



# **Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients**

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**IDEA Workshop**

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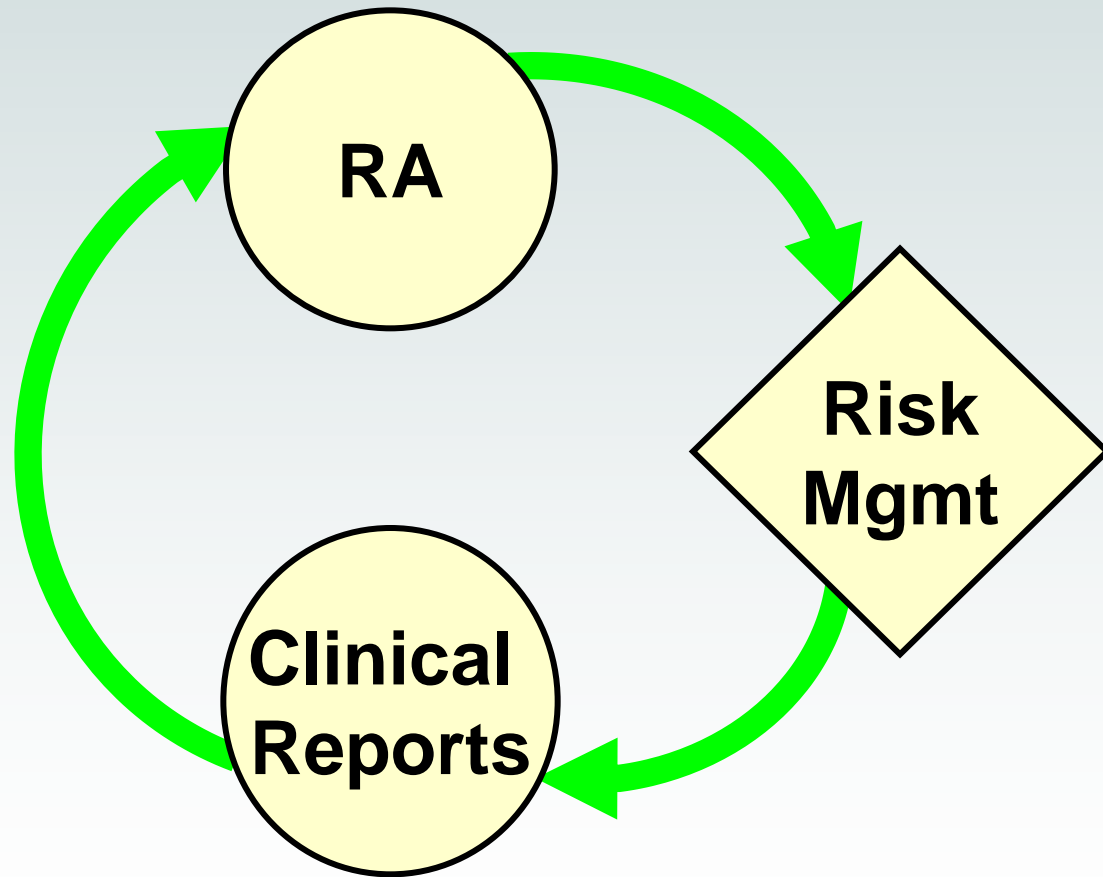
# Quantitative Risk Assessment for Dermal Sensitization Method

- **Does It Work?**

# QRA Dermal Sensitization: Does It Work?



- Evidence of proven effectiveness for other materials
- Need to build evidence in fragrance ingredients
  - Cinnamic aldehyde
  - Citral
  - Isoeugenol



# Cinnamic Aldehyde

- **Average Maximum Dermal Use level in hydroalcoholics 1% (IFRA, 1999); Decreased to 0.05% (IFRA, 2004)**
- **Clinical data**
  - **Johansen & Menne, 1995. Contact Dermatitis, 32:18-23**
    - From 1979-1983 to 1988-1992 a “highly significant reduction in the frequency of positive reactions” was found
  - **Buckley et al., 2000, Br. J. Derm., 142: 279-283**
    - 1980-1996; 25,545 patients
    - “..striking reduction in the frequency of sensitivity to CA (by 18% yearly;  $P < 0.001$ , 95% CI 14.3-21.0)...”
  - **Schnuch et al., 2007. Contact Dermatitis, 57:1-10**
    - January 2003- Dec. 2004; 2268 patients; decreasing frequency
  - **Warshaw et al., 2007. Dermatitis, in press**
    - 2003-2004; statistically less frequent than 1994-2002



