Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients

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Primary vs. Secondary Prevention

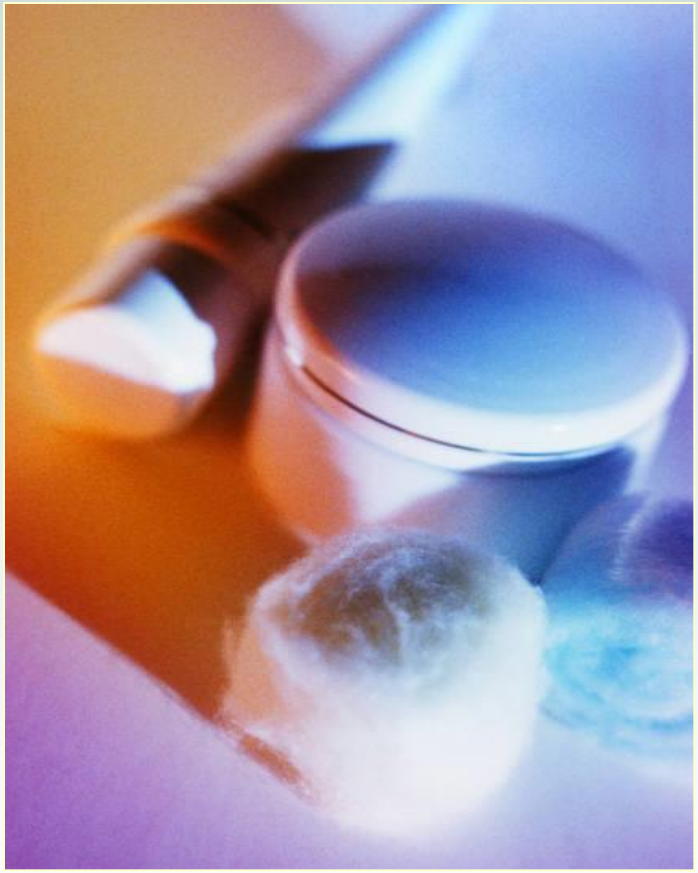
Primary Prevention

- Induction
- Initial phase - Acquire Sensitization; the immunologic memory for a contact sensitizer is created
- Premise of RIFM testing and the basis for IFRA Standards on sensitization

