



Unilever

NEXT GENERATION INTEGRATED STRATEGY FOR SKIN ALLERGY RISK ASSESSMENT

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VANDENBOSSCHE

IDEA WORKING GROUP 16TH / 17TH MAY 2018



WORKSHOP BRIEF

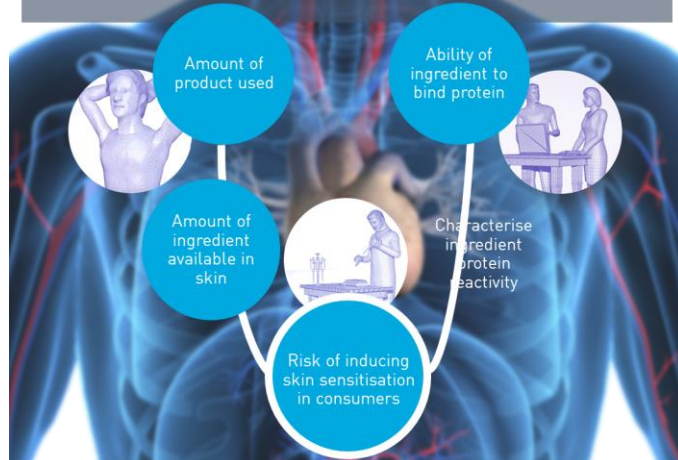


Framework for developing a case study using defined approaches for skin sensitisation animal testing alternatives as a point of departure for applying the QRA for fragrance materials

The case study (one or a few fragrance molecules of participants choice) should cover:

- (1) The data relied on and its sources (in vitro, in silico, ...).
- (2) Basis for dose selection and reason for benchmark selection.
- (3) Basis for calculations used and whether the methodology of calculation is public, and if not, whether access will be given to the methodology of calculation or whether it will remain proprietary,
- (4) The interpretation of the value derived and how it could be used for risk assessment. Note: The case studies presented should focus on NESIL derivation and not just cover the attribution of chemicals into potency classes (e.g. GHS 1A and 1B or ECETOC classes).
- (5) Measure of the uncertainty involved / approach how uncertainty can be evaluated.

Skin allergy risk assessment: our non-animal approach



Our 30+ year investment in developing novel approaches for skin sensitisation risk assessment has meant that non-animal approaches are now our default choice to assure product safety.

To find out more visit:
TT21c.org

Our ongoing research aims to increase our mechanistic understanding of allergic contact dermatitis to ensure we continue to improve the clinical relevance of our skin sensitisation risk assessments.



- We need a risk assessment approach for skin allergy that...
 - doesn't require new animal test data
 - addresses novel exposure scenarios
 - better characterises our uncertainty

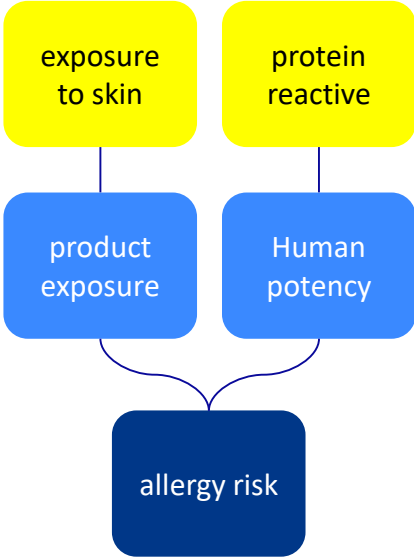
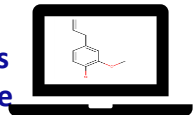
NEXT GENERATION INTEGRATED STRATEGY FOR SKIN ALLERGY RISK ASSESSMENT (SARA)



product use info.



In silico evaluation & expert judgement on whether ingredient is directly or indirectly protein reactive



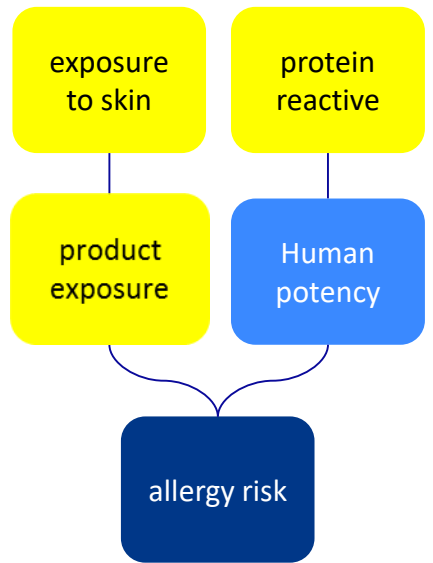
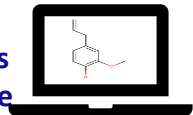
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allergy risk