# Isoeugenol

- **IFRA Standard 1980-1992 0.2%**
- **IFRA Standard 1998 0.02%**
- **Clinical Data**
  - **1980-1996, in the UK, frequency of sensitization increased Buckley et al., 2000, Br. J. Derm., 142: 279-283**
  - **Schnuch et al., 2004, Contact Dermatitis 50:65-76**
    - **FM: significant increase in patients with positive reactions between 1996 & 1998; a significant decline from 1999 to 2002**
    - **Isoeugenol: Same reactions rate with the exception of a peak in 1999**
  - **Schnuch et al., 2007, Contact Dermatitis 57:1-10**
    - **Isoeugenol: Decrease January 2003-December 2004**



# Mortz et al., 2012

## ● British Journal of Dermatology

- study followed school age children who were studied 15 years ago.
- Most notable is that in 1995, 11 children reacted positively to FM 1. However, 15 years later in 2010, none of the 11 reacted to FM 1. Two new reactions were observed to FM 1.
- Authors concluded that sensitization can become lower over the years, but it was difficult to explain.
- In the intervening 15 years, significant changes to the use of the materials in FM 1 have occurred. Perhaps this may account for the changes.



# QRA Dermal Sensitization

| <b>Fragrance Ingredient</b> | <b>Industry Survey or Limit Prior to QRA-based Standard</b> | <b>QRA –based Limit</b>        |
|-----------------------------|---|--------------------------------|
| <b>Cinnamic Aldehyde</b>    | <b>Skin level: 0.05%</b>                                    | <b>↓Deo/AP: 0.02%</b>          |
| <b>Citral</b>               | <b>Hydroalcoholics: 1.7%</b>                                | <b>↓Hydroalcoholics: 0.6%</b>  |
|                             | <b>Deo/AP: 0.05%</b>  | <b>Deo/AP: 0.05%</b>           |
| <b>Isoeugenol</b>           | <b>Skin level: 0.2%</b>                                     | <b>↓Hydroalcoholics: 0.02%</b> |

# Patch Test Database

## U. Hospital Leuven



- **RIFM sponsored surveys**
  - Identify product types containing specific fragrance ingredients
  - Number of positive clinical patch tests reactions
- **Period 2000-2005**
  - 3,323 patients, 9.1% (303) positive to Fragrance Mix
  - 133 exhibited positive patch test to their own cosmetic products
  - 66/133 fragrance-related contact allergic reactions
- **Period 2006 -2007**
  - 499 positive patch test to their own cosmetic products
  - 241/499 related to specific fragrance ingredients

Api et al, Dermatitis, 21(4): 207-213, 2010



# Database U. Hospital Leuven 2000-2007



| Fragrance Ingredient | Product Type           | Positive Patch Test Reactions to Product Confirmed & Not Confirmed |
|----------------------|------------------------|--|
| Cinnamic Aldehyde    | Deodorant              | 4  |
|                      | Intimate Hygiene Wipes | 1  |
|                      | Hair Care              | 1  |
| Citral               | Hydroalcoholic         | 9  |
|                      | Skin Care              | 2  |
|                      | Deodorant              | 1  |
| Isoeugenol           | Hydroalcoholic         | 14   |
|                      | Skin Care              | 4  |
|                      | Deodorant              | 2  |
|                      | Hair Dye               | 1  |

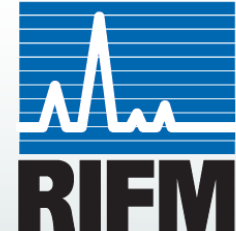
# Patch Test Database

## U. Hospital Leuven



- **Period 2008**
  - 537 positive patch test to their own cosmetic products
  - 297/537 related to specific fragrance ingredients
- **Period 2009**
  - 502 positive patch test to their own cosmetic products
  - 288/502 related to specific fragrance ingredients
- **Period 2010**
  - 473 positive patch test to their own cosmetic products
  - 254/473 related to specific fragrance ingredients
- **Period 2011**
  - 498 positive patch test to their own cosmetic products
  - 256/498 related to specific fragrance ingredients
- **Period 2012**
  - 539 positive patch test to their own cosmetic products
  - 273/539 related to specific fragrance ingredients

