Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients

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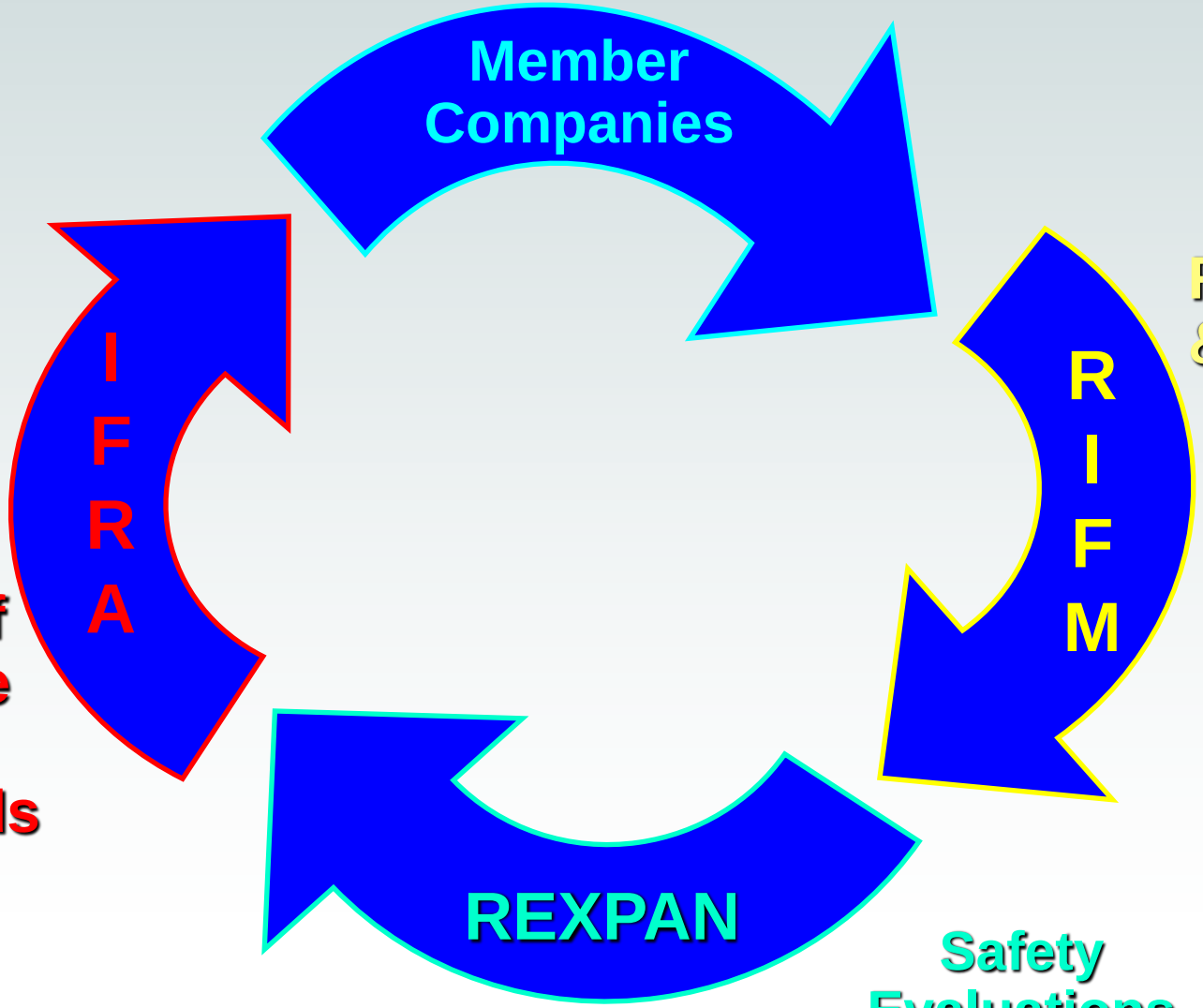
RIFM Background

