IDEA Annual Review

Characterisation and Categorisation of Allergens

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Objectives

- To lay the foundation for an allergen characterisation and categorisation procedure which feeds risk management steps towards reduction of allergic contact dermatitis and which can be subject to continuous review, correlation and improvement.

Definition of a Contact Allergen for the purposes of IDEA
(Workshop August 27-29, 2013)

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- 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.

Relationship between Contact Allergy and Allergic Contact Dermatitis

- 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.

Clinical relevance of a contact allergy in relation to dermatitis

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- Current
  - Exposure to the allergen is causing the dermatitis
- Old (past)
  - Exposure to the allergen caused a past dermatitis
- Unknown
  - No obvious history of exposure or related dermatitis but there must have been exposure to have induced allergy

Knowledge about allergic contact dermatitis

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- Clinical case reports
- Clinical studies of patient groups
- Statistical compilation of patch test reports
- Studies of small outbreaks of dermatitis

Dose-response thresholds

- Important to consider both for induction and elicitation
- In general, more individuals will become sensitised with higher doses or repeated lower doses (exposure)
- Similarly for elicitation reactions (allergic contact dermatitis)

Diagnostic patch testing

- Standardised; ‘gold standard’ to determine presence of contact allergy
- ESCD drafting new guidelines
- Patch test concentrations should cause minimum of irritant/doubtful reactions (few false positives) and a maximum of allergic reactions (few false negatives)
- For fragrance substances, evidence that Finn Chamber technique is better than TRUE Test

Baseline indicators for fragrance allergy

- Fragrance mix I (*Evernia prunastri*, isoeugenol, cinnamal, cinnamyl alcohol, eugenol, hydroxycitronellal, geraniol, amyl cinnamal)
- Fragrance mix II (HICC, citral, farnesol, citronellol, hexyl cinnamal, coumarin)
- *Myroxylon pereirae* (Balsam of Peru)

How many patients have contact allergy to the baseline indicators?

- Denmark (Gentofte):
  - Fragrance mix I: 8%
  - Fragrance mix II: 5%
  - *Myroxylon pereirae*: 4%
  - HICC: 2%

- Germany (IVDK); Fragrance mix I, standardised for age, sex
  - 2005-2008: 6.58%
  - 2010: 7.4%
  - 2011: 8.1%
  - 2012: 9.1%
  - 2013: 8.8%

Perfumes are mixtures

- Such mixtures of allergens reflect normal consumer exposure
  - May contain up to 12 labelled fragrance allergens
  - Deodorants, scented lotions, fine fragrances, aftershaves….
- In animal experiments it has been shown that mixtures may enhance induction and elicitation

Exposure

- Dose required for induction of contact allergy is (usually) higher than required for elicitation of allergic reaction (dermatitis);
- Consumer exposure should be such as to prevent induction of contact allergy (**primary prevention**);
- **Secondary prevention** is protecting sensitized group from developing elicitation reactions (dermatitis);

- To date, only available method to achieve above has been restrictions based on elicitation data;
- In future, scientifically valid and applied QRA may be used

Agreed Conclusions (1)

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- Properly conducted patch tests are the ‘gold standard’ for the clinical detection of contact allergy;
- Positive patch tests are the indication that exposure to a substance is causing contact allergy with a risk of allergic contact dermatitis and should trigger a re-evaluation of the risk;
- Epidemiological evaluation of patch test results allow a compilation of the relative importance of contact allergens in terms of frequency of reaction and indicate contact allergy trends over time;
- Positive patch test data represent the relevant endpoint in humans and are core data which assist in making decisions for preventive strategies in public health.

Proposal for additional conclusion (1a)

- Exposure information is crucial for diagnosing contact allergy and allergic contact dermatitis, for advising patients and for prevention. The most important source of exposure information concerning cosmetic products is ingredient labelling.

Methods to determine sensitisation potential

- Previously:
  - Local lymph node assay (LLNA)
  - Guinea pig maximisation test (GPMT)

- Now:
  - *in silico*
  - *in vitro / in chemico* methods
  - OECD Integrated Approach to Testing and Assessment
  - Hazard identification but not potency assessment

Agreed Conclusion (2)

- Non-clinical methods including non-animal approaches (e.g. those with OECD guidelines) have the potential to allow for the identification of a contact allergens. However non-animal test systems require further refinement for characterisation and categorisation

Characterisation and categorisation

- For allergic hazard potential, ‘sensitivity’ is:
  - Clinical diagnostic capability > limit of predictive toxicology > regulatory limits

- Regulatory classification:
  - Sensitiser/not classified
  - Extreme/strong/moderate/weak/very weak/non-sensitiser
  - CLP, ECHA, SCCS, GHS

Genetic factors

- Normal (Gaussian) distribution of reactivity in humans;
- Polysensitisation can be regarded as a clinical sign of increased susceptibility;
- (increasing age may be a risk factor for polysensitisation);

- **Whatever the influence of genetic susceptibility on sensitization, the relative influence is considerably lower than exposure (dose) and sensitizing potency of an allergen**

Agreed Conclusion (3)

- The role of genetic factors in susceptibility to contact allergy is yet to be defined

Improving dialogue between industry and dermatological community

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- Industry → Dermatologists: provide reference materials to help diagnosis of contact dermatitis
- Dermatologists → Industry: provide results of clinical testing as feedback into risk assessment/management process

- Full ingredient labelling seen as essential by dermatological community…
- In absence, requirement to develop strategy to inform consumer of presence of non-labelled fragrance substances to which they have contact allergy

Agreed Conclusion (4)

- Readily accessible product ingredient information including labelling is critical for evaluating exposure, reliable diagnosis and prevention.

Break out reports (1)

- Studies
  - 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

Break out reports (2)

- Suggested criteria for ranking relative concern of fragrance allergens:
  - **Major**: many reported cases (100), or few reported cases (10) where low exposure, or some severe cases;
  - **Potentially major**: cases but no existing epidemiological survey; non-clinical data indicates a risk;
  - **Moderate**: more than minor but does not fit criteria for major;
  - **Minor**: isolated sporadic cases where there is large/frequent exposure and epidemiological data demonstrates rarity;
  - No current concern.

Break out reports (3)

- Communication
  - Ingredient labelling is central to providing consumer (patient) a means to avoid future exposures that may elicit dermatitis;
  - Ingredient information must be available at time of assessment; ‘apps’ and similar digital resources are considered important supportive systems.
  - Key to monitoring safety is good feedback from clinician/patient and industry

Overall discussion (1)

- Risks to human health presented by contact allergens must be rigorously assessed and properly managed;
- Patch testing is sensitive and specific as a diagnostic tool;
- Relevance is a matter for the clinician investigating the patient;
- A positive patch tests is first indication that exposure to a substance is causing allergy in population;
- Data from individual clinics is a means to compare relative importance of contact allergens;
- Exposure information is crucial for diagnosing contact allergy and allergic contact dermatitis

Overall discussion (2)

- QRA must be evaluated by its impact in minimising frequency of contact allergy;
- Classification and potency sub-categorisation is useful for prioritizing work but does not substitute for primary and secondary prevention strategies;
- Studies are now required to examine effectiveness of QRA;
- Monitoring and evaluation should be independent.

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Thank you very much for your attention