Reduction of Fragrance Contact Allergy

- Where we were
- Where we are
- Where we need to be

Ian R. White
Conflicts

• Self-funding
  • No honoraria
  • No travel grants
  • No expenses
  • No unrestricted grants
  • No educational grants
  • No research grants
  • No payments via third parties
  • No gifts
Where we were: a brief history
ESCD Congress 1996

- No cosmetic ingredient labelling
- No fragrance ingredient labelling
- Fragrance mix (I) Larsen
- balsam of Peru
- HICC not on market
1996 ESCD Fragrance Symposium

• Industry
  – Our industry has focused its attention on reducing the causes of allergy in the not-yet-sensitized.
  
  – Clinical dermatology has concentrated on the elicitation of reactions in the already sensitized.
  
  – The fragrance industry could attribute more importance not only to the inducers (of contact allergy) but also to the most frequent elicitors....
  
  – The fragrance industry is concerned about this problem and is willing to cooperate with dermatologists in this extremely complex and technically difficult area.
1996 ESCD Fragrance Symposium

• Ian R White
  – The fragrance industry has maintained a protectionist stance ...... out of tune with the ethos of the consumer’s right to know and need to be protected…..
  
  – A ‘think tank’ has been set up consisting of a balanced representation of dermatologists, fragrance-compound manufacturers and users to address aspects of the ‘problems’ and ‘needs’.
  
  – It is hoped that with goodwill and sincerity discussions will take place which will answer the present difficulties and provide better understanding and protection for the consumer.
Substances for labelling
SCCNFP/0017/98 adopted December 1999

- Critical review of fragrance allergy in consumer
- Identification of (simple chemical) ingredients well recognised as consumer allergens
- Dose / elicitation
Fragrance allergens and INCI labelling:
Cosmetics Directive 7th amendment (now Regulation)
a secondary preventative measure

• amyl cinnamal
• cinnamyl alcohol
• cinnamal
• *Evernia prunastri/Evernia furfuracea*
• eugenol
• geraniol
• hydroxycitronellal
• iso Eugenol
• coumarin
• hydroxyisohexyl 3-cyclohexene carboxaldehyde
• d-limonene
• butylphenyl methylpropional
• citral
• amylcinnamyl alcohol
• benzyl alcohol
• benzyl salicylate
• anise alcohol
• benzyl benzoate
• benzyl cinnamate
• citronellol
• farnesol
• hexyl cinnamal
• linalool
• methyl 2-octynoate
• α-isomethyl ionone

• regulatory responses
  – Labelling
  • 10ppm leave-on
  • 100ppm rinse-off
Meanwhile....SCCS Opinions

- HydroxyisoHexyl 3-cyclohexene carboxaldehyde
- *Evernia prunastri* (oakmoss)
- Linalool
- ‘Quenching’
Understanding fragrance allergy using an exposure-based risk assessment approach

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Conducting a sound skin sensitization risk assessment prior to the introduction of new ingredients and products into the market place is essential. The process by which low-molecular-weight chemicals induce and elicit skin sensitization is dependent on many factors, including the ability of the chemical to penetrate the skin, react with protein, and trigger a cell-mediated immune response. Based on our chemical, cellular and molecular understanding of allergic contact dermatitis, it is possible to carry out a quantitative risk assessment. Specifically, by estimating the exposure to the allergen and its allergenic potency, it is feasible to assess quantitatively the sensitization risk of an ingredient in a particular product type. This paper focuses on applying exposure-based risk assessment tools to understanding fragrance allergy for 2 hypothetical products containing the fragrance allergen cinnamic aldehyde. The risk assessment process predicts that an eau de toilette leave-on product containing 1000 ppm or more cinnamic aldehyde would pose an unacceptable risk of induction of skin sensitization, while a shampoo, containing the same level of cinnamic aldehyde, would pose an acceptable risk of induction of skin sensitization, based on limited exposure to the ingredient from a rinse-off product application.

Key words: skin; allergic contact sensitization; fragrances; exposure; potency; risk assessment; margin of safety. © Munksgaard, 2001.

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Determine human experimental threshold (HRIPT) in µg/cm² (e.g. via LLNA EC3)

Apply 1-10x safety factor for human variability

Apply 1-10x safety factor for vehicle matrix

Apply 1-10x safety factor for exposure variables

Acceptable exposure level (µg/cm²) is compared to expected level (µg/cm²)

QRA schema – Quantitative Risk Assessment

Originates from the Fragrance ‘think tank’, late 20th century
Quantitative Risk Assessment (QRA)

- Substance exposure: $x \mu g/cm^2$
- Consumer exposure: $z \mu g/cm^2$
- AEL
- NOEL: $y \mu g/cm^2$

substance exposure - log $\mu g/cm^2$
Fragrance QRA - based on general principles of toxicology but....