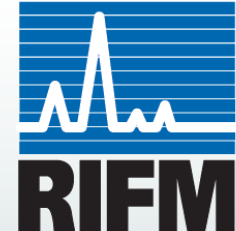
# Database U. Hospital Leuven 2008-2012



| Fragrance Ingredient           | Total Positive Patch Test Reactions to Product Confirmed & Not Confirmed |      |      |      |      |
|--------------------------------|--|------|------|------|------|
|                                | 2008   | 2009 | 2010 | 2011 | 2012 |
| Amyl Cinnamic Aldehyde (2007)  | 0  | 3    | 1    | 0    | 0    |
| Cinnamic Alcohol (2007/2008)   | 1  | 1    | 16*  | 0    | 2    |
| Cinnamic Aldehyde (2007/2008)  | 0  | 1    | 4    | 0    | 3    |
| Geraniol (2007)                | 8  | 8    | 7    | 0    | 2    |
| Hydroxycitronellal (2007/2008) | 1  | 6    | 5    | 0    | 3    |
| Eugenol (2007/2008)            | 0  | 3    | 11   | 3    | 0    |
| Isoeugenol (2007/2008)         | 1  | 1    | 2    | 0    | 0    |
| Oakmoss absolute (2008)        | 2  | 10   | 6    | 4    | 2    |

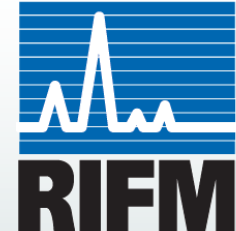
\*Most often linked to ketoprofen photosensitivity

# Database U. Hospital Leuven 2008-2012



| Fragrance Ingredient          |        | Total Positive Patch Test Reactions to Product Confirmed & Not Confirmed |      |      |      |      |
|-------------------------------|--------|--|------|------|------|------|
|                               |        | 2008   | 2009 | 2010 | 2011 | 2012 |
| HMPCC                         | (2007) | 12   | 20   | 24   | 5    | 5    |
| Citronellol                   | (2007) | 1  | 5    | 10   | 0    | 2    |
| Coumarin                      | (2008) | 0  | 0    | 1    | 1    | 1    |
| Farnesol                      | (2006) | 1  | 3    | 5    | 0    | 1    |
| $\alpha$ -Hexylcinnamaldehyde | (2007) | 0  | 13   | 8    | 0    | 4    |
| Citral                        | (2006) | 2  | 0    | 1    | 0    | 9    |

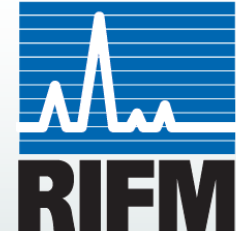
# Database U. Hospital Leuven 2008-2012



| Fragrance Ingredient           | Total Positive Patch Test Reactions to Product Confirmed |      |      |      |      |
|--------------------------------|--|------|------|------|------|
|                                | 2008   | 2009 | 2010 | 2011 | 2012 |
| Amyl Cinnamic Aldehyde (2007)  | 0  | 1    | 0    | 1    | 0    |
| Cinnamic Alcohol (2007/2008)   | 1  | 0    | 4*   | 0    | 2    |
| Cinnamic Aldehyde (2007/2008)  | 0  | 0    | 1    | 0    | 1    |
| Geraniol (2007)                | 8  | 4    | 4    | 0    | 2    |
| Hydroxycitronellal (2007/2008) | 1  | 4    | 2    | 0    | 0    |
| Eugenol (2007/2008)            | 0  | 0    | 2    | 3    | 0    |
| Isoeugenol (2007/2008)         | 1  | 0    | 0    | 0    | 0    |
| Oakmoss absolute (2008)        | 0  | 2    | 2    | 0    | 0    |

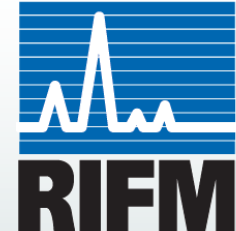
\*Most often linked to ketoprofen photosensitivity

# Database U. Hospital Leuven 2008-2012



| Fragrance Ingredient          |        | Total Positive Patch Test Reactions to Product Confirmed |      |      |      |      |
|-------------------------------|--------|--|------|------|------|------|
|                               |        | 2008   | 2009 | 2010 | 2011 | 2012 |
| HMPCC                         | (2007) | 12   | 12   | 13   | 5    | 5    |
| Citronellol                   | (2007) | 1  | 3    | 2    | 0    | 2    |
| Coumarin                      | (2008) | 0  | 0    | 0    | 1    | 1    |
| Farnesol                      | (2006) | 1  | 2    | 1    | 0    | 1    |
| $\alpha$ -Hexylcinnamaldehyde | (2007) | 0  | 10   | 5    | 0    | 4    |
| Citral                        | (2006) | 2  | 0    | 1    | 0    | 9    |

