NGRA is an exposure-led, hypothesis-driven approach which integrates new approach methodologies [NAMS] to ensure safety without generating animal data. We have developed an NGRA framework [Figure 1] for skin allergy that aligns with the Cosmetics Europe Skin Allergy NGRA framework (Gilmour N et al., 2020). This framework is applied to a hypothetical skin allergy assessment of a consumer product at two exposures - 0.1% coumarin in a face cream and 1% in a deodorant. For the purposes of the case study, animal data, clinical data and read-across were not used, and the use of dermal sensitisation threshold (DST) was not appropriate. The full case study has been submitted to Regulatory Toxicology and Pharmacology (Reynolds G et al., submitted).

Local Exposure Estimation & Problem Formulation

Table 1. Applied dose estimation estimates (SCCS, 2021).

<table>
<thead>
<tr>
<th>Product type</th>
<th>Face cream</th>
<th>Deodorant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>1.5 µg/cm²</td>
<td>1.5 µg/cm²</td>
</tr>
<tr>
<td>Skin surface area (face / axial) (cm²)</td>
<td>565</td>
<td>200</td>
</tr>
<tr>
<td>Local dermal exposure (µg/cm²)</td>
<td>2.7</td>
<td>75</td>
</tr>
</tbody>
</table>

Data Generation

Data was generated in DPRA, KeratinoSens™, h-CLAT, U-SENS™ assays for coumarin and 7-OH coumarin. Coumarin was positive in all tests, except for DPRA where peptide depletion below the positive threshold. 7-OH coumarin was negative in KeratinoSens & h-CLAT, positive in USENS & inconclusive in DPRA.

For coumarin, the expected SARA model derived ED₀₁ is 11,000µg/cm², whilst for 7-OH coumarin the expected ED₀₁ is 110,000µg/cm² (Figure 2) i.e. 7-OH coumarin is predicted to be 10-fold less potent than coumarin). Therefore, a risk assessment based on coumarin potency data only would not be appropriate.

Determine Point of Departure (PoD)

The margin of exposure (MoE) was calculated from the ED₀₁ for coumarin and the dermal exposures for each product type. Results were summarised using 95% and 50% credible intervals (Figure 3).

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References


Figure 1. Skin allergy risk assessment framework. Grey boxes represent approaches which were not used for this NGRA case study.

Figure 2. Ranking of chemicals within the SARA database by median ED₀₁ (central 95% and 50% credible intervals).

Figure 3. Distribution for the MoE between the ED₀₁ for coumarin and the estimated dermal exposure for face cream and deodorant products. Line colours indicate the SARA inferred probability that the exposure is low risk. Background colours indicate the assigned risk classification for each benchmark exposure within the model (blue: low risk, yellow: high risk).