- The dermal sensitization QRA is a **theoretical model** and no validation has been done nor is a strategy for validation proposed;
- Unknown if levels identified are safe for the consumer;
- For established fragrance allergens causing allergy in the consumer, clinical and epidemiological data must be used as the critical decision point in risk assessment.
- Does not consider the protection of consumers who have already been sensitized;
- Does not cover population with skin disease without prior sensitization to fragrance ingredients;
- Allergen load of structurally similar substances is not considered;
- Aggregated exposures from different products (including occupational exposures) are not considered.
The need for change

• QRA is an **untested** model that remains untested despite ardent promotion

• If the industry standards have worked, why have so many people become sensitized and continue to do so?
Where are we now?
Fragrance allergens: 2012 SCCS Opinion
*(precipitator for IDEA project)*

- Review of clinical manifestations
- Epidemiology
- Role of skin metabolism
- Oxidation
- Review of allergens in current list
- Add new allergens, esters, oxidised forms
Established fragrance allergens in man  
(from 2012 SCCS Opinion)

• **Simple chemicals**  
  – 54 (12 high risk)

• **Natural extracts**  
  – 28 (8 high risk)

In general:  
0.8 µg/cm² or 0.01% in cosmetic products may be considered safe  
(in absence of specific information)
Oxidation & metabolism

pre- & pro-hapten Geraniol

pre-hapten Cinnamyl alcohol

A-T Karlsberg et al
The IDEA project
(International Dialogue for the Evaluation of Allergens)

- Designed to provide a broadly agreed and transparent framework for assessing fragrance sensitizers globally.

- An opportunity to build partnerships between the fragrance industry and stakeholders to improve the risk assessment of those fragrance ingredients identified as allergens for better consumer protection.

- The IDEA work plan, endorsed by EU Commissioner for Health, is a roadmap designed to achieve the goals.

- IDEA consists of workshops bringing scientists together to reach consensus on improving existing methodologies.
  - Recommendations made at the workshop are then followed up by industry or in research projects.
  - Annual public Review under the auspices of DG SANCO (European Commission).
Definitions for the purposes of IDEA
(Workshop August 27-29, 2013)

• A contact allergen is a substance that is capable of inducing delayed type sensitisation in humans, which may manifest as allergic contact dermatitis.

• The elicitation of allergic contact dermatitis requires sufficient exposure and is subject to significant inter-individual variability.

• Contact allergy may be induced by skin contact with low molecular weight haptens and may evolve into allergic contact dermatitis if the exposure exceeds the individual threshold in sensitized individuals.

• Contact allergy is demonstrated by a positive patch test and identifies the population at risk of developing allergic contact dermatitis.
Diagnostic patch test data

• Test fits the criteria for which it has been designed, to be sensitive and specific as a diagnostic tool

• Relevance of a positive patch test for an individual patient is a matter for the dermatologist investigating the patient

• First indication that exposure to a substance is causing allergy in the population

• Means to compare the relative importance of contact allergens in terms of the frequency of reactions

• Allows following contact allergy trends over time

• Does not prove what exposures caused the induction of contact allergy

• Does not give any dose-response information

• Does not inform on what types of exposure may be tolerated, either for induction or elicitation

• Informs those who produce and/or use the substance that:
  • it is a skin sensitiser
  • a potential cause of contact allergy
  • and therefore of allergic contact dermatitis
QRA 2 flowchart (includes aggregate exposure)

1. Hazard Characterization

Determine sensitization potential – *in silico, in vitro*, animal & human studies, chemistry, QSAR,

Non-sensitizer

Sensitizer

2. Dose Response or Hazard Quantification

Determine sensitization potency

Conduct confirmatory HRIPT

Determine Weight of Evidence No Expected Sensitization Induction Level (Woe NESIL)

Include SAFs for:
- Inter-individual variability
- Product
- Frequency/duration of use
- Occlusion
- Skin condition/site

Determine overall Sensitization Assessment Factor (Overall SAF)

3. Exposure Assessment

Calculate Acceptable Exposure Level (AEL) = Woe NESIL/Overall SAF

Not acceptable AEL:CEL < 1

Calculate AEL:CEL ratio

Acceptable AEL:CEL ≥ 1

4. Risk Characterization

Determine Consumer Exposure Level (CEL) and the aggregate exposure CEL for body sites (Clang)

Non QRA required
Determine human experimental threshold (HRIPT) in µg/cm² (e.g., via LLNA EC3)

Apply 10x safety factor for human variability

Apply 0.3-3x safety factor for product matrix

Apply 1-3x safety factor for use frequency

Apply 1-10x factor for skin condition

Acceptable exposure level (µg/cm²) is compared to aggregate exposure level (µg/cm²)

This approach encompasses skin types and conditions found in the general population.
Where do we need to be?
Studies (1): Effectiveness of QRA 2
(subject to participation of clinics)

- Retrospective studies problematic
  - Need for accurate baseline data for prevalence to assess effectiveness of QRA and develop procedure for clinical alerts

- Common protocol
  - Fragrance mixes I & II, 14 individual ingredients, *Evernia furfuracea*, oxidised linalool and oxidised limonene
  - Other substances, routine testing of ‘blocks’

- Detailed information on exposures etc

- Primary readout is prevalence of contact allergy (endpoint of concern)
  - Secondary readout is prevalence of allergic contact dermatitis
Consumer exposure

- **Risk assessment & management**
  - hazard x exposure = risk
    - is it an allergen? Potency
    - how exposed? Dose
    - QRA 2..... ‘safe consumer exposure’

- **Clinical epidemiology**
  - what is actually happening?

- Risk to human health must be rigorously assessed and properly managed
Studies (2): Effectiveness of QRA 2
(subject to participation of industry)

– New fragrance chemicals entering market
  • No prior consumer exposures
  • QRA 2 analysis and consumer then exposed based on QRA 2-predicted safe levels

– Industry advises on exposure potential
  • Baseline patch test studies on naïve population
  • Patch tests studies over time to monitor levels of contact allergy

– Feedback into and modification of QRA 2, as necessary
Collaborating departments required

- Fragrance mixes I & II, 14 individual ingredients, *Evernia furfuracea*, oxidised linalool and oxidised limonene

- Monitor novel substances