Fragrance Ingredient Safety



Code of Practice & Standards

Research & Testing

Safety Evaluations

Quantitative Risk Assessment for Dermal Sensitization Method

Primary vs. Secondary Prevention

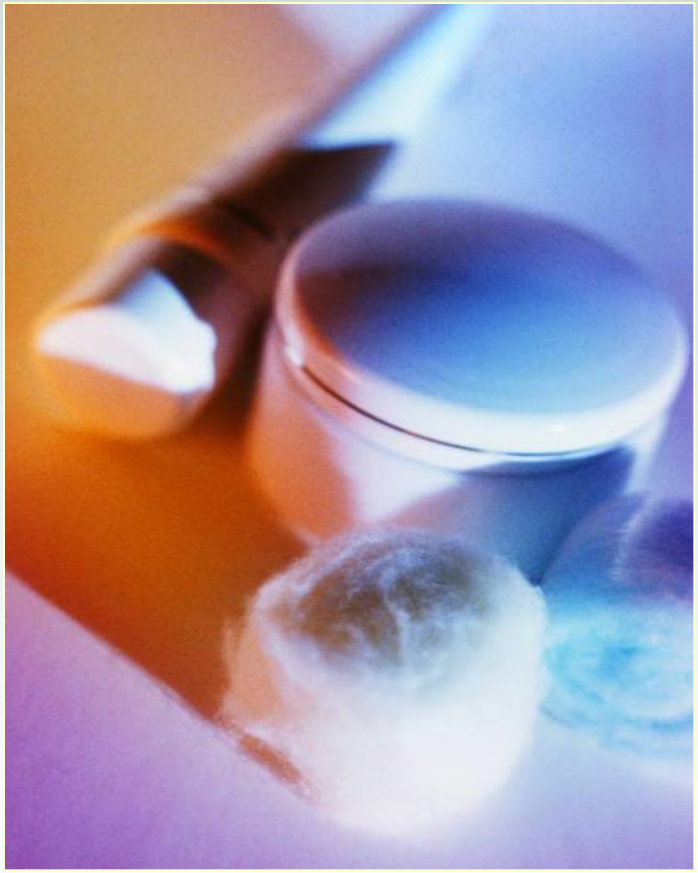
Primary Prevention

- 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

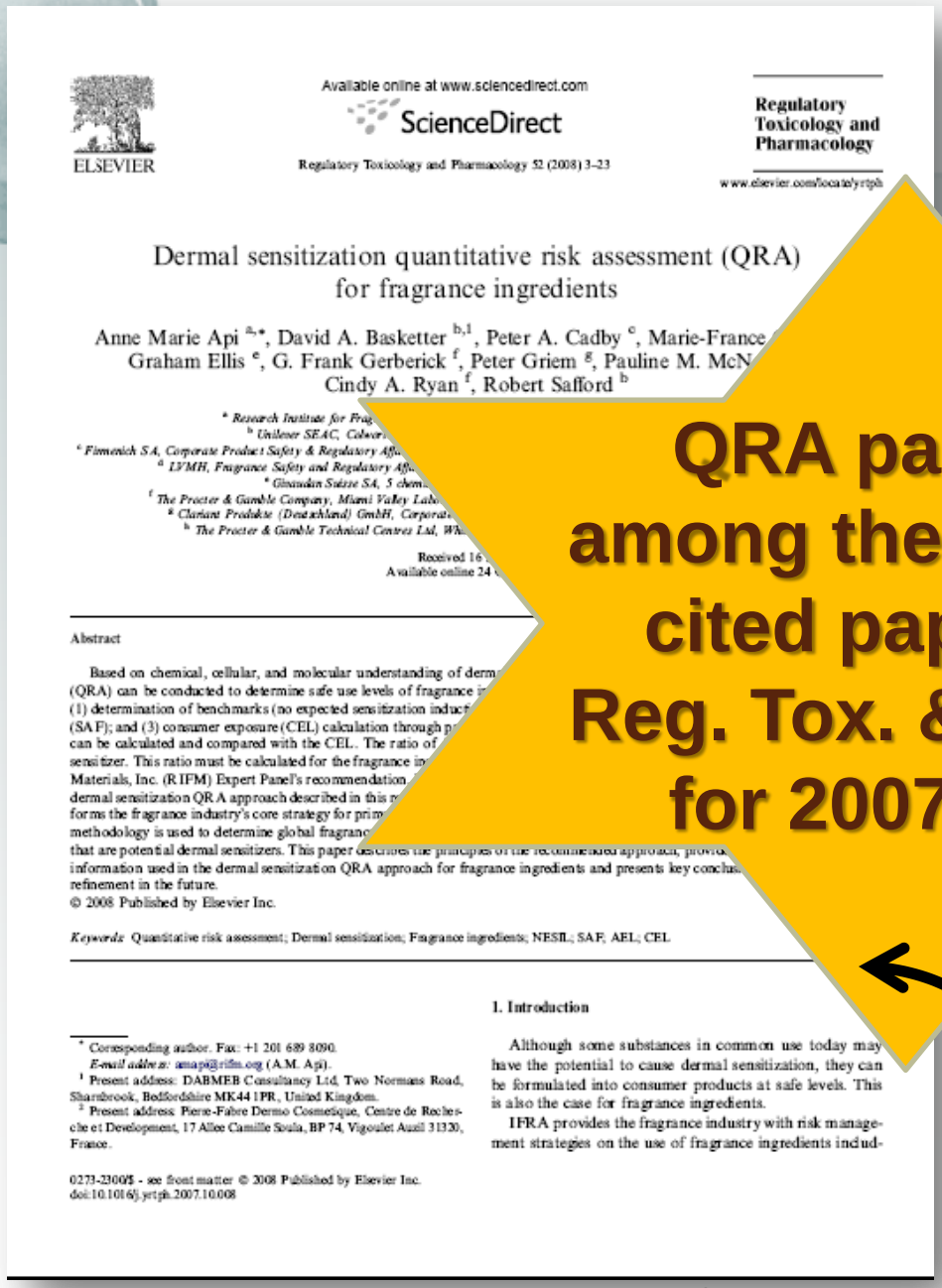
- Elicitation
- Manifestation of Sensitization; the specific migratory inflammatory cells, upon renewed contact with the contact sensitizer, will proliferate and induce a cascade of inflammatory events in the exposed skin area.
- Concern from dermatologists

