within QRA for NESIL, Acceptable Exposure Level (AEL) and Consumer Exposure Level (CEL) is dose per unit area of skin (μg/cm²).
- The QRA can be used in combination with clinical results from the dermatology community and company post-market surveillance data to confirm the effectiveness of fragrance ingredient use limits.
- The QRA represents an important step forward in skin sensitization risk assessment but there will likely be ongoing refinements.

*QRA Expert Group Membership*

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Implementation of the QRA Methodology for Fragrance Ingredients

40th Amendment May 2006 – 4 fragrance ingredients, Citral, Farnesol, Phenylacetaldehyde, Tea Leaf Absolute

41st Amendment May 2007 – 28 Standards (51 fragrance ingredients)
- 14 revised Standards, for materials already restricted, 25 materials (including isomers)
- 14 new Standards, 26 materials (including isomers)

42nd Amendment July, 2008 - 18 Standards (31 fragrance ingredients)
- 10 revised Standards, 16 materials
- 8 new Standards, 15 materials
- Additional purity Standard on Oakmoss & Treemoss Extracts
- 14 revised Standards from the 42nd Amendment due to Capping (Capping: The maximum permitted levels will be those that already existed as skin contact limit. QRA Category 6 oral care and Category 11 non-skin are excluded)

43rd Amendment May, 2009 - 12 Standards (12 fragrance ingredients)
- 1 revised Standard, 1 material (+ capping)
- 11 new Standards, 11 materials

45th Amendment June 2010 - 4 Standards - Only two existing Standards remain to be converted to QRA

QRA Recognition

- The QRA publication is one of the top ten papers cited for 2007-2008. An important step forward as scientific method
- Refinements will occur as new data becomes available
- SCCP opinion of June 2008 is not an endorsement but not a total decline; the European Commission encourages the continued development of the method.
- Full trust from the fragrance industry and its customers regarding application and use of the QRA method
- Industry will continue implementation and validation
- Suppliers and customers are working to address concerns and to seek continued dialogue with SCCP and EU Commission
- Accepted by Australian regulators
- Interest by US FDA and US EPA