Understanding contact hypersensitivity: from mechanism to risk assessment

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• Contact hypersensitivity: the problem and the current animal models
• Mechanistic understanding of ACD and the development of in vitro models

ACD, Allergic Contact Dermatitis
• The two most frequent manifestation of chemical-induced allergy are contact hypersensitivity and respiratory sensitization.

• Epidemiological studies suggest that the prevalence of contact allergy is ~15-20% (e.g. Peiser et al., 2012), making hypersensitivity reactions a major health problem in relation to environmental chemical exposure.

→ As a consequence chemical allergy is of considerable importance to the toxicologist, whom has the responsibility of identifying and characterizing the skin and respiratory potential of chemicals, and estimating the risk they pose to human health.

→ Regulatory authorities worldwide require testing for allergic contact dermatitis (ACD) and appropriate hazard labeling to minimize exposures.
Contact allergy to markers of cosmetic allergy over the 25 years in the USA

MDGN, Methylidibromo glutaronitrile
MCI/MI Methylchloroisothiazolinone / methylisothiazolinone (preservatives)

Basketter and Corsini, Cosmetics, 2016
Hypersensitivity: in vivo models

- Well established methods for contact and respiratory hypersensitivity
- Current models and assays as inadequate predictors for systemic hypersensitivity reaction

- **Guinea Pig Tests**
  - Maximization Test
  - Occlusive Patch Test
  - Respiratory Challenge
  - Systemic Anaphylaxis

- **Mouse Tests**
  - *Local lymph node assay*
  - Mouse Ear Swelling Test
The challenge is how to obtain the same quality of information using in silico or in vitro methods.

<table>
<thead>
<tr>
<th>Category</th>
<th>Classification Criteria</th>
<th>LLNA EC3</th>
<th>Human Evidence (HRIP or HMT)</th>
<th>GPMT Response</th>
<th>BT Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Skin sensitizer</td>
<td>Evidence that skin sensitization occurs in a substantial number of people, or positive results from an appropriate animal test.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1A: Slight skin sensitizer</td>
<td></td>
<td></td>
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<tr>
<td>1B: Other skin sensitizers</td>
<td>Low to moderate frequency of occurrence in humans, and/or low to moderate potency in animals. May consider severity.</td>
<td>&gt;2%</td>
<td>Positive^{2} response at &gt;500 mg/cm^{2}</td>
<td>≥30% to &lt;60% responders at &gt;0.1% to ≤1% intradermal induction dose or ≥30% responders at &gt;1% intradermal induction dose</td>
<td>≥15% to &lt; 60% responders at &gt;0.2% to ≤20% topical induction dose or ≥15% at &gt;20% topical induction dose</td>
</tr>
</tbody>
</table>

Abbreviations: BT = Buehler test; CPSC = U.S. Consumer Product Safety Commission; GPMT = guinea pig maximization test; HMT = human maximization test; HRIP = human repeat insult patch test; LLNA EC3 = estimated substance concentration that produces a stimulation index of 3 in the murine local lymph node assay; NA = not applicable.

^{1}Human evidence can also include diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure or other epidemiology evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

^{2}Human evidence can also include diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure or other epidemiology evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.
Four goals have been identified for a full replacement of skin sensitization animal data:

1. Hazard identification: prediction of potential sensitizer (yes/no answer)
2. Classification and labeling (i.e. GHS, EU-CLP): more than yes/no answer, i.e. some potency determination
3. Hazard characterization: prediction of sensitizer and its potency, i.e. non-sensitizer, weak, moderate, strong, extreme (dose-response information)

**Potency is important as:**

1. Potency data can lead to improvements in hazard classification and so risk management
2. Potency data can facilitate improved risk assessment for skin sensitization

**DEFINITION**

- **Allergic contact dermatitis** (ACD) is a cell-mediated immune response to small molecular weight chemicals that contact and penetrate the skin.