Secondary Prevention

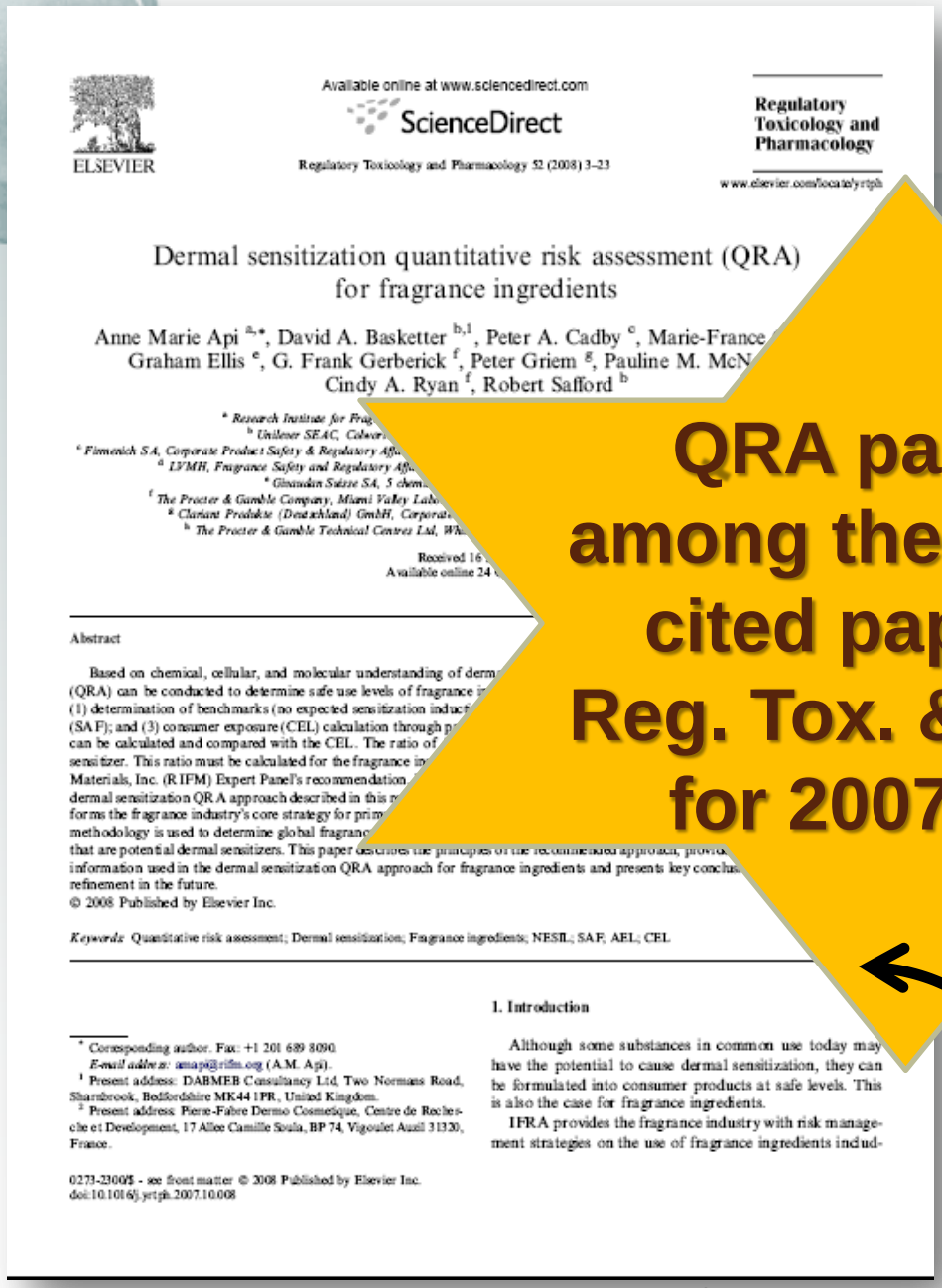
- Elicitation
- Manifestation of Sensitization; the specific memory migratory inflammatory cells, upon renewed contact with the contact sensitizer, will proliferate and induce a cascade of inflammatory events in the exposed skin area.

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



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Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients

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Abstract

Based on chemical, cellular, and molecular understanding of derm
(QRA) can be conducted to determine safe use levels of fragrance i
(1) determination of benchmarks (no expected sensitization induct
(SAF); and (3) consumer exposure (CEL) calculation through p
can be calculated and compared with the CEL. The ratio of
sensitizer. This ratio must be calculated for the fragrance in
Materials, Inc. (RIFM) Expert Panel's recommendation
dermal sensitization QRA approach described in this r
forms the fragrance industry's core strategy for prim
methodology is used to determine global fragranc
that are potential dermal sensitizers. This paper
information used in the dermal sensitization QRA approach for fragrance ingredients and presents key conclu
refinement in the future.
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Keywords: Quantitative risk assessment; Dermal sensitization; Fragrance ingredients; NESIL; SAF; AEL; CEL

1. Introduction

Although some substances in common use today may have the potential to cause dermal sensitization, they can be formulated into consumer products at safe levels. This is also the case for fragrance ingredients.

IFRA provides the fragrance industry with risk management strategies on the use of fragrance ingredients includ-

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QRA paper is among the 10 most cited papers in Reg. Tox. & Pharm. for 2007-2008

Regulatory , Toxicology & Pharmacology

Special Issue Oct. 2008

Dermal Sensitization QRA for Fragrance Ingredients

7 manuscripts including

QRA method
***et al.* - HRIPT**
entific review
& Api - HRIPT
method
- Dose Metric

7 peer reviewed publications

General Risk Assessment Principles

- **Acceptable Exposure Level (RfD or AEL) Estimate of a daily exposure to an agent that is assumed to be without a health impact in the human population**

$$\text{Acceptable Exposure Level (RfD or AEL)} = \frac{\text{NOEL}}{\text{Uncertainty Factor (UF)}}$$