QRA: Why?



- Goal or ideal state is to eliminate 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 scientifically rigorous 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.

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**

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

Induction of Dermal Sensitisation Quantitative Risk Assessment

- Application to induction of skin sensitization - also a threshold phenomenon
- Using exposure-based risk assessment
  - Induction:
    - Determine hazard - understand pre-clinical/clinical data
    - Determine known benchmarks
    - Calculate sensitization assessment factors
    - Set standard of acceptability - Acceptable Exposure Level
    - Understand consumer exposure e.g. shampoo, facial cream etc…
    - Compare Acceptable Exposure Level and consumer exposure
- Risk assessment conclusions for induction of contact allergy

Application of Induction QRA To Fragrance Ingredients

- Step 1 – Potential hazard identification – can have numerous studies
  - Example: cinnamic aldehyde
    - >30 guinea pig studies
    - >20 LLNAs
    - > 5 Human Maximisation studies
    - >10 HRIPTs
    - >250 DPTs
- Step 2 – Dose response, What is the known benchmark and how to define it
  - Which data to use
  - Robustness of the data
  - Use of a Weight of Evidence (WoE) approach
    - Definition of Known Benchmark – No Expected Sensitising Induction Level (NESIL)
    - Development of guidelines to apply WoE approach to NESIL determination

Application of Induction QRA To Fragrance Ingredients

- Step 3 – Exposure assessment
- Step 4 - Risk characterization

➢ Calculation of Acceptable Exposure Level

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

➢ Comparison of Acceptable Exposure Level (AEL) to calculated consumer exposure (CEL)

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:**
  - **Takes into account key factors:**
    - **Determine the No-Expected-Sensitization Induction-Level (NESIL) based on the Weight of Evidence (WoE)**
    - **Calculate Sensitization Assessment Factor (SAF)**

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**
  - **Rationale for dose metric as quantity of chemical per unit area of the skin (e.g. µg/cm²) is based on experimental investigations, basic immunological principles and historical data (humans and experimental animals)**
- **Guideline #2: Hierarchy of human data**
  - **A NOEL from a well run HRIPT will have precedence over NOELs from other repeated exposure human volunteer tests**
- **Guideline #3: LOEL from historical human volunteer tests**
  - **A Lowest Observed Effect Level from other human tests that is lower than the HRIPT NOEL will be considered unless there is a rationale to disregard**

WoE NESIL Guidelines

- **Guideline #4: Use of human volunteer data other than HRIPT**
  - **In the absence of an HRIPT NOEL a NOEL from a different human volunteer test (e.g. HMT) can be used provided that it is supported by an LLNA EC3 value**

- **Guideline #5: Use of guinea-pig tests as secondary data sources**
  - **Adjuvant tests in animals and non-adjuvant tests in guinea pigs shall not be used as primary sources for defining NESILs but can contribute to determining potency classification**

- **Guideline #6: LLNA data only**
  - **LLNA data only available - consider a confirmatory HRIPT. A cautious approach will be used for selection of the dose level used in such confirmatory HRIPTs**

WoE NESIL Guidelines

- **Guideline 7: Hierarchy of human versus animal data**
  - **A NOEL from a well run HRIPT will (even if higher) have precedence over all other NOELs. Significant discrepancy between a HRIPT NOEL and an LLNA EC3 value will require further consideration. An LLNA EC3 value that exceeds an HRIPT NOEL will not define the NESIL**

- **Guideline 8: Diagnostic Patch Test (DPT) data**
  - **Data from DPT studies can not be used directly in a WoE approach for NESILs determination. Such studies can be useful to help determine the need for additional data**