- There are a variety of **characteristics** that determine whether a chemical can function as a contact sensitizer (or allergen):
  - ability to penetrate into the skin
  - reactivity with protein
  - epidermal and dermal inflammation
  - dendritic cell activation, migration to lymph nodes and recognition as antigenic by T cells.

*E. Corsini et al. / Food and Chemical Toxicology 61 (2013) 74–81*
SECRETED
IL-1β,
IL-18, IL-33

 CONTACT ALLERGENS

 Oxidation of cell surface thiols

 Oxidative/electrophil stress

 GSH depletion

 Danger signals production

 DAMPs

 TLR 2/4

 TRAF6

 DC migration

 PKC

 NADPH oxidase

 P

 Activation of caspase-1

 ASC

 NLRP3

 Pro-IL-1β
 pro-IL-18
 Pro-IL-33

 Neosynthesis

 NF-κB
 Akt/ASK1

 SAPK/JNK,
 ERK, p38

 Keap1-Nrf2

 Co-stimulatory molecules, cytokines, chemokines,

 Phase 2 detoxifying genes

 (HMOX1, NQO1)

 uced DC/KC activation.

 E. Corsini et al. / Food and Chemical Toxicology 61 (2013) 74–81
VALIDATE METHODS AND OECD
- DPRA (OECD TG442C)
- Keratinosens (OECD TG442D)
- hCLAT (OECD approved)
- IL-8 Luc Assay (draft)
- Lusens (draft)
Development of alternative in vitro test

In vivo toxicity
(i.e. contact hypersensitivity)

Validation

Early-validation

OPTIMIZATION

TEST

VALIDATED TEST

REGULATORY ACCEPTANCE

In vitro model
WHAT WE HAVE ACHIEVED AND WHAT WE NEED

- We have in vitro methods to support the discrimination between skin sensitizers (i.e. UN GHS Category 1) and non-sensitizers in combination with other complementary information (i.e. in the context of an IATA).

- Depending on the regulatory framework, positive results may be used on their own to classify a chemical to UN GHS Category 1.

- They cannot be used on their own to sub-categorize skin sensitizers into UN GHS subcategories 1A and 1B or to predict potency for safety assessment decisions.

To achieve a complete replacement of animals in skin sensitisation assessment, currently validated methods are useful for hazard identification, classification and labelling.

Currently validated methods are necessary. IATA = Integrated Approaches to Testing and Assessment
Several in vitro methods to assess contact hypersensitivity are available.

Five methods have been successfully validated.

**GAPs:** bioavailability information (extrapolation of in vitro concentration to in vivo dose), applicability domains (solubility, metabolism, chemistry, respiratory allergens, mixtures, biologicals), potency.

The identification of the mechanisms influencing the vigor of T cell responses, that can explain the strength of contact hypersensitivity reactions to weak, moderate, strong, and extreme sensitizers is a challenge still to be solved.

A reduction of allergic contact dermatitis (ACD) can be achieved by:

- correct detection of skin sensitizers;
- characterization of potency;
- understanding of human skin exposure;
- application of adequate risk assessment and management strategies.
How to make contact allergy history:

- by improved risk assessment
- better education of risk assessors
- better education of consumers on the proper use of products
- better marketing surveillance by authorities to control proper product safety evaluation
THANK YOU FOR YOUR ATTENTION

QUESTIONS?
QRA is based on

1. Hazard identification: Determination of the No Expected Induction Sensitization Level (NESIL)

2. Application of Sensitization Assessment Factors (SAF 10-1000)

3. Determination of the Acceptable Exposure Level (AEL): \[ AEL = \frac{\text{NESIL}}{\text{SAF}} \]

4. Determination of Consumer Exposure Level (CEL)

5. Acceptable Risk: \( AEL > CEL \) or \( \frac{AEL}{CEL} \) ratio > 1

6. Risk management (e.g. allergy warning labels)