



Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients

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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**

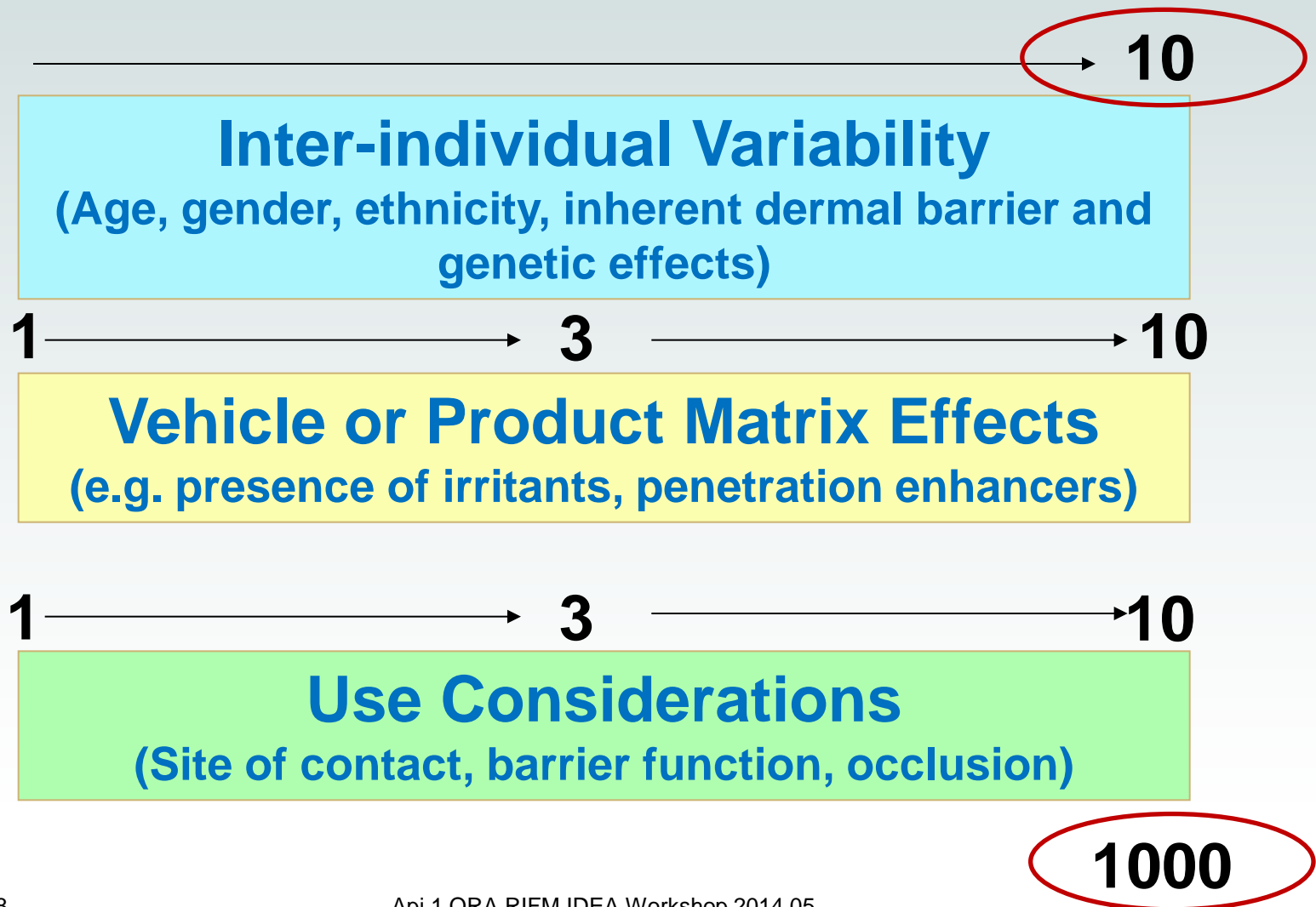


SAF Application

- **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



SAF Examples

Factor	Consideration	SAF values
Inter-Individual Variability	Age, gender, ethnicity, inherent dermal barrier and genetic effects	10
Vehicle or Product Matrix Effects	e.g. presence of irritants, penetration enhancers	1 or 3 or 10
Use Considerations	Site of contact, barrier function, occlusion	1 or 3 or 10

SAF Examples

Product	Inter-Indiv. Variation	Matrix Effects (Rational 6,26,28-32)	Use Considerations	Total SAF
Deodorant	SAF = 10	SAF = 3 Product Matrix different from experimental conditions; may contain irritating actives	SAF = 10 Area = underarm; skin easily irritated, highly follicular; area may be shaved. Occlusion similar to experimental conditions 33-36	300
Shampoo	SAF = 10	SAF = 3 Product Matrix very different from experimental conditions; may contain irritating ingredients	SAF = 3 Area is the head; highly follicular; scalp is more permeable 33,49	100

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 permeable^{33,49}
 - 33 Feldmann and Maibach, 1967
 - 49 Zhai *et al*, 2004