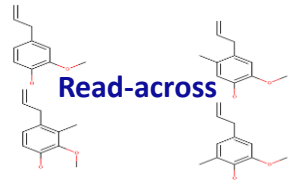
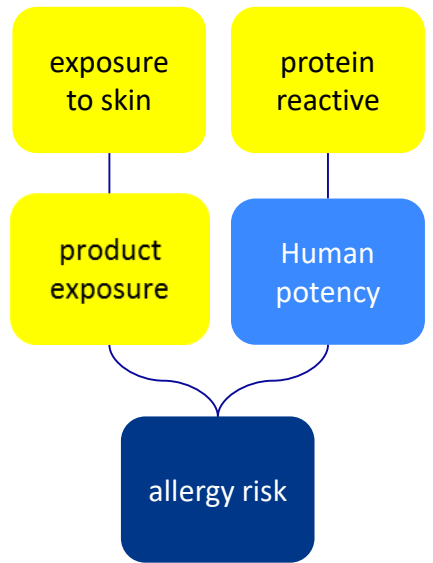
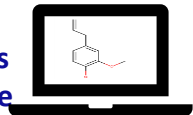
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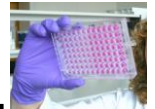
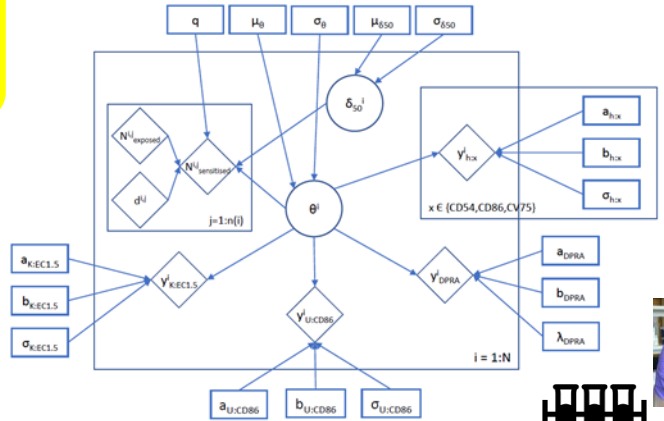
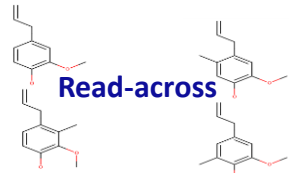
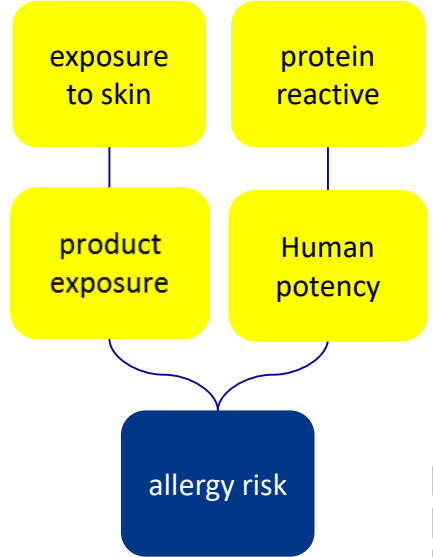
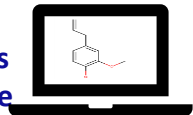
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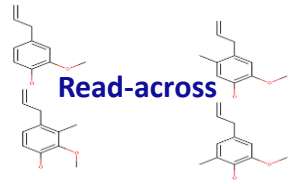
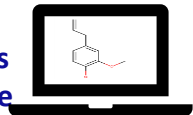
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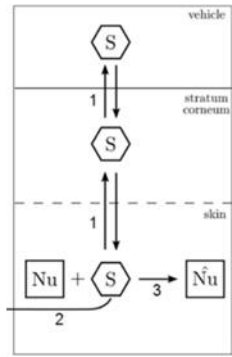
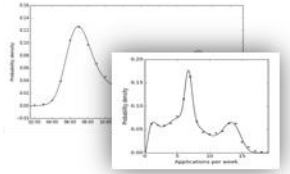
product use info.



In silico evaluation & expert judgement on whether ingredient is directly or indirectly protein reactive



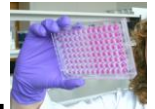
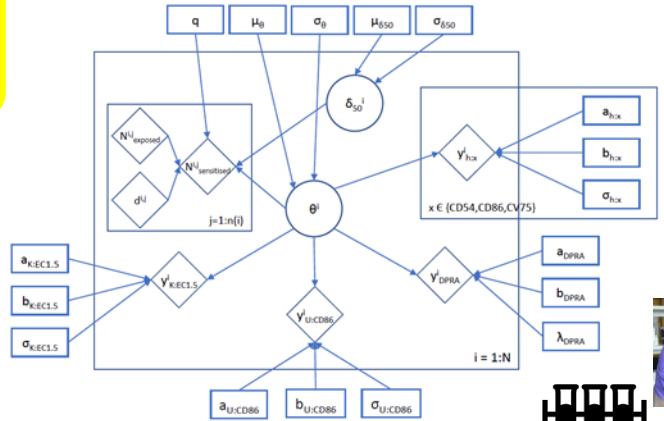
applied dose & skin toxicokinetic models



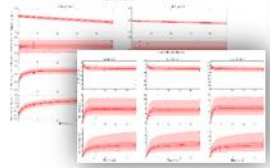
exposure to skin protein reactive

product exposure Human potency

allergy risk



skin absorption & peptide kinetics data



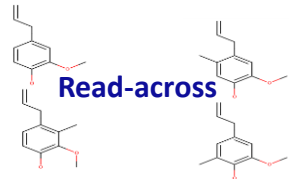
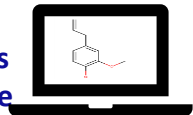
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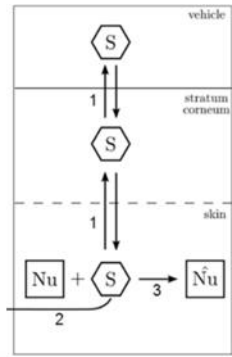
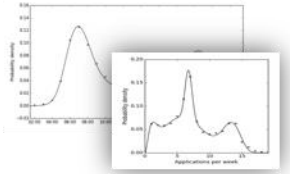
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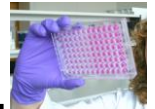
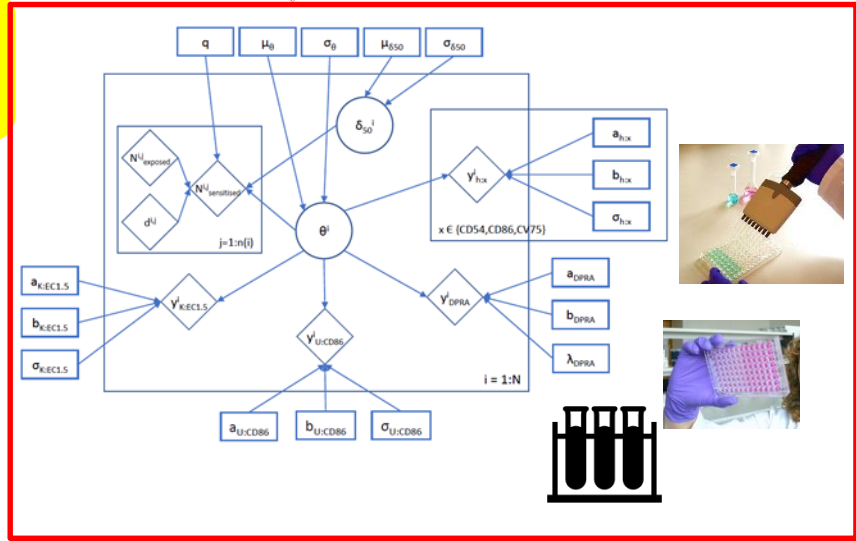
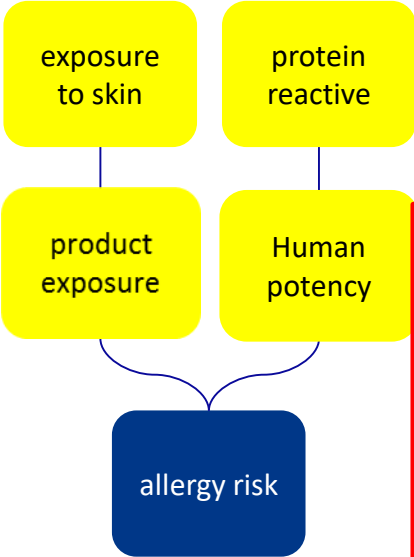
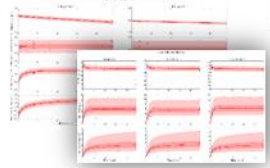
In silico evaluation & expert judgement on whether ingredient is directly or indirectly protein reactive