QRA For Dermal Sensitization Fragrance Ingredients

Application to induction of skin sensitization - a threshold phenomenon

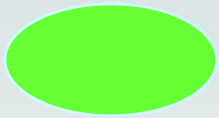
- Step 1: Hazard Identification
  - Determine potential (hazard) to induce sensitization from:
    - Pre-clinical studies e.g. Guinea-Pig Test, Local Lymph Node Assay (LLNA)
    - Human data (historical) – Maximization, RIPTs, DPTs
    - Structure based predictive approach

QRA For Dermal Sensitization Fragrance Ingredients

- Step 2: Dose response assessment (What is the known benchmark and how to define it)
  - Takes into account key factors:
    - Definition of Known Benchmark - Determine the No-Expected-Sensitization Induction-Level (NESIL) based on the Weight of Evidence (WoE)

Influence Of Area Exposed On Sensitization

62.5mg DNCB

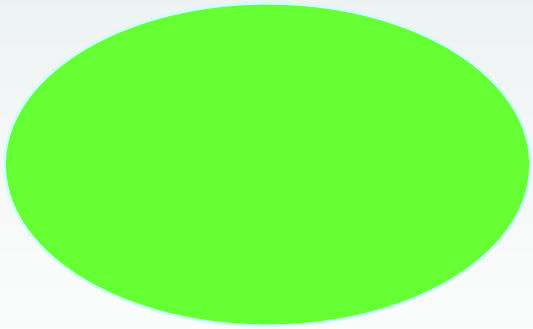


1.8 cm^2 Site

Sensitization Rate

85%

62.5mg DNCB



7.1 cm^2 Site

8%

Reviewed in *Contact Dermatitis* 1992, 27:281-286

Dose Response: NESIL Determination

- **Establishment of scientifically sound NESILs is key to conduct of dermal sensitization QRA methodology**
  - **Weight of evidence approach to use of data**
  - **Uses all of the available scientifically robust data**
  - **Identifies studies inappropriate for consideration**
  - **Can be derived from animal and human data**
  - **Uses a defined dose metric - dose/unit area (mg/cm2)**
  - **Guidelines established for NESIL determination**

WoE NESIL GUIDELINES

- **Guideline #1: Dose metric for exposure**
  - **quantity of chemical per unit area of the skin (e.g. µg/cm²)**
- **Guideline #2: Hierarchy of human data**
- **Guideline #3: LOEL from historical human volunteer tests**
- **Guideline #4: Use of human volunteer data other than HRIPT**

WoE NESIL Guidelines

- **Guideline #5: Use of guinea-pig tests as secondary data sources**
- **Guideline #6: LLNA data only**
- **Guideline 7: Hierarchy of human versus animal data**
- **Guideline8: Diagnostic Patch Test (DPT) data**

