

DERMAL SENSITIZATION QUANTITATIVE RISK ASSESSMENT (QRA) FOR FRAGRANCE INGREDIENTS

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ABSTRACT

Some of the chemicals in common use today may have the potential to cause dermal sensitization. However, the fact that a chemical is a skin sensitizer does not mean it cannot be formulated into consumer products at safe levels. This is also the case for fragrance ingredients. Based on advances in our understanding of a range of factors associated with the induction of dermal sensitization, it is possible to conduct an exposure-based quantitative risk assessment (QRA) for induction of dermal sensitization to determine safe levels of fragrance ingredients in different consumer product types. Key steps of the quantitative risk assessment process are determination of benchmarks (No Expected Sensitization Induction Level or NESIL); application of sensitization assessment factors (SAF) and calculation of consumer exposure (CE) through product use. Using these parameters, an acceptable exposure level (AEL) can be calculated and compared with the consumer exposure level (CEL). The ratio of the AEL to CEL must be favorable to support the safe use of the skin sensitizer. This ratio must be calculated for the skin sensitizer in each product type. This poster provides an overview of the principles of exposure-based QRA as applied to fragrance ingredients and provides a practical example using a fragrance ingredient in different product types.

QRA FOR DERMAL SENSITIZATION

Application to induction of skin sensitization?— a threshold phenomenon

- Determine potential (hazard) to induce sensitization
 - Pre-clinical studies e.g. Guinea-Pig Test, Local Lymph Node Assay (LLNA)
 - Human data (historical)
 - Structure based predictive approach
- Dose response
 - Determine the No-Expected-Sensitization Induction-Level (NESIL) based on the Weight of Evidence (WoE)
 - Calculate Sensitization Assessment Factor (SAF)
- Exposure
 - Dose metric: expressed in Dose/Area
 - Understand consumer exposure in different product categories
 - How consumer are exposed to a material in terms of amount, duration and frequency
- Risk characterization
 - Acceptable exposure levels to fragrance ingredients that are dermal sensitizers can be determined in specific real life consumer product types

RISK CHARACTERIZATION

Calculation of Acceptable Exposure Level

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

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

AEL > CEL to be Acceptable

NESIL

NESIL DETERMINATION

- NESIL - No Expected Sensitization Induction Level
- Establishment of scientifically sound NESILs is key to conduct of this QRA methodology
 - Weight of evidence approach to use of data
 - Uses all of the available scientifically robust data
 - Can be derived from animal and human data
 - Identifies studies inappropriate for consideration
 - Expressed as dose/unit area (mg/cm²)
 - Guidelines established for NESIL determination

WoE NESIL GUIDELINES

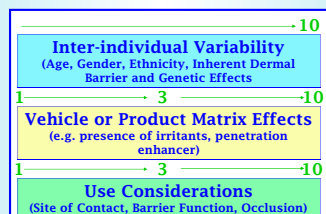
- Dose metric for exposure - dose/unit area
- Hierarchy of human data
 - NOEL from high quality HRIPT (published methodology, well-documented, at least 100 subjects) has precedence over NOELs from other human tests
- LOEL from historical clinical tests
 - If lower than NOEL from HRIPT will be considered
- Use of clinical data other than HRIPT
 - In absence of HRIPT NOEL other human NOEL will be used if supported by a well conducted LLNA
- Use of guinea-pig tests as secondary data sources
 - Adjuvant tests in animals and non-adjuvant tests in Guinea pigs are used as supporting information but not for NESIL derivation
- LLNA data only
 - In absence of suitable human data weighted average LLNA EC3 are used but should be confirmed in HRIPT
- Hierarchy of human versus animal data
 - HRIPT NOEL has precedence over higher NOELs from preclinical tests
- Diagnostic Patch Test data
 - Elicitation data are used as additional information and for support of current consumer exposure but not for NESIL derivation

SAF

SAF DEFINITION

- Sensitisation Assessment Factor (SAF)
- 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 SUMMARY

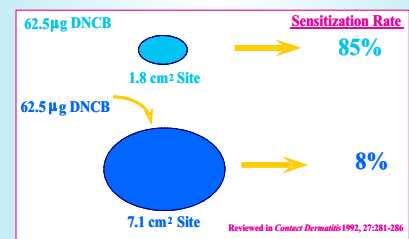


SOME SAF VALUES

Deodorants/Antiperspirants	300
Eye, Body Lotion, Shaving Cream and Men's Facial Products	300
Depilatories	300
Lip Products	300
Hydroalcohols Applied To Recently Shaved Skin	300
Toothpaste, Mouthwash	100
Hydroalcohols Applied To Unshaved Skin	100
Nail Enamel/Polish Remover, Women's Facial, Make-up Remover, Hair Sprays and Styling Aids, Leave-in Hair Conditioner Products	100
Rinse Off Products (Shampoo, Body Wash/Gels, Conditioner, Bar Soaps, Face Wash/Gel/Scrubs, Bath Gels, etc.)	100
Non-skin/Incidental Skin Contact Products	10

EXPOSURE

IMPORTANCE OF DOSE/UNIT AREA

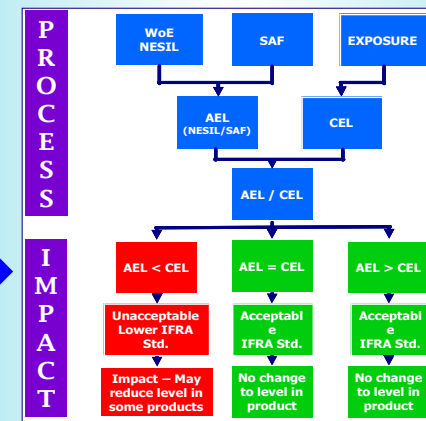


EXPOSURE DATA(DOSE/AREA)