Examples of SAF Values

Deodorants/Antiperspirants	300
Eye, Body Lotion, Shaving Cream, Men's Facial Products	300
Lip Products	300
Toothpaste, Mouthwash, Denture Adhesive	300
Hydroalcoholics Applied To Recently Shaved Skin	300
Hydroalcoholics Applied To Unshaved Skin	100
Diapers	100
Nail Enamel/Polish Remover, Women's Facial, Make-up Remover, Hair Sprays and Styling Aids, Leave-in Hair Conditioner Products	100
Shampoo, Body Wash/Gels, Conditioner, Bar Soaps, Face Wash/Gel/Scrubs, Bath Gels Etc.,	100
Non-skin/Unintentional Use Products	10

Step 5: Risk Characterization



NESIL

- Which pre-clinical and/or clinical data are available:
- ? Guinea-pig data
- ? Local Lymph Node Assay (EC₃ in $\mu\text{g}/\text{cm}^2$)
- ? Human data (historical) (HRIPT NOEL in $\mu\text{g}/\text{cm}^2$)
- Based on weight of evidence/default value in $\mu\text{g}/\text{cm}^2$

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 ($\mu\text{g}/\text{g}$ product) x Amount product applied (g)]/Surface area exposed (cm^2)
- Calculated consumer exposure in $\mu\text{g}/\text{cm}^2$

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

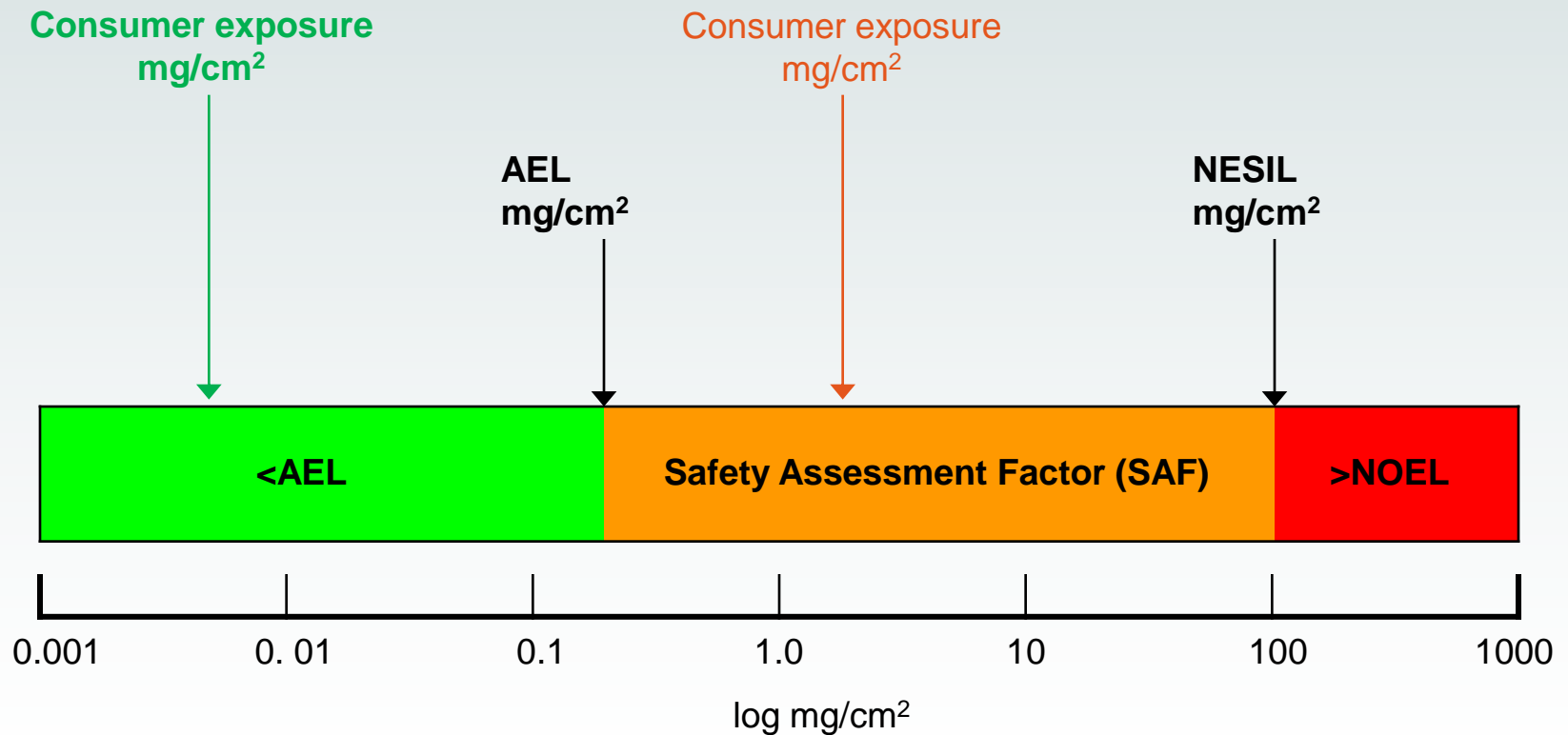


- Comparison of Acceptable Exposure Levels (AEL) to calculated Consumer Exposure Level (CEL)

$AEL \geq CEL$ to be Acceptable

$$\frac{AEL \geq 1}{CEL}$$

Risk Characterization





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**

More Information



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