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

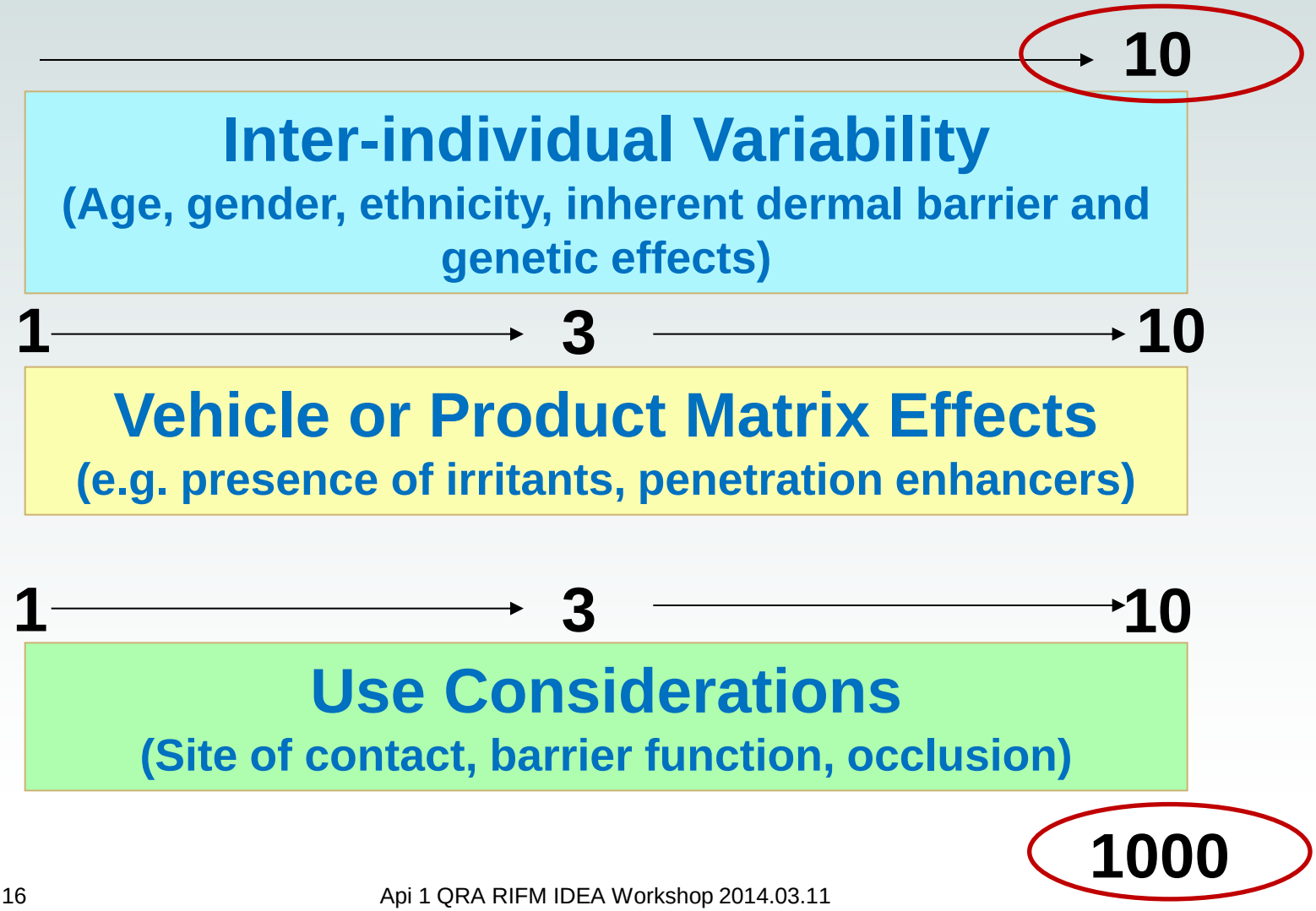
SAF Application

- 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


10
Inter-individual Variability
(Age, gender, ethnicity, inherent dermal barrier and genetic effects)
1
3
10
Vehicle or Product Matrix Effects
(e.g. presence of irritants, penetration enhancers)
1
3
10
Use Considerations
(Site of contact, barrier function, occlusion)
1000

Calculation Of Consumer Exposure (CEL)

- **Step 4: Exposure assessment**
  - **Understand human exposure through characterization of:**
    - **Exposed populations**
    - **Magnitude of exposure under various conditions**
    - **Duration**
    - **Frequency**
  - **Calculated as dose/unit area/per diem (mg/cm2/day)**
  - **Hierarchy established for use of exposure data:**
    - **All sources of data considered**
    - **Measured data for same product type from different sources - most conservative value used unless rationale to contrary**
    - **Key studies in which participants used their own products**
  - **Hierarchy established for human parameters data:**
    - **Surface area measurements for same area of the body - smallest surface area used unless rationale to contrary**

Step 5: Risk Characterization

NESIL

- Which pre-clinical and/or clinical data are available:
- ? Guinea-pig data
- ? Local Lymph Node Assay (EC_3 in $\mu g/cm^2$)
- ? Human data (historical) (HRIPT NOEL in $\mu g/cm^2$)
- Based on weight of evidence/default value in $\mu g/cm^2$

