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...
QUANTITATIVE RISK ASSESSMENT: CASE STUDY

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

Total exposure to product = 12181mg *

Retention factor = 0.01

Product remaining on skin = 121.81mg **

Skin surface area of application = 1430 cm² ***

Product exposure(mg/cm²) = 0.085mg/cm²

Level of ingredient in product (%) = 0.0005%

Consumer Exposure Level (ug/cm²) = 0.000425 µg/cm²

* 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

- Consumer Exposure Level (CEL): 0.0004 µg/cm²
- Acceptable Exposure Level (AEL): 0.01 µg/cm²
- No Expected Skin Sensitisation Induction Level (NESIL): 1 µg/cm²

Risk Assessment:

Product X

MCI/MI Level - log mg/cm²

0.0001 0.001 0.01 0.1 1 10
HOW CAN WE IMPROVE OUR QUANTITATIVE RISK ASSESSMENT APPROACH?

1. Identify sensitisation potential
   QSAR / read across

2. Identify sensitisation potency
   LLNA (GPMT, Buehler)

3. Define Human / HRIPT Threshold
   No Expected Skin Sensitisation Induction Level (NESIL)

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

5. Acceptable Exposure Level (AEL)

6. Compare AEL with Consumer Exposure Level (CEL)

7. Decision on whether or not to market

- Benchmarking
- Other Clinical data

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
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.
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.

Davies et al. 2011. Toxicol Sci. 119. 308-18
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

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. Allergic Contact Dermatitis: Epidermal inflammation following re exposure to substance due to T cell mediated cell death

MODEL PREDICTION = HAPTENATED SKIN PROTEIN

human T cell-mediated immune response
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
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:

![Graph showing the correlation between the number of specific T cells and time, with two threshold levels: X @ conc. 1 and X @ conc. 2, indicating adverse and non-adverse conditions.]

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?

- 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

Consumer habits and practices data

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 the context of a 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.
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