NON-ANIMAL RISK ASSESSMENT FOR SKIN SENSITISATION

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We risk assess to prevent skin sensitisation in consumers

» What risk does ingredient X at conc. Y in product Z pose to the consumer?

How can we apply our mechanistic understanding of skin sensitisation to human health risk assessment?

» removing the need for new animal test data...
What risk of skin sensitisation does MCI/MI* at 5ppm (0.0005%) in shampoo pose to the consumer?

*(Methylchloroisothiazolinone/Methylisothiazolinone)
### CONSUMER EXPOSURE TO INGREDIENT IN SHAMPOO

- **Amount of product used per day**: 12.181g
- **Retention factor**: 0.01
- **Skin surface area of application**: 1430 cm²
- **Level of ingredient in product (%)**: 0.0005%

**Total exposure to product**

\[
\text{Total exposure to product} = \frac{12181 \text{mg} \times 0.01}{1430 \text{ cm}^2} = 0.085 \text{mg/cm}^2
\]

**Product remaining on skin**

\[
\text{Product remaining on skin} = 121.81 \text{mg} \times 0.01 = 1.2181 \text{mg} = 0.085 \text{mg/cm}^2
\]

**Product exposure (mg/cm²)**

\[
\text{Product exposure (mg/cm²)} = \frac{121.81 \text{mg}}{1430 \text{ cm}^2} = 0.085 \text{mg/cm}^2
\]

**Consumer Exposure Level (µg/cm²)**

\[
\text{Consumer Exposure Level (µg/cm²)} = 12181 \text{mg} \times 0.0005% = 0.000425 \text{µg/cm}^2
\]

* 95th percentile from Industry studies on product type Hall et al 2007
** QRA technical guidance dossier
*** EPA Exposure handbook 1998
DERIVATION OF NO EXPECTED SKIN SENSITISATION INDUCTION LEVEL (NESIL) FOR MCI/MI

Mouse Local Lymph node assay
- EC3 = 0.009%
- Extreme sensitiser
- 2.25µg/cm²

Human repeat insult patch test
- 1µg/cm² is established as No Observed Effect Level (NOEL)
- Clear Lowest Observed Effect Level (LOEL) at 4µg/cm²

Weight of Evidence No Expected Skin Sensitisation Induction Level = 1 µg/cm²
SENSITISATION ASSESSMENT FACTORS: SAF

Apply to NESIL to extrapolate from controlled experimental situation to real life exposure scenarios
(Ref: Felter et al 2002)

Three areas of extrapolation/SAF’s
• Inter-individual susceptibility
• Matrix effects
• Use considerations

Product specific
• For a shampoo a SAF of 100 is applied
RISK OF SKIN SENSITISATION FROM INCLUSION OF MCI/MI AT 5PPM (0.0005%) IN SHAMPOO IS ACCEPTABLE

Risk ?

Product

0.0004µg/cm² Consumer Exposure Level (CEL)
0.01µg/cm² Acceptable Exposure Level (AEL)
No Expected Skin Sensitisation Induction Level (NESIL) 1µg/cm²
HOW CAN WE IMPROVE OUR QUANTITATIVE RISK ASSESSMENT APPROACH?

1. **Define Human / HRIPT Threshold**
   - No Expected Skin Sensitisation
   - Induction Level (NESIL)

2. **Apply Sensitisation Assessment Factors (SAFs):**
   - Inter-individual variability (x10)
   - Vehicle/product matrix effects (x1 - x10)
   - Use considerations (x1 – x10)

3. **Acceptable Exposure Level (AEL)**

4. **Compare AEL with Consumer Exposure Level (CEL)**

5. **Decision on whether or not to market**

6. **Benchmarking**

7. **Other Clinical data**

**Additional information:**

- Consumer habits and practices data
Induction of skin allergy is a multi-stage process driven by toxicity pathways
- mechanistic understanding is captured in Adverse Outcome Pathway (AOP)
- non-animal test methods have been developed; each aims to predict impact of a chemical on one key event
- how can we make risk assessment decisions by integrating this scientific evidence?