applied dose & skin toxicokinetic models



skin absorption & peptide kinetics data

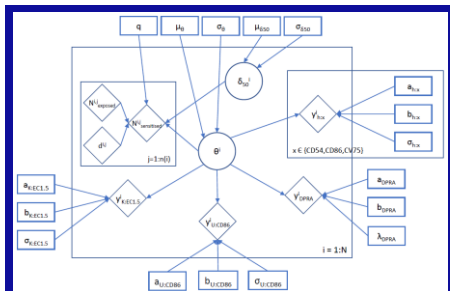


GENERATING HUMAN POTENCY PREDICTIONS

Data



Model



A set of **parameterised rules** specifying how the data are related to each other
 Rule **structure** is fixed but rule **parameters** unknown

Model Update

Learn the underlying **parameters** including those governing the HRIPT dose response.

Diagnostics

Check the updated parameters are consistent with the HRIPT data in the database.

Model Output

Generate human potency prediction for **new chemical**

$$p(\theta, \phi | Y) \propto p(Y | \theta, \phi) p(\phi | \theta) p(\theta)$$



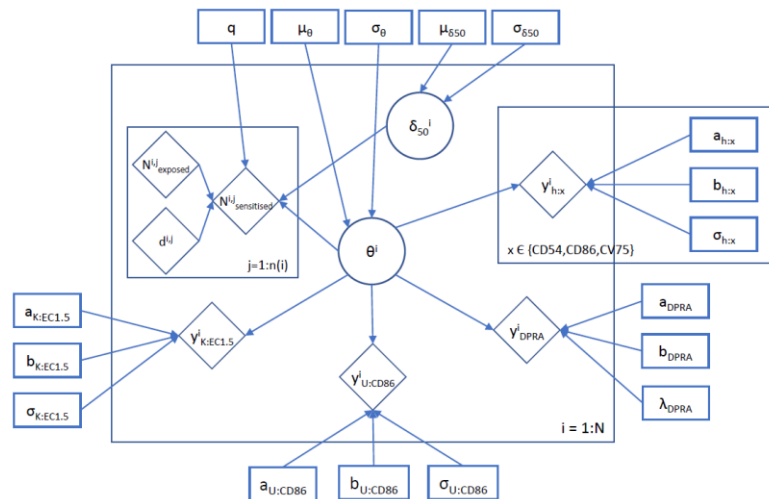
SARA WOE HUMAN POTENCY MODEL: INPUTS

The SARA Weight of Evidence (WoE) human potency model is a high-dimensional probability distribution describing data from the following sources:

- HRIPT (dose, cohort size, number sensitised)
- LLNA (EC3) – *not used for results on following slides*
- DPRA (cys/lys depletion)
- KeratinoSens (EC_{1.5}, EC₃, IC₅₀)
- hClat (CD54 EC₂₀₀, CD86 EC₁₅₀, CV75)
- U-SENS (CD86)

Previously considered:

- SENS-IS (Categorical potency)
- DEREK-NEXUS (read-across EC3s based on Tanimoto distance)
- The framework is designed to allow for missing and censored data. We do not need data from all sources for a chemical-specific prediction.