SAF Definition

- **Extrapolation from controlled experimental situation to real life exposure scenarios**
  - **Defined more effectively 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

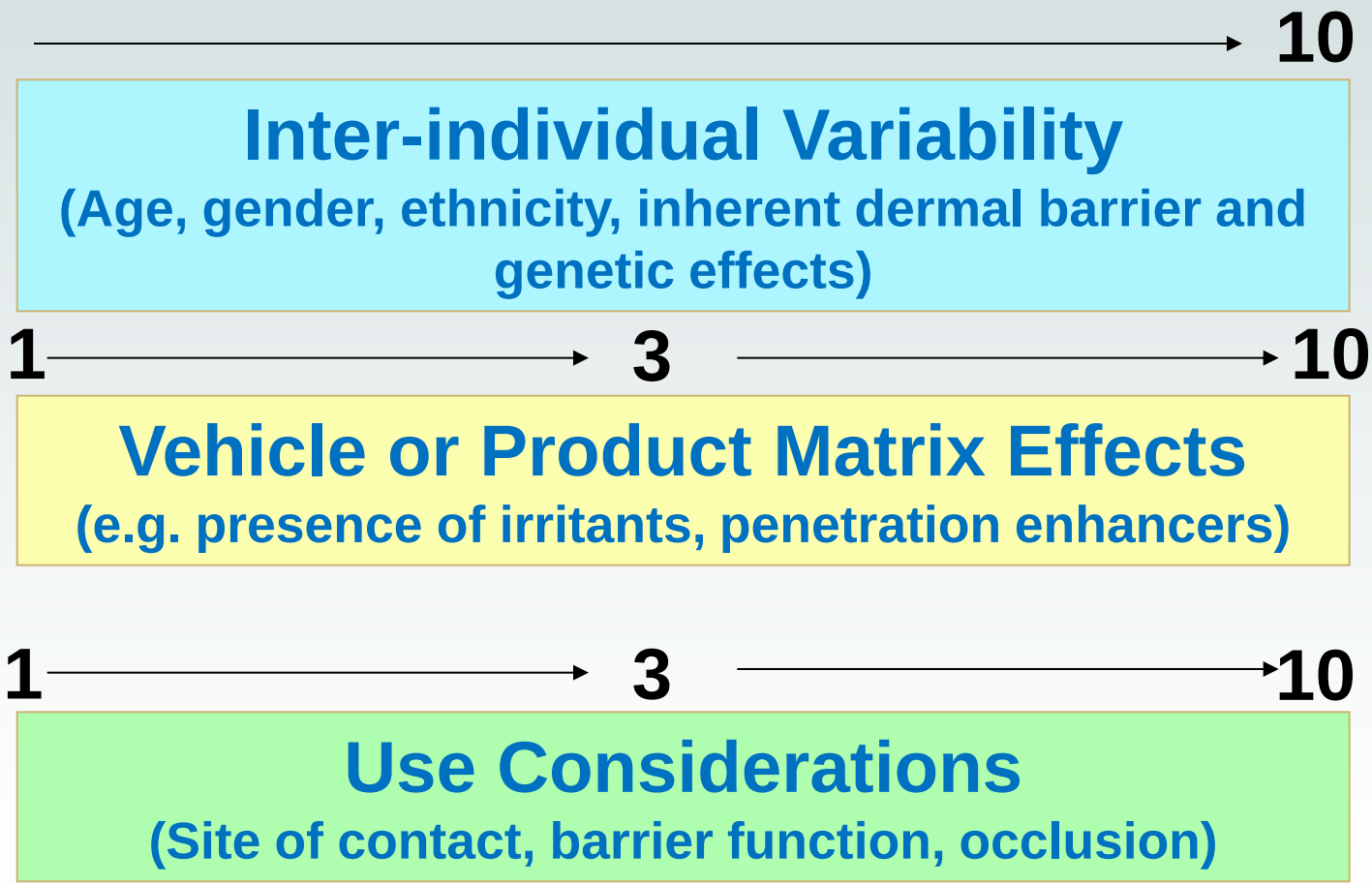
SAF Application

- 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

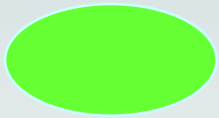

10
Inter-individual Variability
(Age, gender, ethnicity, inherent dermal barrier and genetic effects)
1
3
10
Vehicle or Product Matrix Effects
(e.g. presence of irritants, penetration enhancers)
1
3
10
Use Considerations
(Site of contact, barrier function, occlusion)

SAF Examples

Product	Inter-Indiv. Variation	Matrix Effects	Use Considerations	Total SAF
Deodorant	SAF = 10 Same as general toxicology	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 Same as general toxicology	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