Modified from ‘Adverse Outcome Pathway (AOP) for Skin Sensitisation’, OECD report
NON-ANIMAL RISK ASSESSMENT FOR SKIN SENSITISATION: APPLICATION OF MATHEMATICAL MODELLING

1. Generate relevant non-animal data for both the chemical (hazard) and the exposure scenario
2. Use linked mathematical models to predict human allergic immune response (with non-animal data as model input parameters)
3. Apply human immune response model prediction for risk assessment decision

1. Skin Penetration
2. Electrophilic substance: directly or via auto-oxidation or metabolism
3-4. Haptenation: covalent modification of epidermal proteins
5-6. Activation of epidermal keratinocytes & Dendritic cells
7. Presentation of haptenated protein by Dendritic cell resulting in activation & proliferation of specific T cells
8-10. Allergic Contact Dermatitis: Epidermal inflammation following re-exposure to substance due to T cell-mediated cell death

haptenated skin protein prediction

No. CD8+ T cells
time
dose X
dose Y
Adverse Non-Adverse
MATHEMATICAL MODELLING OF NON-ANIMAL SKIN PENETRATION DATA

Apply pharmacokinetic modelling to ingredient permeation data and determine the free concentration of ingredient available to cause the molecular initiating event, i.e. modification of proteins in viable skin.

HAPtenated skin protein model scope (including transformation)
Applying non-animal data to predict whether a given human exposure is adverse or not

1. Skin Penetration

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7. Presentation of haptenated protein by Dendritic cell resulting in activation & proliferation of specific T cells

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MODEL PREDICTION = HAPTENATED SKIN PROTEIN

human T cell-mediated immune response
Immunologists, toxicologists & mathematical modellers – 2 day workshop in May 2010, London

What are the characteristics of the T cell response that could reflect human skin sensitiser potency?

- **Magnitude**: What is the extent of sensitiser-induced T cell response (volume, kinetics & duration)?
- **Quality**: Within sensitiser-induced T cell response, what is the balance between the T cell sub-populations?
- **Breadth**: What proportion of the T cell clonal repertoire has been stimulated by a given sensitiser?

SKIN SENSITISATION MATHEMATICAL MODEL SCOPE

**Key**
- **sDC** - Skin DC
- **mDC** - Migratory DC
- **aCD** – Active DC (cs and p)
- **csDC** – Co-stimulatory DC
- **pDC** – Peptide loaded DC
- **nDC** – Not active DC
- **N** – Naïve T cells (all CD8+)
- **CM** – Central memory
- **PM** – Proliferating memory
- **EM** – Effector memory
- **E** – Effector
- **TRM** – Tissue resident memory

**Diagram Description**
- The diagram illustrates the flow of cells and interactions between skin, lymph, and blood/resting lymphatics.
- Skin contains cells such as sDC, mDC, and others, which can migrate to the lymph node tissue.
- Lymph node tissue includes active lymph node tissue with cells like mDC, aDC, csDC, pDC, and nDC.
- Blood/resting lymphatics show the migration of cells such as N, CM, PM, EM, and EOC.

The diagram visually represents the mathematical model scope of skin sensitisation, detailing the pathways and interactions of different types of dendritic cells and their roles in the immune response.
WHAT T CELL POPULATIONS CORRELATE WITH CLINICAL ADVERSITY?

We need human data to benchmark the threshold at which the number of antigen-specific T cells correlates with clinical adversity:

Working with collaborators to inform, test and improve our model:
» patients undergoing sensitisation (e.g. treatment of viral warts)
» patients already sensitised to chemicals, correlating the degree of sensitisation with the number of antigen-specific T cells
OUR NON-ANIMAL QUANTITATIVE RISK ASSESSMENT APPROACH FOR SKIN SENSITISATION?

Consumer habits and practices data

Identify sensitisation potential QSAR / read-across

Generate/apply skin bioavailability & haptenation as model input data for given skin exposure & product type

Generate mathematical model prediction of T cell response for given skin exposure & likely non-adverse/adverse threshold (with explicit uncertainties)

Ability to generate supporting clinical biomarker data to demonstrate absence of adverse T cell response at consumer exposure levels

Decision on whether or not to market

Benchmarking

Other Clinical data
CONCLUSIONS

• Improving our quantitative risk assessment approach for skin sensitisation can be achieved through mechanistic interpretation of non-animal data in context of defined skin exposure.

• Quantitative mathematical modelling of Skin Sensitisation AOP allows us to predict whether human immune response for a given exposure scenario to sensitiser will be adverse (or not).

• To apply our mathematical model to risk assessment decision-making we will also need to generate clinical/human-relevant datasets to confirm/challenge model predictions.
ACKNOWLEDGEMENTS

Maja Aleksic, Richard Cubberley, Michael Davies, Julia Fentem, Nikki Gellatly, Todd Gouin, Gaurav Jain, Sandrine Jacquailleot, Cameron MacKay, Craig Moore, Deborah Parkin, Juliette Pickles, Fiona Reynolds, Ouarda Saib, David Sheffield, Vicki Summerfield, Jeff Temblay, Carl Westmoreland & Sam Windebank

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