Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients

Anne Marie Api, PhD
Vice President, Human Health Sciences
Research Institute for Fragrance Materials, Inc.
Tel.: 201.689.8089  Fax: 201.689.8090
amapi@rifm.org

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QRA: Why?

● Goal or ideal state is to prevent fragrance allergy in the general population

● Core strategy for primary prevention of dermal sensitization to fragrance ingredients in consumer products

● Prevent induction of sensitization to fragrance ingredients (primary prevention) more effectively than we have in the past

Lead with a rigorous scientific strategy
QRA For Dermal Sensitization

Application to induction of skin sensitization - a threshold phenomenon

- Determine potential (hazard) to induce sensitization
  - Pre-clinical studies
  - Human data (historical)
  - Structure based predictive approach

- Dose-response assessment
  - Determine WoE NESIL
  - Calculate SAF

- Exposure assessment
  - Dose metrics: expressed in Dose/Area
  - Understand consumer exposure per product type

- Risk characterization
Sensitization Assessment Factor (SAF)

● Step 3: Calculate SAF

● Extrapolation from controlled experimental situation to real life exposure scenarios
  ● Defined more effectively as the areas of assessment in extrapolating from experimental to real-life scenarios
  ● Use of WoE approach to determine values for the defined areas of assessment
  ● Decisions supported by peer-reviewed scientific literature references
● Three areas of extrapolation
  ● Inter-individual susceptibility
  ● Matrix effects
  ● Use considerations
SAF Application

- Inter-individual variability
  - Age
  - Gender
  - Ethnicity
  - Genetic effects
  - Sensitive subpopulations
  - Inherent dermal integrity

- Default uncertainty factor of 10 in line with the uncertainty factor for this area applied in general toxicology

Felter et al. 2002 Contact Dermatitis 47: 257-266
SAF Application

- Vehicle or product matrix effects
  - Product matrix to which consumers exposed in normal use vs. the vehicle in experimental NOEL studies
  - Most vehicles in experimental studies are simple
  - Consumer products are much more complex
  - Presence of irritants, penetration enhancers
  - HRIPT vehicle contains ethanol

- Defined values of 1, 3 or 10 for different product types
SAF Application

- Use considerations
  - Site: part of the body exposed to the product and site of the body exposed for the generation of the experimental NOEL
    - Mucosal membrane, scalp, underarm
  - Barrier integrity: integrity of barrier function relative to that of the skin in the experimental NOEL condition
    - Shaving, occupational dermatitis
  - Occlusion: presence of occlusion decreases the possibility of evaporation, increases hydration

- Defined values of 1, 3 or 10 for overall evaluation of use considerations
SAF Summary

Inter-individual Variability
(Age, gender, ethnicity, inherent dermal barrier and genetic effects)

Vehicle or Product Matrix Effects
(e.g. presence of irritants, penetration enhancers)

Use Considerations
(Site of contact, barrier function, occlusion)
### SAF Examples

<table>
<thead>
<tr>
<th>Factor</th>
<th>Consideration</th>
<th>SAF values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-Individual Variability</td>
<td>Age, gender, ethnicity, inherent dermal barrier and genetic effects</td>
<td>10</td>
</tr>
<tr>
<td>Vehicle or Product Matrix Effects</td>
<td>e.g. presence of irritants, penetration enhancers</td>
<td>1 or 3 or 10</td>
</tr>
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<td>Site of contact, barrier function, occlusion</td>
<td>1 or 3 or 10</td>
</tr>
</tbody>
</table>
### SAF Examples

<table>
<thead>
<tr>
<th>Product</th>
<th>Inter-Indiv. Variation</th>
<th>Matrix Effects (Rationale)</th>
<th>Use Considerations</th>
<th>Total SAF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deodorant</strong></td>
<td>SAF = 10</td>
<td>SAF = 3</td>
<td>SAF = 10&lt;br&gt;Area = underarm; skin easily irritated, highly follicular; area may be shaved. Occlusion similar to experimental conditions&lt;sup&gt;33-36&lt;/sup&gt;</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Product Matrix different from experimental conditions; may contain irritating actives</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Shampoo</strong></td>
<td>SAF = 10</td>
<td>SAF = 3</td>
<td>SAF = 3&lt;br&gt;Area is the head; highly follicular; scalp is more permeable&lt;sup&gt;33,49&lt;/sup&gt;</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Product Matrix very different from experimental conditions; may contain irritating ingredients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SAF Examples