# Database U. Hospital Leuven 2011-2012



| Fragrance Ingredient          | Product Type        | Positive Patch Test Reactions to Product Confirmed |        |
|-------------------------------|---------------------|--|--------|
| <b>Amyl Cinnamic Aldehyde</b> | Shaving product     | 1  | (2011) |
| <b>Cinnamic Alcohol</b>       | Cleansing Product   | 1  | (2012) |
|                               | Hair Care & Shampoo | 1  | (2012) |
| <b>Cinnamic Aldehyde</b>      | Skin Care           | 1  | (2012) |
| <b>Geraniol</b>               | Skin Care           | 1  | (2012) |
| <b>HMPCC</b>                  | Hydroalcoholic      | 1  | (2012) |
|                               | Bath/Shower         | 1  | (2012) |
|                               | Skin Care           | 1  | (2012) |
|                               | Sun                 | 1  | (2012) |
|                               | Deo                 | 1  | (2012) |

# Database U. Hospital Leuven 2011-2012



| <b>Fragrance Ingredient</b>                    | <b>Product Type</b> | <b>Positive Patch Test Reactions to Product Confirmed</b> |        |
|--|---------------------|---|--------|
| <b>Citronellol</b>                             | Deo                 | 2   | (2012) |
| <b>Coumarin</b>                                | Sun                 | 1   | (2011) |
|  | Skin Care           | 1   | (2012) |
| <b>Farnesol</b>                                | Deo                 | 1   | (2012) |
| <b>Eugenol</b>                                 | Hydroalcoholic      | 1   | (2011) |
|  | Sun                 | 2   | (2011) |
| <b><math>\alpha</math>-Hexylcinnamaldehyde</b> | Shaving Products    | 1   | (2012) |
|  | Bath/Shower         | 1   | (2012) |
|  | Deo                 | 2   | (2012) |



# Database U. Hospital Leuven 2011-2012



| Fragrance Ingredient | Product Type      | Positive Patch Test Reactions to Product Confirmed |        |
|----------------------|-------------------|--|--------|
| <b>Citral</b>        | Bath/Shower       | 4  | (2012) |
|                      | Cleansing Product | 1  | (2012) |
|                      | Hair/Shampoo      | 1  | (2012) |
|                      | Deo               | 1  | (2012) |
|                      | Skin Care         | 2  | (2012) |

# Challenges in Measuring QRA Effectiveness



- **IFRA Standards based on the QRA only applies to consumer products**
- **Other exposures may influence prevalence (e.g. popularity of “natural” remedies, aromatherapy, etc.)**
- **Time of acquisition of allergy may be many years so the delay in effect may be long**

# Challenges in Measuring QRA Effectiveness



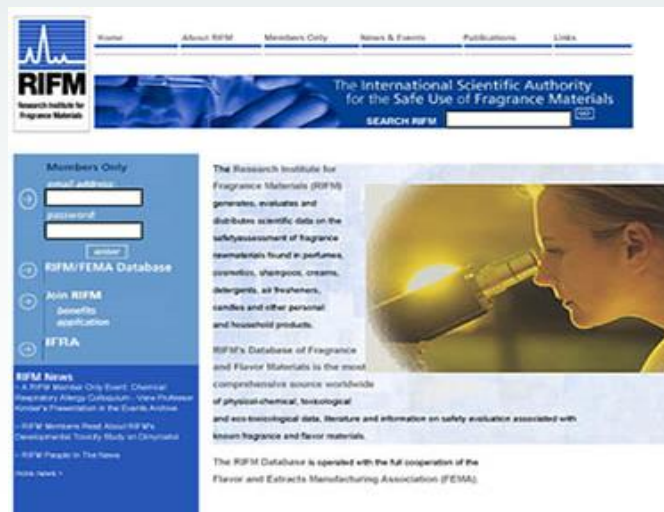
- QRA levels effectiveness needs to be checked in multiple product categories
- Need information on clinically relevant reactions specific to product type
- How do we determine if the product caused the reaction?
- How do we determine what the level of the fragrance ingredient in the product (e.g. is the product an old one with an old level of the IFRA Standard)?
- How can we proceed?

# More Information



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safety/assessment of fragrance  
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lotions, soaps, detergents, air fresheners,  
candles and other personal  
and household products.

RIFM's Database of Fragrance  
and Flavor Materials is the most  
comprehensive source worldwide  
of physical chemical, toxicological  
and eco-toxicological data, literature and information on safety evaluation associated with  
known fragrance and flavor materials.

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