Influence Of Area Exposed On Sensitization

62.5mg DNCB

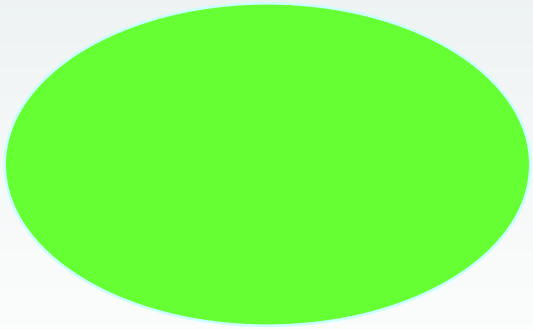


1.8 cm^2 Site

Sensitization Rate

85%

62.5mg DNCB



7.1 cm^2 Site

8%

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

Importance Of Dose/Unit Area

- Patch type and dose/unit area calculation of a 1% solution

Patch Type	Patch Area (cm^2)	Patch Volume (ml)	Dose/Unit Area (mg/cm^2)
8mm Finn	0.5	15	300
19mm HillTop	1.13	200	1770
Profess-ional Products	3.61	200	554
2x2cm Webril	4	400	1000

- Dose/unit area calculations for products* containing 0.1% active

Product Type	Dose/Unit Area (mg/cm^2)
Fine Fragrance Spray	75
Antiperspirant/ Deodorant	5
Facial Skin Cream	2.5
Body Skin Cream	1
Laundry Hand Wash	0.01
Washed Fabric	0.0001

*Historical (not most recent) exposure data used for calculation of dose/area

Calculation Of Consumer Exposure (CEL)

- Step 3: 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/cm^2/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

Consumer Exposure Level (Dose/Area)

Product Type	Exposure	
	Source	mg/cm^2/day
Deo/AP Solid	Cowan-Ellsberry, 2008	9.1
Hydroalcoholic, Unshaved	Cano & Rich*	2.2
Women's Facial Cream	Colipa	0.2
Shaving Cream	SCCP	0.07
Eye Product	CTFA	2.17
Body Cream	Colipa	0.5
Lip Products	Colipa	11.7
Hair Sprays	Loretz *et al*., 2006	2.2
Toothpaste	Colipa	0.13
Mouthwash	SCCP	1.4
Shampoo	Loretz *et al*., 2006	0.2
Body Wash/Gels	SCCP	0.01

*Cano & Rich, 2001; Tozer *et al*., 2004

Consumer Exposure Level

Exposure assessment for shampoos:

- Calculated exposure = 23,630 mg/day (CTFA)
- Area = 1430 cm^2 (EPA, 1997; area hands + ½ head)
- Retention Factor = 1% or 0.01 (SCCNFP, 2003)