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

Risk Characterization For Fragrance Ingredients

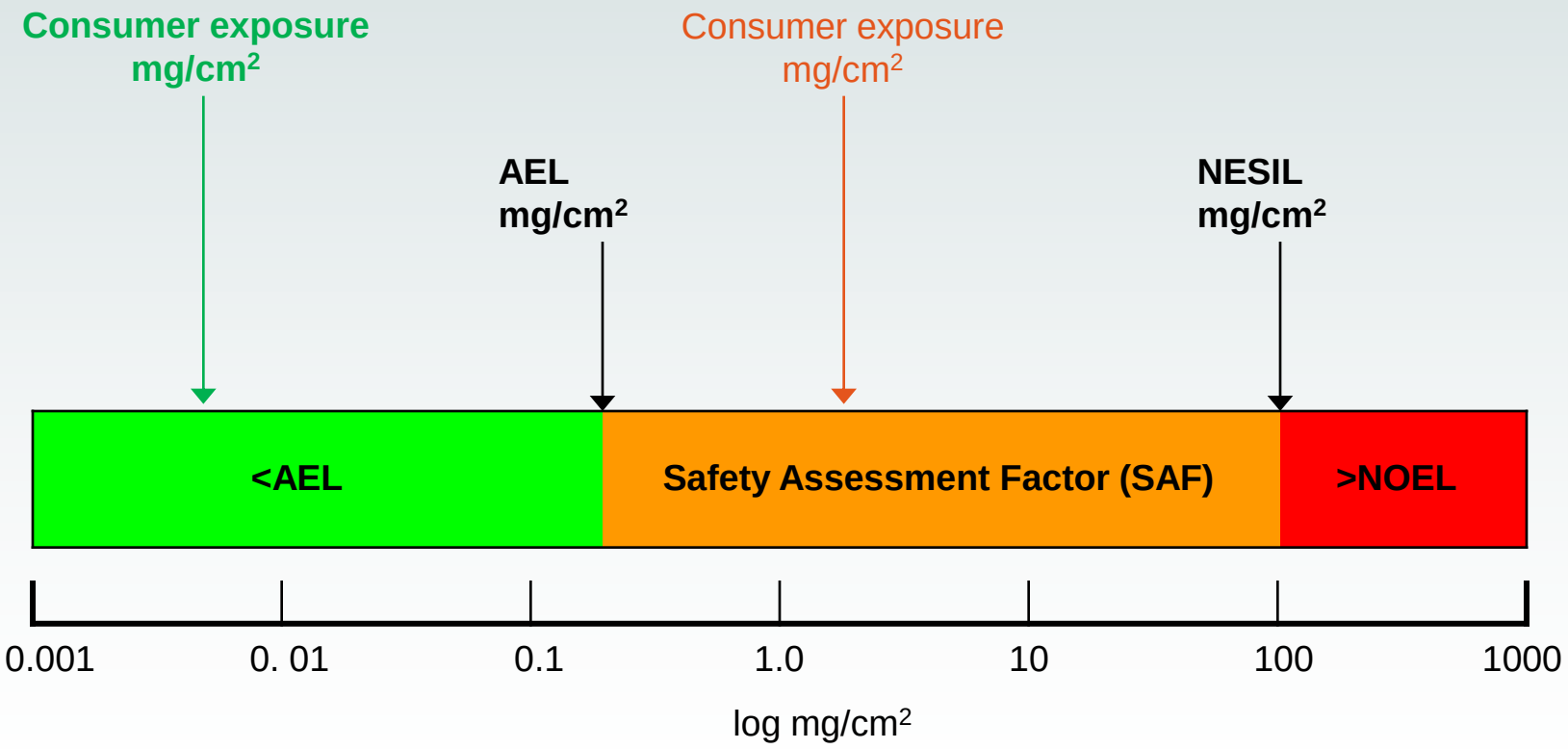
- Acceptable Exposure Levels (AELs) to fragrance ingredients that are dermal sensitizers can be determined in specific real life consumer product types

$$\text{Acceptable Exposure Level (AEL)} = \frac{\text{WoE NESIL}}{\text{Sensitization Assessment Factor (SAF)}}$$

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

AEL ≥ CEL to be Acceptable

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 – 10 materials

QRA Implementation Status

- All existing Standards based on dermal sensitization have been converted to QRA based Standards
- QRA Standards on individual materials have not been modified
  - As such restrictions on individual fragrance ingredients are not changed

Quantitative Risk Assessment for Dermal Sensitization Method

- IDEA QRA Workshop Outcome March 2013

Summary: Key Actions March 2013

- Include aggregate exposure in the QRA
- Review supporting information for SAFs to explicitly include application to damaged skin
- Communication – expand the dialogue with international dermatologists
- Explore relationship between induction and elicitation thresholds
- Measure effectiveness of the QRA in limiting the induction of contact allergy
- Incorporate occupational exposure to consumer products

More Information

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