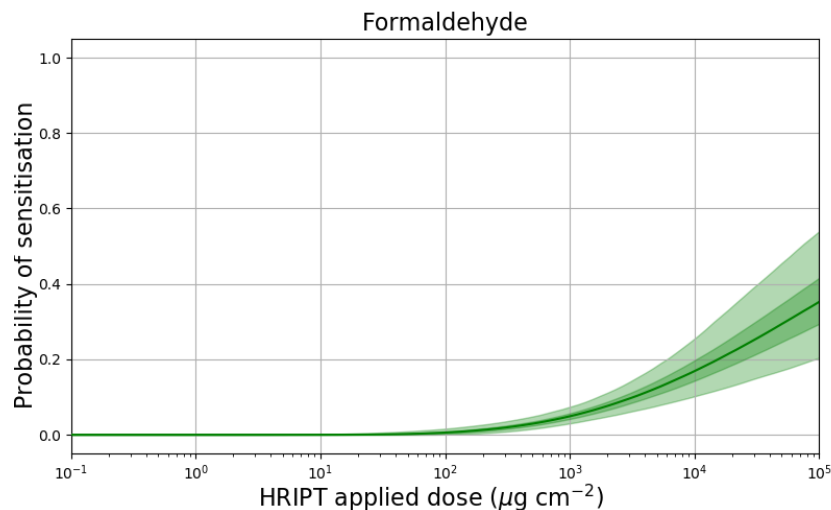


SARA WOE HUMAN POTENCY MODEL: DIAGNOSTICS

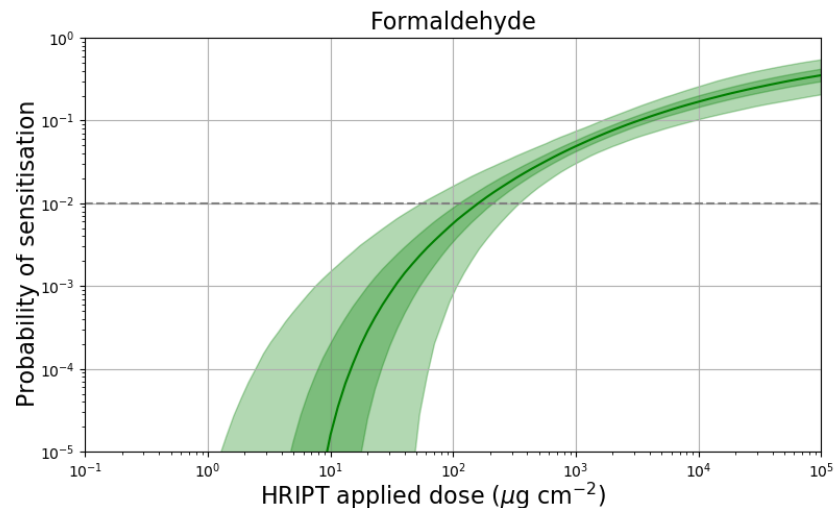


THE PROBABILITY OF INDUCING SENSITISATION IN A RANDOMLY SELECTED INDIVIDUAL UNDER THE CONDITIONS OF A HRIPT

Linear y-axis scale



Logarithmic y-axis scale

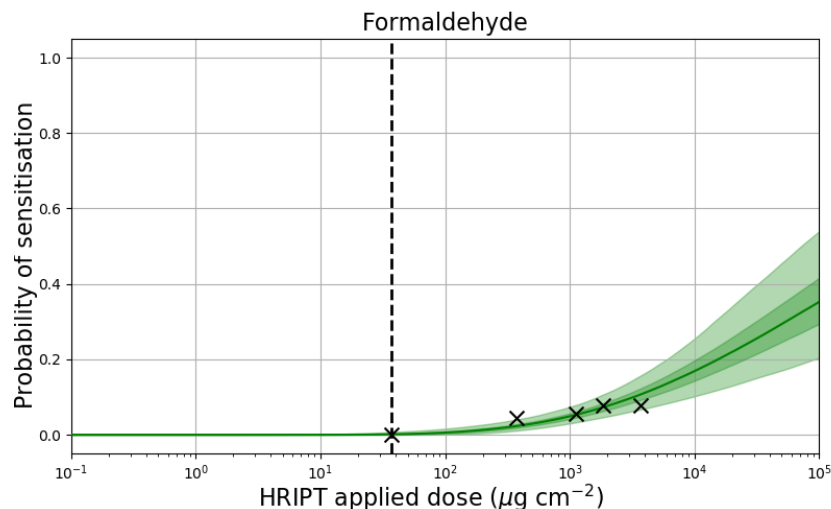


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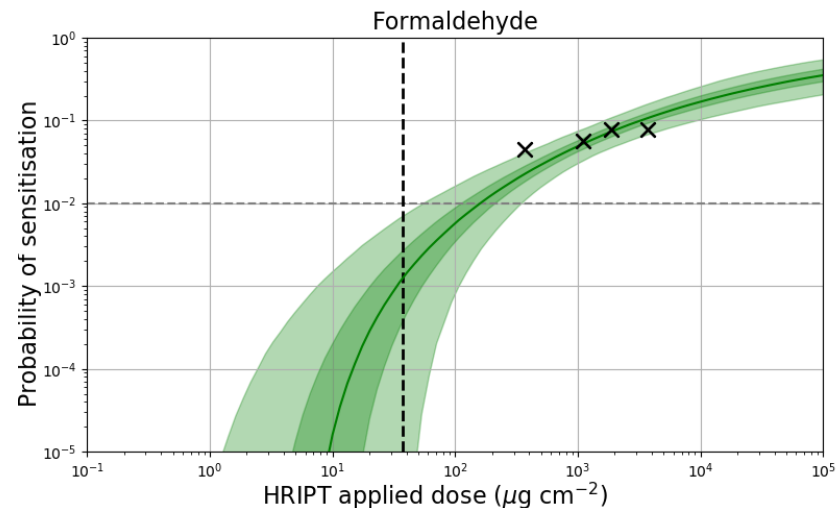


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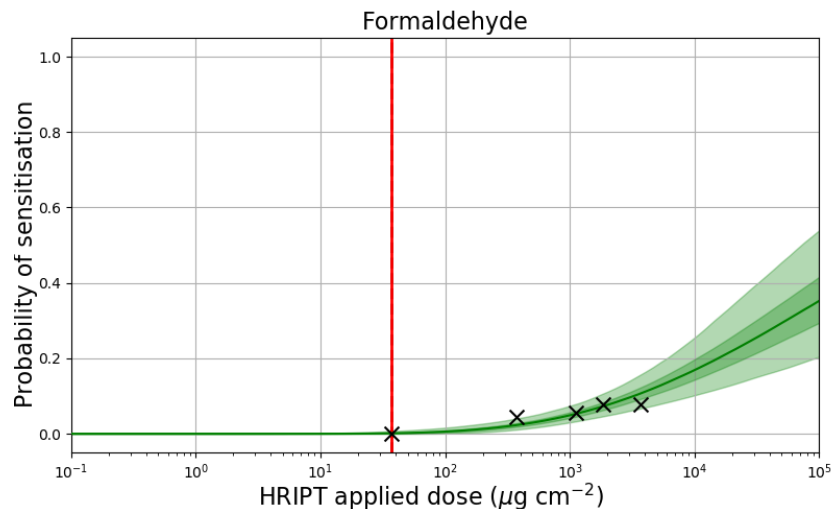


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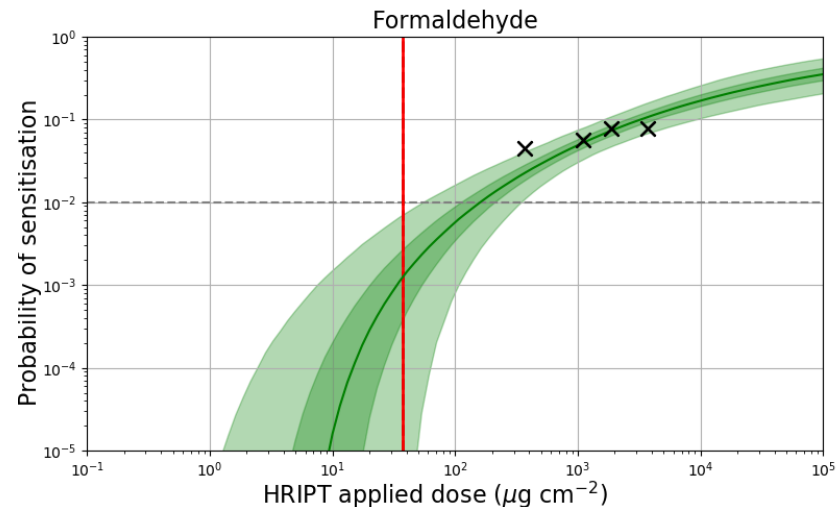