- Matrix Effects (Rationale 6,26,28-32)
  - 6, Felter et al., 2002
  - 26 Kligman, 1966
  - 28 Robinson et al., 2000
  - 29 Smith et al., 2000
  - 30 Cumberbatch et al., 1993
  - 31 Scheuplein and Ross, 1970
  - 32 Schaefer and Redelmeier, 1996
SAF Examples

● Use SAF for underarm area = 10
  ● skin easily irritated, highly follicular; area may be shaved. Occlusion similar to experimental conditions33-36
    ● 33 Feldmann and Maibach, 1967
    ● 34 Benfeldt et al., 1999
    ● 35 Edman, 1994
    ● 36 Bucks, et al., 1989

● Use SAF for head area = 3
  ● Head is highly follicular; scalp is more permeable33,49
    ● 33 Feldmann and Maibach, 1967
    ● 49 Zhai et al, 2004
### Examples of SAF Values

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deodorants/Antiperspirants</td>
<td>300</td>
</tr>
<tr>
<td>Eye, Body Lotion, Shaving Cream, Men’s Facial Products</td>
<td>300</td>
</tr>
<tr>
<td>Lip Products</td>
<td>300</td>
</tr>
<tr>
<td>Toothpaste, Mouthwash, Denture Adhesive</td>
<td>300</td>
</tr>
<tr>
<td>Hydroalcoholics Applied To Recently Shaved Skin</td>
<td>300</td>
</tr>
<tr>
<td>Hydroalcoholics Applied To Unshaved Skin</td>
<td>100</td>
</tr>
<tr>
<td>Diapers</td>
<td>100</td>
</tr>
<tr>
<td>Nail Enamel/Polish Remover, Women’s Facial, Make-up Remover, Hair Sprays and Styling Aids, Leave-in Hair Conditioner Products</td>
<td>100</td>
</tr>
<tr>
<td>Shampoo, Body Wash/Gels, Conditioner, Bar Soaps, Face Wash/Gel/Scrubs, Bath Gels Etc.,</td>
<td>100</td>
</tr>
<tr>
<td>Non-skin/Unintentional Use Products</td>
<td>10</td>
</tr>
</tbody>
</table>
Step 5: Risk Characterization

**NESIL**
- Which pre-clinical and/or clinical data are available:
  - ? Guinea-pig data
  - ? Local Lymph Node Assay (EC₃ in µg/cm²)
  - ? Human data (historical) (HRIPT NOEL in µg/cm²)
  - Based on weight of evidence/default value in µg/cm²

**SAF**
- Considerations for calculation of Sensitization Assessment Factor:
  - For the product type the SAF is:
    - Inter-individual = 10
    - Product Matrix = 1-10
    - Use considerations = 1-10
  - Overall SAF is the multiple of the three defined areas

**Exposure**
- Calculation for daily exposure to the contact allergen in the product type:
  - = [Amount of contact allergen in product (µg/g product) x Amount product applied (g)]/Surface area exposed (cm²)
  - Calculated consumer exposure in µg/cm²
Risk Characterization For Fragrance Ingredients

- Acceptable Exposure Levels (AELs) to fragrance ingredients that are dermal sensitizers can be determined in specific real life consumer product types

\[
\text{Acceptable Exposure Level (AEL)} = \frac{\text{WoE NESIL}}{\text{Sensitization Assessment Factor (SAF)}}
\]
Risk Characterization For Fragrance Ingredients

- Comparison of Acceptable Exposure Levels (AEL) to calculated Consumer Exposure Level (CEL)

\[
AEL \geq CEL \quad \text{to be Acceptable}
\]

\[
\frac{AEL \geq 1}{CEL}
\]
Risk Characterization

Consumer exposure $\text{mg/cm}^2$

AEL $\text{mg/cm}^2$

NESIL $\text{mg/cm}^2$

Safety Assessment Factor (SAF)

<NOEL

log $\text{mg/cm}^2$
QRA Implementation Status

- 40th Amendment May 2006 – 4 materials
- 42nd Amendment May 2007 – 28 Standards on 51 materials
- 43rd Amendment July 2008 - 18 Standards on 31 materials
- 44th Amendment May 2009 – 12 Standards
- 45th Amendment June 2010 – 4 materials
- 46th Amendment June 2011 – 6 materials
- 47th Amendment Spring 2013 – 6 Standards on 9 materials
Research Institute for Fragrance Materials, Inc.
Tel.: +1-201.689.8089

amapi@riffm.org
RIFM: www.riffm.org