Exposure = 23,630 mg/day * 0.01 ÷ 1430 cm^2
= 0.2 $mg/cm^2/day$

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

Step 4: Risk Characterization

NESIL

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

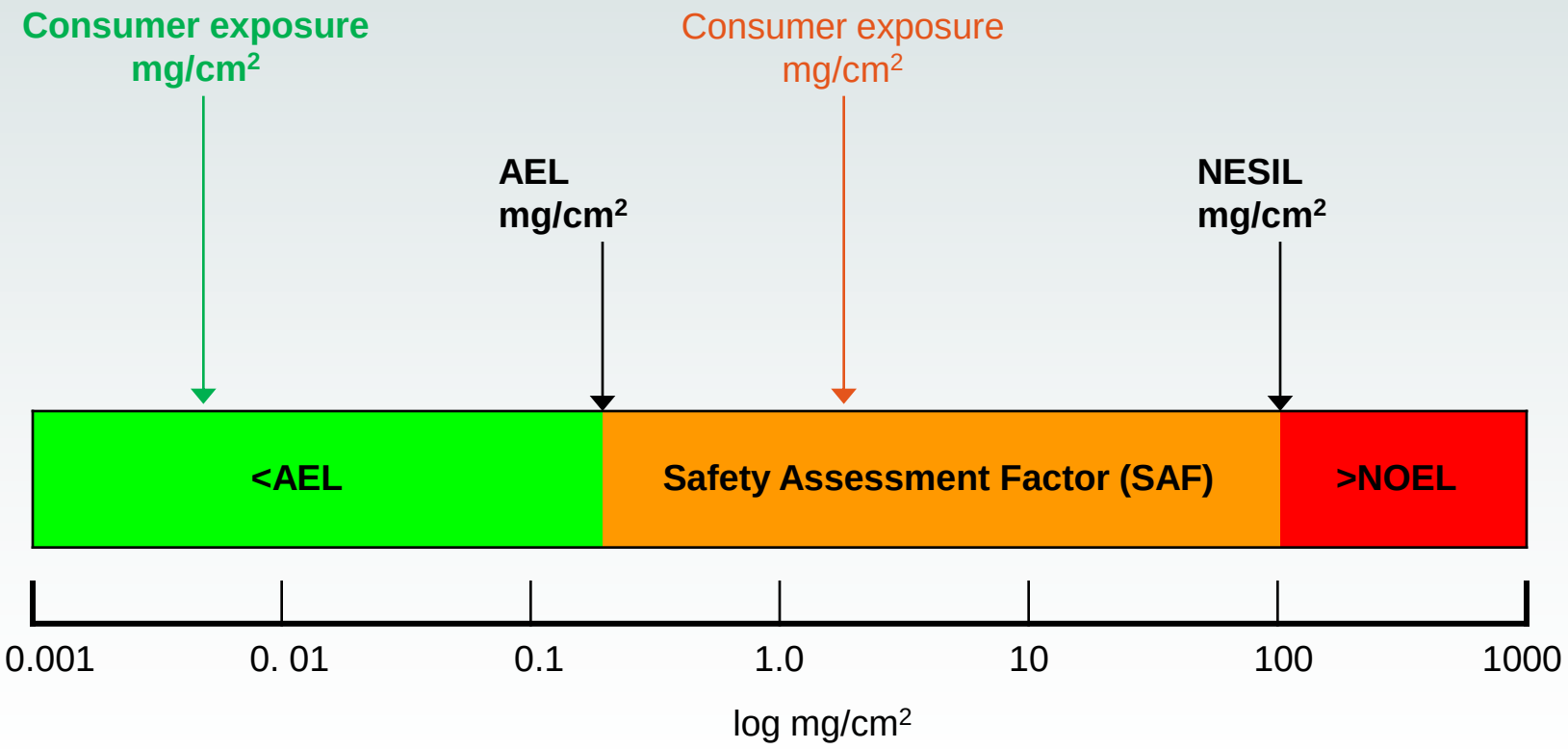
SAF

- Considerations for calculation of Sensitisation 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 µg/cm^2

Risk Characterization



Skin Sensitization Risk Assessment

Exposure-Based Risk Assessment - Induction of Contact Allergy

Prospective

New chemicals

- Prevention of induction of contact allergy in a naive population
- Enables determination of correct standards for publication e.g. Cosmetics Directive, IFRA Standards for different product types…..
- Elicitation of allergic contact dermatitis minimized through prevention of induction of contact allergy

Retrospective

Existing chemicals

- Allows confirmation of current risk assessment for known contact allergens in consumer products
- Provides more robust risk assessment for comparison with the clinical picture
- Enables changes to be implemented for published standards for different product types
- Achieves reduction of elicitation incidence rate over time through preventing induction of contact allergy

Citral

- **Hazard Identification**
  - Guinea pig data - weak sensitizer [14]
  - Local Lymph Node Assay
    - EC3 = 1414 µg/cm2 [11]
  - LOEL
    - HRIPT: 3876 µg/cm2 in EtOH 5/8
    - HMT: 2759 µg/cm2 in pet. 29/150
  - Other Data
    - 1240 µg/cm2 in pet. 0/50
    - 775 µg/cm2 in EtOH 0/41
    - 338 µg/cm2 in EtOH 0/40
- **Confirmatory HRIPT - NOEL**
  - 1400 µg/cm2 in 3:1 DEP:EtOH 0/101
- **WoE NESIL = 1400 µg/cm2**

QRA Dermal Sensitization Citral

Weight of Evidence NESIL

- Guinea-pig data – weak sensitizer [14]
- Local Lymph Node Assay
  - EC_3 = 1414 µg/cm^2 [11]
- Human data
  - HRIPT NOEL = 1400 µg/cm^2
- WoE NESIL = 1400 µg/cm^2