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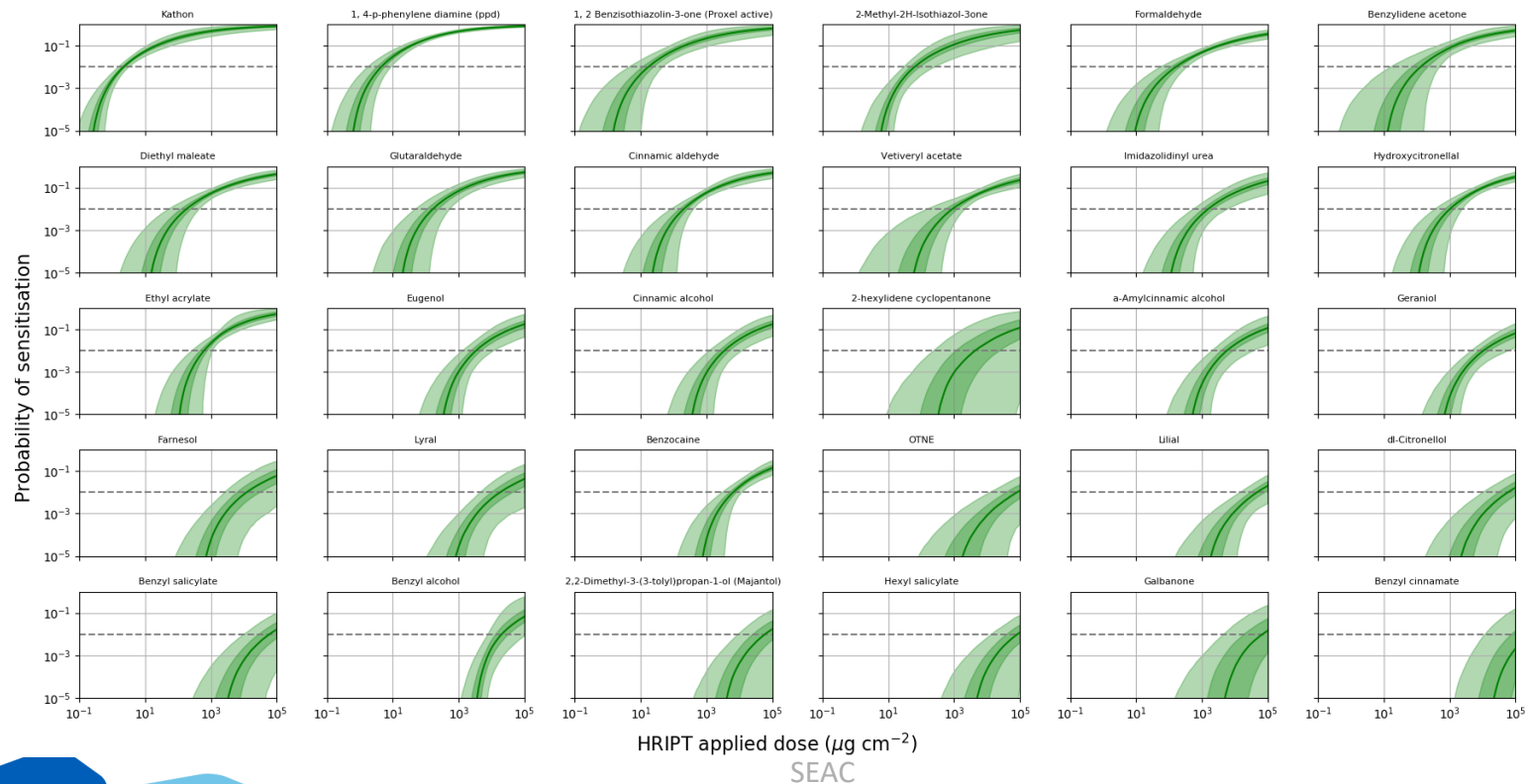


Logarithmic y-axis scale



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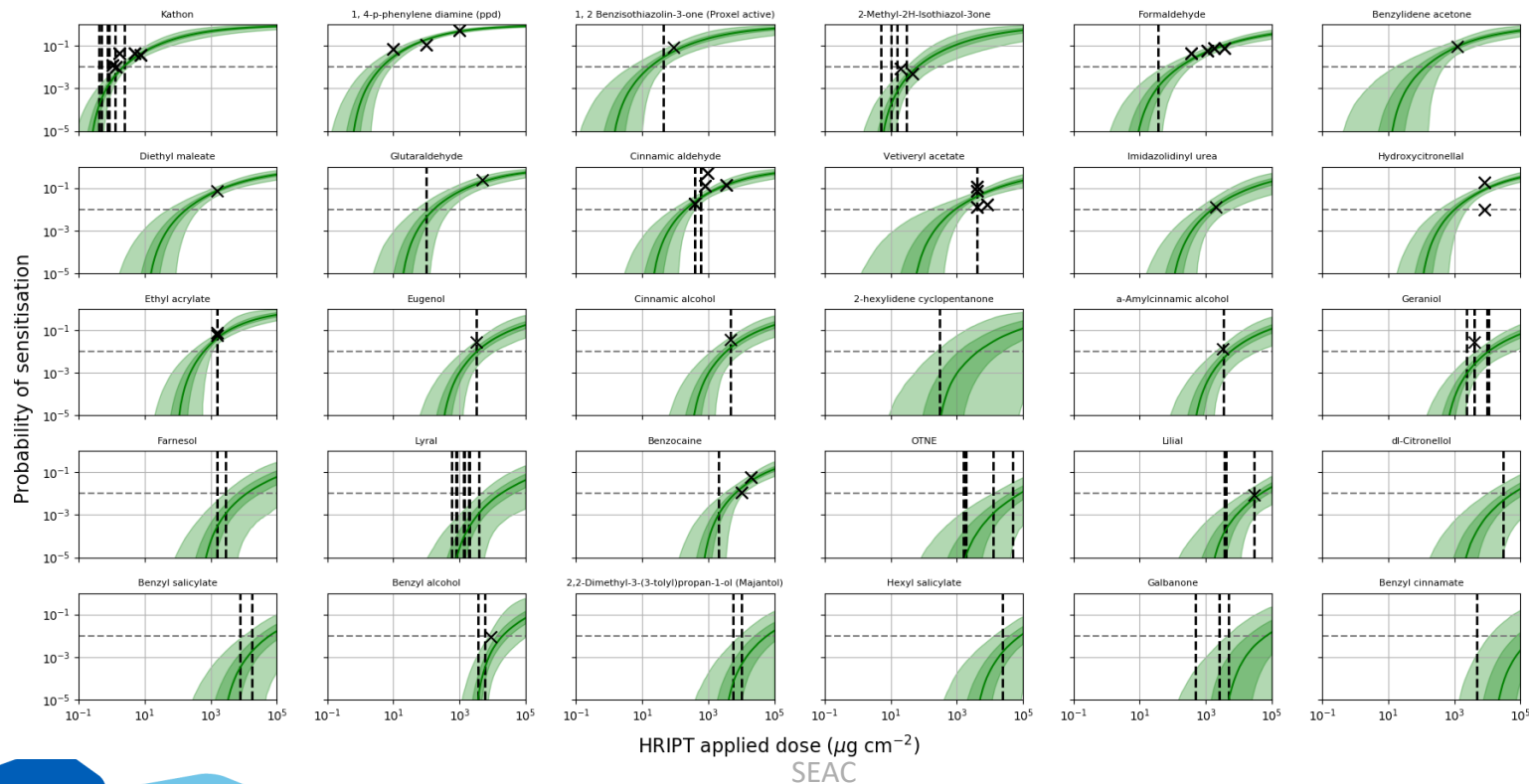
DOSE RESPONSE ESTIMATES FOR CHEMICALS WITH HRIPT DATA