Product Type	Exposure	
	Source	mg/cm ² /day
Deo/AP	CTFA	8.5
Hydroalcoholic, Unshaved	Cano & Rich*	2.2
Women's Facial Cream	Colipa	2.7
Women's Facial Make-up	CTFA	3.2
Eye Product	CTFA	2.2
Body Cream	Colipa	0.6
Men's Facial Cream	SCCP	2.1
Hair Sprays	CTFA	2.2
Hair Styling Aids	SCCP	1.0
Shampoo	CTFA	0.2
Body Wash/Gels	CTFA	0.02
Conditioner, rinse-off	CTFA	0.2
Shaving Cream/ Depilatory	SCCP	0.07
Lip Products	Colipa	11.7
Make-up Remover	SCCP	0.9
Nail Care	SCCP	1.0
Bar Soaps	SCCP	0.06
Face Washes, Gels, Scrubs	CTFA	0.2
Bath Gels, Foams, Mousses	SCCP	0.01
Toothpaste	Colipa	1.3
Mouthwash	SCCP	1.4

SUMMARY

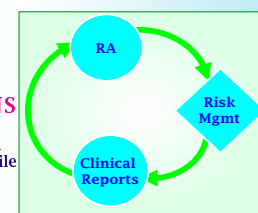
DERMAL QRA FOR FRAGRANCE INGREDIENTS SUMMARY



KEY CONCLUSIONS

- General risk assessment principles can be applied to contact allergy
- Following the identification of a fragrance ingredient as a potential skin sensitizer, a weight of evidence approach is used to determine a NESIL
- SAFs can and have been predefined for certain product types
- The metric of dose per unit area is used for induction of contact allergy
- QRA could be used both prospectively and retrospectively
- The use of QRA for fragrance ingredients will facilitate the establishment of IFRA Standards through better definition of product categories versus the current system of only two product categories (skin contact and non-skin contact).
- QRA can be used in combination with the clinical results from the dermatology community and company post-market surveillance data to confirm the effectiveness of fragrance ingredient use limits.

QRA DERMAL SENSITIZATION CYCLE



RECOMMENDATIONS FOR REFINEMENT

- Improved exposure data would be very worthwhile
- As more experience is gained with use of LLNA EC3 values as an indicator of human allergenic potency, its influence in WoE NESIL may be refined.
- Additional data (e.g. the influence of evaporation, of retention factors) may lead to SAF refinement.
- Aggregate exposure is an area where more evaluation is needed and more data may need to be generated.
- Occupational/professional exposure will be important to address in the future.

PRACTICAL EXAMPLE QRA FOR CITRAL

Weight of Evidence NESIL

- Guinea-pig data - weak sensitizer [30]
- Local Lymph Node Assay
 - EC₃ = 1414 µg/cm² [11]
- Human data
 - HRIPT NOEL = 1400 µg/cm²
 - Weight of Evidence NESIL = 1400 µg/cm²

SAF

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

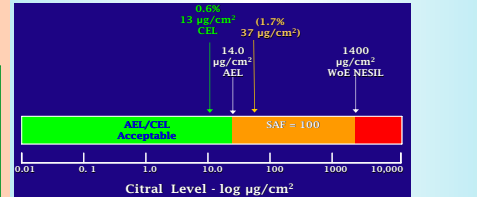
Exposure

- Calculation for Daily = [Amount of Citral in product x Amount product applied (mg)]/Surface area exposed (cm²)
- Consumer exposure
 - Hydroalcoholic (unshaved skin) = 0.6 % x 2.2 mg/cm² = 13 µg/cm²
 - Deo/AP = 0.04% x 8.5 mg/cm² = 4.6 µg/cm²

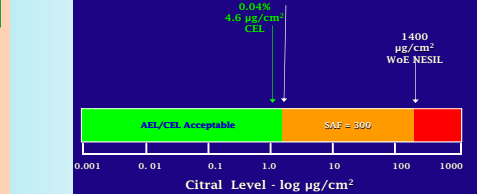
APPLICATION OF QRA TO USE OF CITRAL IN HYDROALCOHOLIC PRODUCTS FOR UNSHAVED SKIN AND IN SOLID ANTIPERSPIRANT PRODUCT TYPES

Citral	Hydroalcoholic Product for Unshaved Skin	Solid Antiperspirant
WoE NESIL	1400 µg/cm ²	1400 µg/cm ²
SAF (from Table 2)	100 (10 X 3 X 3)	300 (10 X 3 X 10)
AEL	14.0 µg/cm ²	4.7 µg/cm ²
CEL Product	2.2 mg/cm ² /day ¹	11.6 mg/cm ² /day ²
AEL/CEL	14.0 µg/cm ² / (14.0 µg/cm ² x 0.001 mg/µg) = 2.2 mg/cm ² /day = 0.0064	4.7 µg/cm ² / (4.7 µg/cm ² x 0.001 mg/µg) = 8.5 mg/cm ² /day = 0.0052
Concentration of citral in the product based on AEL ≥ CEL	≤ 0.64%	≤ 0.05%
Risk Assessment	Acceptable if citral level is less than 0.64%	Acceptable if citral level is less than 0.05%
IFRA Standard	No limit (quenching Standard)	No limit (quenching Standard)
Current Average Maximum Use Level	1.7% or 37.4 µg/cm ² /day	No data

QRA DERMAL SENSITIZATION CITRAL IN HYDROALCOHOLICS—UNSHAVED SKIN INDUCTION



QRA DERMAL SENSITIZATION CITRAL IN SOLID AP—INDUCTION



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