CASE STUDY PRESENTATION:
A QUANTITATIVE AOP FOR SKIN SENSTITISATION RISK ASSESSMENT

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SAFETY & ENVIRONMENTAL ASSURANCE CENTRE (SEAC), UNILEVER R&D
TRADITIONAL SKIN SENSITISATION RISK ASSESSMENT

1. Consumer habits and practices data
2. Identify sensitisation potential
   - QSAR/read-across/analytical chemistry
3. Identify sensitisation potency
   - LLNA (GPMT, Buehler)
4. Define Human / HRIPT Threshold
   - No Expected Skin Sensitisation Induction Level (NESIL)
5. Apply Sensitisation Assessment Factors (SAFs):
   - Inter-individual variability (x10)
   - Vehicle/product matrix effects (x1 - x10)
   - Use considerations (x1 – x10)
6. Acceptable Exposure Level (AEL)
7. Compare AEL with Consumer Exposure Level (CEL)
8. Decision on whether or not to market
9. Benchmarking
10. Other Clinical data
NEW SKIN SENSITISATION RISK ASSESSMENT PARADIGM?

Modified from ‘Adverse Outcome Pathway (AOP) for Skin Sensitisation’, OECD
DEVELOP A MATHEMATICAL MODEL OF ALLERGIC CONTACT DERMATITIS TO ENABLE RISK ASSESSMENT DECISION-MAKING FOR NEW CHEMICALS

Model Inputs
- Concentration of ingredient due to exposure
- Molecular Initiating Event
- Cellular response
- Organ response
- Vehicle
- Stratum Corneum
- Diffusion
- Partitioning
- Viable Skin
- Receptor Fluid
- Lymphatic Vessel
- Lymph Node

Model Outputs
- Dendritic cell
- Proliferating CD8+ T cell
- Naïve CD8+ T cell
- Hapten-specific T cell activation
- Chemical X
dose of chemical applied to skin

Model Inputs:
- Exposure
- Skin Bioavailability
- Reactivity
- Kinetics

Model Outputs:
- Development of a mathematical model to enable risk assessment decision-making for new chemicals.
Quantitative relationships between sensitizing dose of DNCB and reactivity in normal subjects

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MODELLING SKIN BIOAVAILABILITY OF EXPERIMENTAL SENSITISER 2,4-DI-NITRO CHLOROBENZENE (DNCB)

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>in vitro skin pen</th>
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<tbody>
<tr>
<td>Dose</td>
<td>38.25 μg/cm²</td>
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<tr>
<td>Vehicle Volume</td>
<td>20 μL</td>
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<tr>
<td>Surface area</td>
<td>0.64 cm²</td>
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Estimation of Bioavailability in Skin - based on OECD Test Guideline 428
- Penetration system modelled and partitioning and diffusion rates determined by fitting - Davies et al 2011 Toxicol. Sci. 119, 308-18
MODELLING OF SKIN PROTEIN HAPTENATION \( \rightarrow \) SKIN DENDRITIC CELL ANTIGEN PROCESSING, PRESENTATION & MIGRATION TO DRAINING LYMPH NODE

Concentration of ingredient due to exposure → Molecular Initiating Event → Cellular response → Organ response

- Vehicle
- Stratum Corneum
- Receptor Fluid
- Diffusion
- Partitioning
- Viable Skin
- Lymphatic Vessel
- Lymph Node
- Dendritic cell
- Proliferating CD8⁺ T cell
- Naïve CD8⁺ T cell

**Graphs:**
- Haptenated nucleophiles in the skin
- Skin DC density (cells cm⁻²)
- Fraction of hapten-pMHC on skin DCs
- LN DC density (cells mm⁻³)
- Fraction of hapten-pMHC on LN DCs

**Time t (days):**
- 0, 5, 10, 15, 20, 25

**Legend:**
- Fraction \( \in [0,1] \)

**Unilever Logo:**
Sensitisation assessed by challenge with DNCB 4 weeks after application

Prediction of maximum immune synapse rate in the 4 weeks following application

Friedmann et al 1983
- Single exposure to DNCB
- 7.1cm² volar forearm
- 100μL acetone vehicle
Sensitisation assessed by challenge with DNCB 4 weeks after application.

**Prediction of maximum immune synapse rate in the 4 weeks following application**

**Friedmann 2007**
- Single exposure to DNCB
- Various exposure areas, sites, vehicles & volumes

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**The relationships between exposure dose and response in induction and elicitation of contact hypersensitivity in humans**

P.S. Friedmann

DOI: 10.1111/j.1365-2133.2007.08162.x

**Table**

<table>
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<tr>
<th>Diameter (cm)</th>
<th>Area (cm²)</th>
<th>Total (µg)</th>
<th>Concentration (µg cm⁻²)</th>
<th>Number of subjects</th>
<th>Percentage sensitised</th>
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OVERALL SUMMARY

• We have developed a mechanistic, mathematical model of DNCB-induced CD8\(^+\) T cell activation in humans with the purpose of informing skin sensitisation risk assessment

• The model predicts various measures of sensitiser-induced CD8\(^+\) T cell activation for different DNCB exposure scenarios using a combination of chemical- & exposure-specific non-animal data on skin bioavailability and reactivity

NEXT STEPS

1. Progress human CD8\(^+\) T cell response model development to allow mechanistic prediction of allergic contact dermatitis

2. Determine the uncertainty in our model predictions through characterising parameter & model uncertainty
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