Evaluation of Next-Generation Risk Assessment (NGRA) Approach for Skin Allergy using four ingredients and two product exposure scenarios

Evita Vandenbossche, Maria Baltazar, James Butcher, Richard Cubberley, Nicola Gilmour, Cameron MacKay, Ruth Penlington, Joe Reynolds & Gavin Maxwell
SEAC, Unilever, Colworth Science Park, Sharnbrook, Bedford, UK, MK44 1LQ

Abstract No. P13-05

Our aim is to apply mechanistic and clinical understanding to develop a risk assessment approach for skin allergy that doesn’t require new animal test data, addresses novel exposure scenarios and better characterises uncertainty.

The Integrated Strategy for Skin Allergy Risk Assessment (SARA) is a model-based approach designed to estimate the risk of inducing sensitisation to a product ingredient within a consumer population. The approach uses a probabilistic, weight of evidence (WoE) human potency model designed to use historical in vivo (HRIPT) and in vitro (DPRA, Keratinosens, NCLAT and U-SENS) hazard information to estimate the risk of inducing sensitisation under a HRIPT exposure scenario. Furthermore, the model assumes there is a HRIPT threshold for sensitisation by all individuals in an arbitrary large population. Estimates of this population threshold are made in the form of a probability distribution explicitly characterising the uncertainty in the prediction. Extrapolation from the HRIPT population threshold to a safe consumer exposure level is currently made with uncertainty factors chosen to accommodate the increased risk which may arise from, for example, an increase in the exposure frequency. However, we continue to explore the use of skin toxicokinetic (TK) modelling to better characterise the differences in sensitisation risk that potentially arise from differences in exposure patterns [1,2].

Introduction

Toxicokinetic-toxicodynamic (TKTD) modelling of the key events captured in the Skin Sensitisation AOP has been central to our Next Generation Risk Assessment (NGRA) approach for Skin Allergy [1] over the past five years. However, the TKTD model does not yet achieve a desired degree of confidence due to a lack of sensitiser-specific data for benchmarking the TD model.

Following this insight, we have taken a data-driven approach to infer human sensitiser potency [3], thereby creating a tiered NGRA approach for Skin Allergy, which catalysed by a recent Cosmetics Europe (CE) workshop, we have since evaluated using four ingredients across two product types using data from the CE Skin Tolerance database [4].

Step 1. Initial estimates of external exposure to skin via shampoo & face cream products

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Shampoo</th>
<th>Face cream</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of product used per day</td>
<td>10.44</td>
<td>1.54</td>
</tr>
<tr>
<td>Retention factor</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>Skin surface area (cm²)</td>
<td>1600</td>
<td>545</td>
</tr>
<tr>
<td>Amount of product in contact with skin (mg)</td>
<td>130.6</td>
<td>152.6</td>
</tr>
<tr>
<td>Percentage ingredient in product (%)</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Amount of ingredient in contact with skin (µg)</td>
<td>297</td>
<td>3072</td>
</tr>
<tr>
<td>Local thermal exposure (µg/cm²)</td>
<td>0.145</td>
<td>5</td>
</tr>
</tbody>
</table>

* Denimolinos sens var PSF positive for FLG.Sens using DCSs model of positive DCSs

Step 2. Expert assessment of protein reactivity mechanism

- Coumarin (pro-) Michael Acceptor
- Methyl heptine carbonate (Michael Acceptor)
- Lactic acid (non-reactive)
- DNBC (SNA)

Step 3. Use Weight of Evidence (WoE) human potency model to make an initial prediction of the dose response in a Human Repeat Insult Patch Test (HRIPT) using available in vivo and in vitro information.

Human potency model (schematic above) is a probability distribution describing data from the following sources:
- HRIPT (dosage, cohort size, number sensitised)
- Mouse Local Lymph Node Assay (LLNA) (EC3 value)
- DPRA (cyclysa depletion)
- Keratinsens (EC3, EC50)
- hClAT (CD54 EC50, CD66 EC50, Ec75)
- U-SENS (EC50, EC75)
- Previously considered:
  - SENS-IS (Categorical potency)
  - BREFEX-NUXI (read-across EC3s based on Tanimoto distance)

Data for all chemicals are stored within a matrix. The model does not need all the data for a particular chemical to make a prediction. The model is able to make a prediction of sensitiser potency (with uncertainty) in a HRIPT based on the available information. LLNA and HRIPT data removed for case study ingredients.

Step 4. Human potency prediction of Allergy Risk (Risk shown right.)

It is assumed that market exposure conditions, which for example could include higher application frequencies of the ingredient to more sensitive areas of skin, could result in lower thresholds on the applied dose required to induce sensitisation. For the shampoo and face cream products, it is assumed that the market thresholds are no more than 30 and 10-fold smaller than the HRIPT threshold respectively. The estimated distribution for the HRIPT population threshold is shifted by each of these-fold changes and then compared against the market exposure level (red line, see step 1). This allows us to calculate an upper estimate to the probability that we will exceed the population threshold for sensitisation for each product type.

Step 5. For the market and HRIPT exposure scenarios, it is expected that the internal exposure to a product ingredient will differ. Toxicokinetic and applied dose modelling may be a means to characterise the differences in the internal exposure to a product ingredient. We continue to explore how such information can be utilised to extrapolate from estimates of sensitisation thresholds in the HRIPT to market thresholds.

Conclusion

1. SARA human potency model utilises any combination of historical in vivo and in vitro data
   - Other data sources can be added
2. SARA human potency model predicts the probability of sensitisation occurring in a HRIPT
   - Predictions account for variability in input data
   - Incorporates uncertainty in human dose response
3. SARA human potency model can be used to predict the probability of sensitisation occurring under market exposure scenarios

Next steps

Activities are ongoing to explore:
- The value of additional sources of input data (in vitro, in silico and historical in vivo)
- The use of modelling of other areas of uncertainty
- How bioavailability information (TK) can be used to refine initial risk prediction.
- How to improve clinical relevance of our risk assessments

References


For more info: www.tiz21c.org/eurotox2018/