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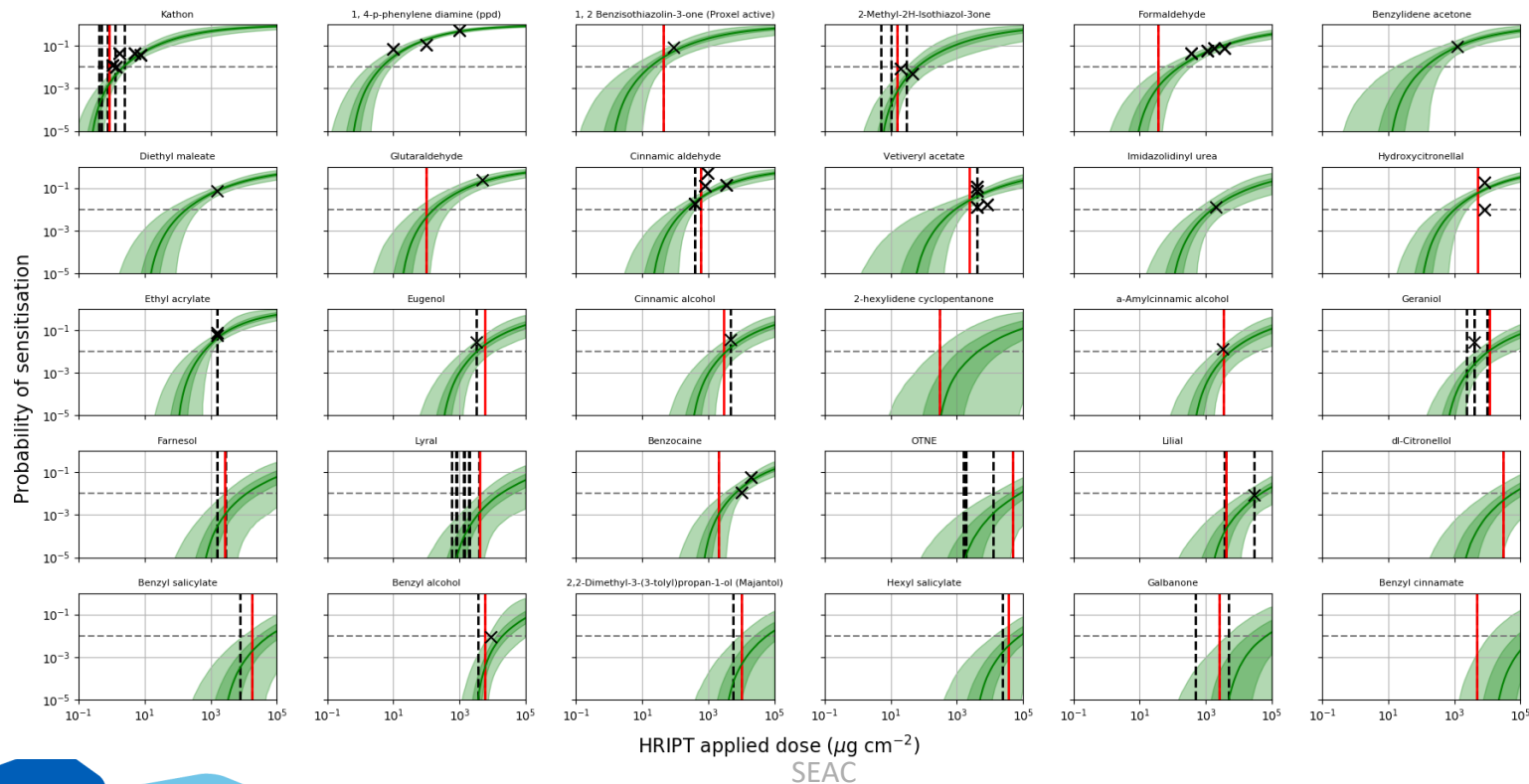
COMPARISON WITH HRIPT DATA



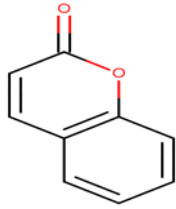
SARA WOE HUMAN POTENCY MODEL: DIAGNOSTICS

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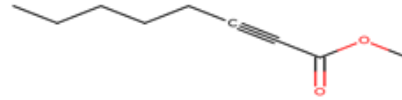
COMPARISON WITH NESIL