SAF

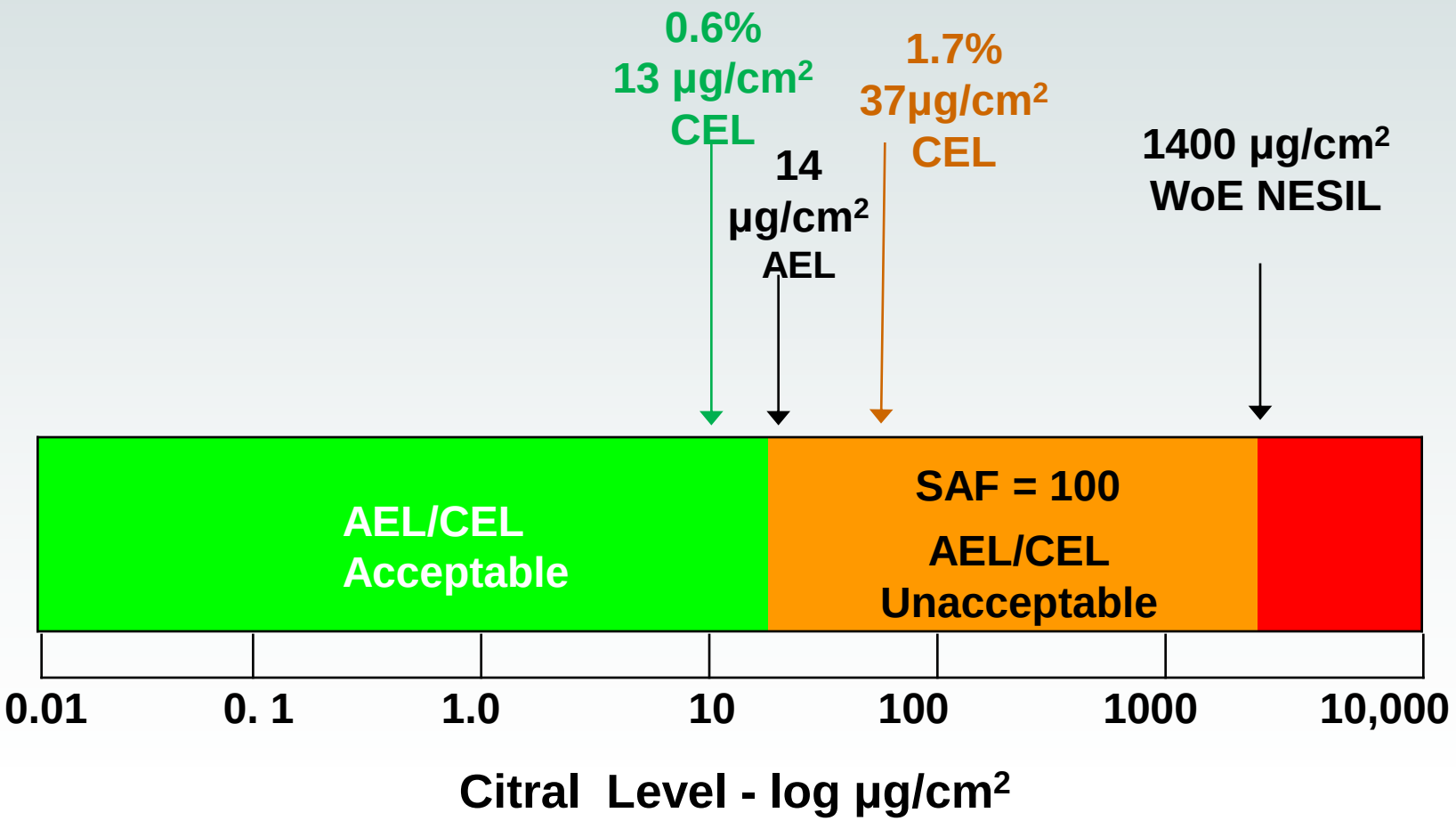
- Considerations
  - Inter-individual variability
  - Product matrix differences
  - Variations in use patterns
- Hydroalcoholic Unshaved SAF is 100
- Deo/AP SAF is 300