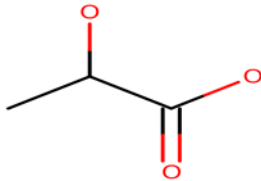
CASE STUDY INGREDIENTS: SARA MODEL



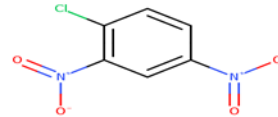
coumarin



Methyl heptine
carbonate

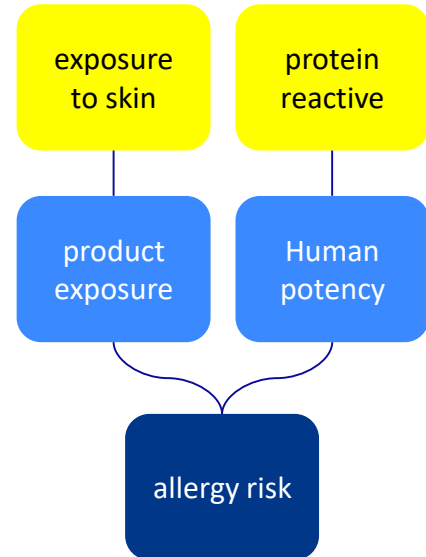


Lactic acid



DNCB

SEAC

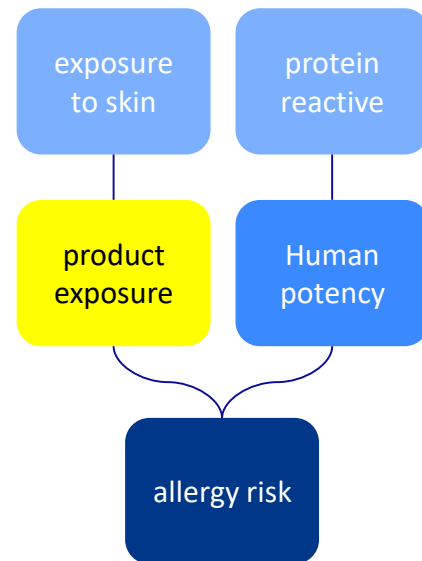


PRODUCT EXPOSURE: 0.2% IN SHAMPOO AND FACE CREAM



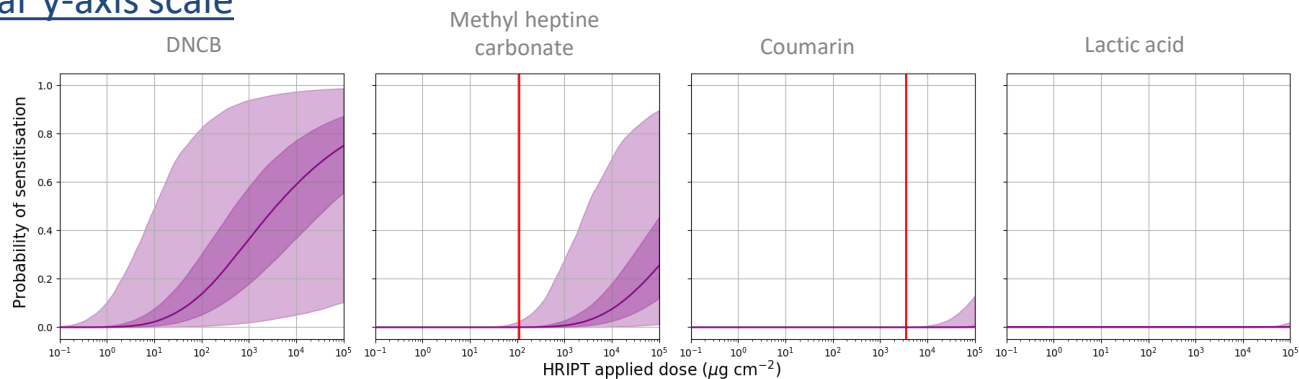
Parameter	Shampoo	Face cream
Amount of product used per day (g/day)	10.46	1.54
Retention factor	0.1	1
Skin surface area (cm ²)	1440	565
Amount of product in contact with skin (mg)	104.6	1536
Percentage ingredient in product (%)	0.2	0.2
Amount of ingredient in contact with skin (µg)	209	3072
Local dermal exposure (µg/cm ²)	0.145	5

* Deterministic worse case (90th percentile) for Europe based upon SCCS notes of guidance (SCCS/1564/15)

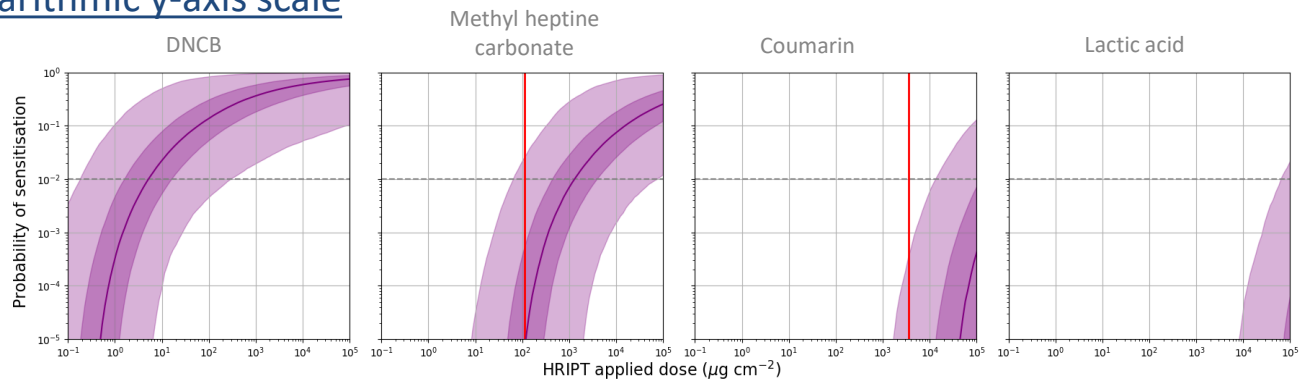


MODEL OUTPUT: PREDICTION OF PROBABILITY OF SENSITISATION OCCURRING IN HRIPT FOR CASE STUDY CHEMICALS

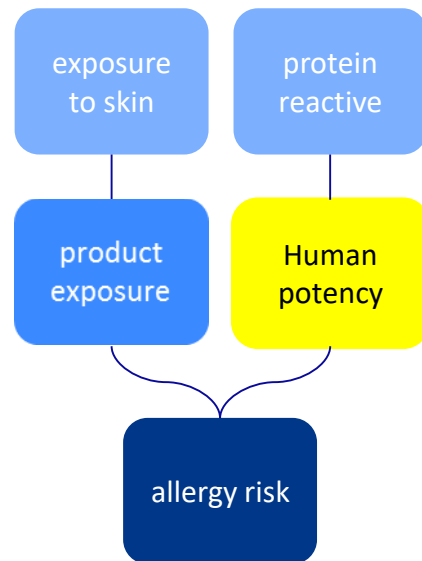
Linear y-axis scale



Logarithmic y-axis scale



SEAC



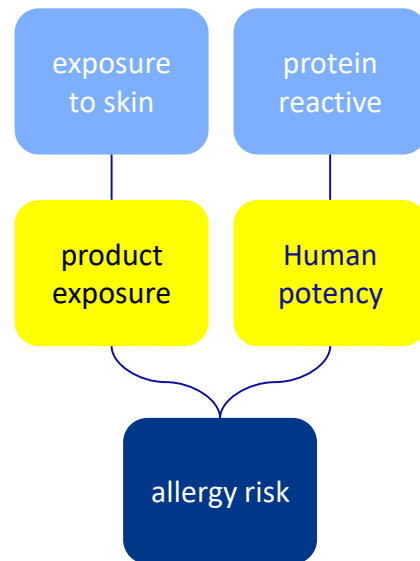
EXTRAPOLATION: HRIPT EXPOSURE TO MARKET EXPOSURE



Address uncertainty in exposure differences between HRIPT and market:

- Application frequency and duration
- Exposure site and skin conditions
- Matrix
- Occlusion

- 10 fold for face cream and
- 30 fold for shampoo

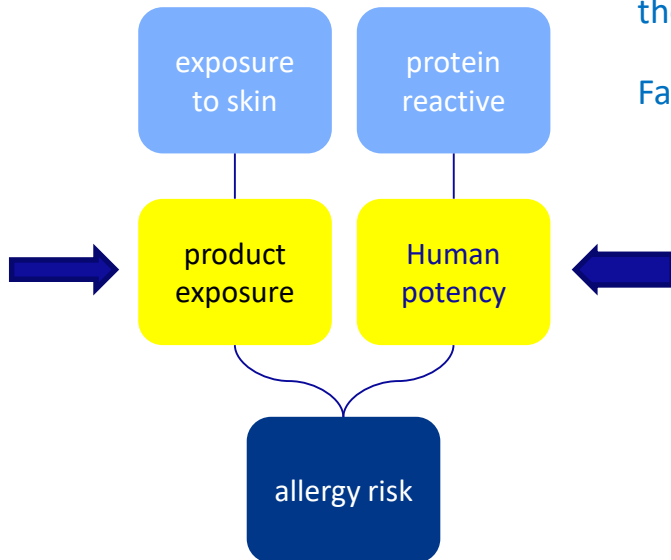


RISK CHARACTERISATION



Consumer exposure level

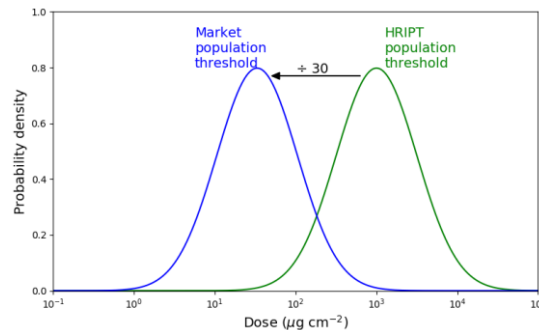
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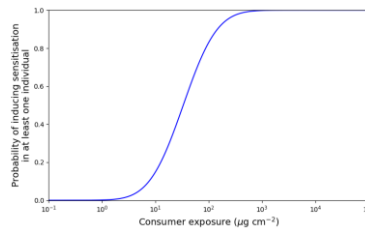
Population threshold for sensitisation in HR IPT... how much lower could it be in the market?

Factors affecting difference:

- Frequency
- Skin site
- Occlusion
- Matrix



Probability of consumer exposure exceeding market population threshold

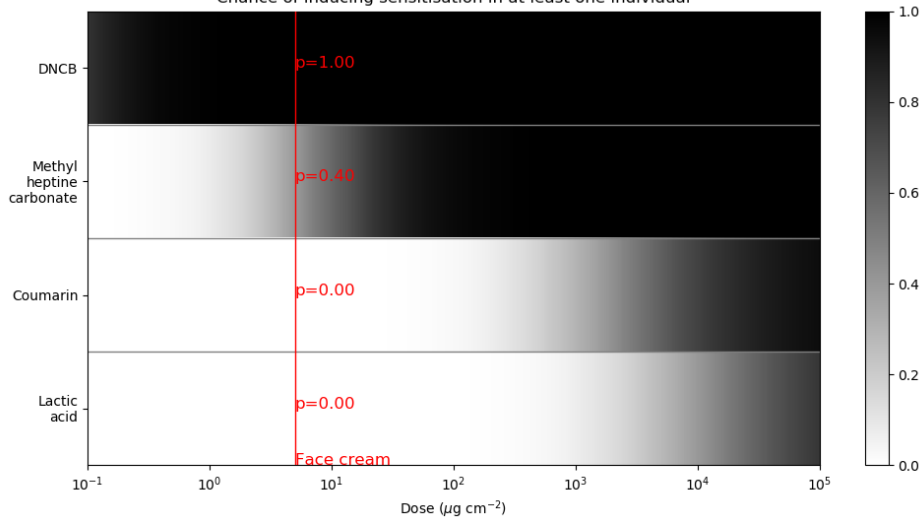


PROBABILITY OF GREATER THAN 1 CONSUMER BECOMING SENSITISED



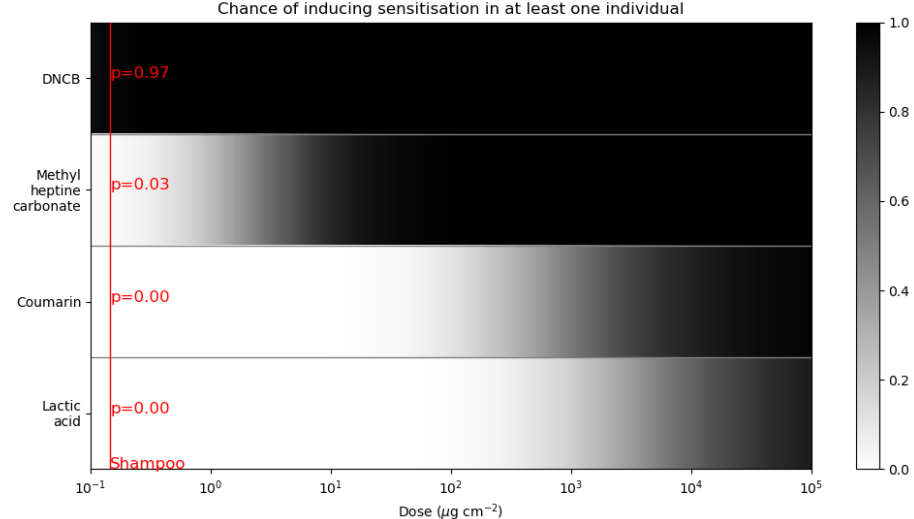
Face cream

Chance of inducing sensitisation in at least one individual



Shampoo

Chance of inducing sensitisation in at least one individual



SARA WOE HUMAN POTENCY MODEL: CONCLUSIONS



- 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**

We need a risk assessment approach for skin allergy that...

- doesn't require new animal test data
- addresses novel exposure scenarios
- better characterises our uncertainty

SARA WOE HUMAN POTENCY MODEL: NEXT STEPS



1. Update submitted to OECD for DA evaluation
2. Publication in preparation
3. Further define applicability domain of input data and model
4. Explore value of additional sources of input data (*in vitro*, *in silico* and historical *in vivo*)
5. Explore how to improve modelling of other areas of uncertainty
6. Explore how bioavailability information (TK) can be used to refine initial risk prediction.
7. Explore how to improve clinical relevance of our risk assessments

THANK-YOU

SEAC