Exposure

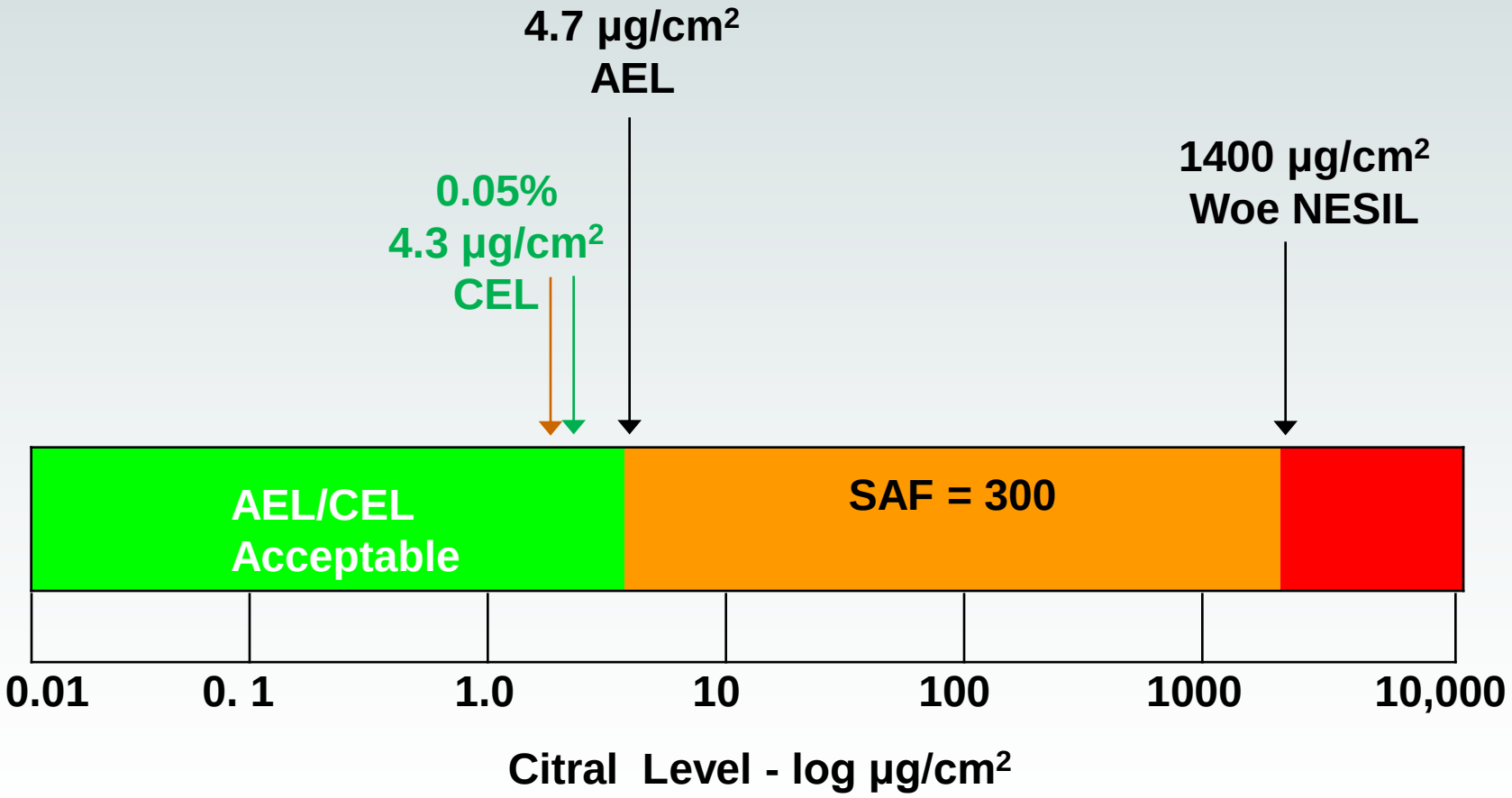
Consumer exposure to:

- Hydroalcoholic (unshaved skin) = 2.2 mg/cm^2
  - AEL = 1400/100 = 14.0 µg/cm^2
  - AEL/CEL (14.0 ug/cm^2 X 0.001 mg/µg) ÷ 2.2 mg/cm^2/day = 0.006
  - AEL≥CEL ≤ 0.6%
- DEO/AP = 9.1 mg/cm^2
  - AEL = 1400/300 = 4.7 µg/cm^2
  - AEL/CEL = 0.0005
  - AEL≥CEL ≤ 0.05%

QRA Dermal Sensitization - Citral: Hydroalcoholic Unshaved Skin - Induction



QRA Dermal Sensitization - Citral: Solid AP - Induction



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
  - only 2 existing Standards remain to be converted to a QRA based Standard
- 47th Amendment Spring 2013

Quantitative Risk Assessment for Dermal Sensitization Method

- Refinements and Benefits

Refinements to QRA

- **Exposure**
  - New exposure data (Hall, 2011) was considered.
  - RIFM sponsored work to investigate the effects of aggregate dermal exposure. This is also being incorporated into the methodology.
- **Acceptable Exposure Levels**
  - A more detailed explanation of AELs and how they are applied is being considered. There also is a need for more details on the pragmatic approach and a review of aspects of having high calculated values in (mainly) rinse-off products.
- **Retrospective analysis**
  - More analyses
- **Retail Consumer Products Only**
  - The method does not apply to occupational use of consumer products or consumer products that are covered by other regulations (e.g. medical devices, OTC drugs, drugs).

Benefits of QRA Method

- Lead with a scientifically rigorous strategy
- Major improvement over the former approach
  - addresses elements of exposure-based risk assessment - unique to induction of dermal sensitization
  - consistent with the principles of general toxicology risk assessment
- Risk management strategies
  - 10 different product categories for skin contact products.
  - Category 11 - non-skin or incidental skin contact products
- Exposure - key element of category determination
  - enables maintenance of relevant exposure and therefore safety

More Information

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