Evaluation of Next-Generation Risk Assessment (NGRA) Approach for Skin Allergy using six ingredients and two product exposure scenarios

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Our aim is to apply mechanistic and clinical understanding to develop a Next Generation Risk Assessment (NGRA) approach for skin allergy that doesn't require new animal test data, addresses novel exposure scenarios and better characterises our uncertainty. Our NGRA approach for skin allergy is a tiered approach that integrates predictive chemistry expertise, historical *in vivo* data and existing or new *in vitro* data using two model-based, defined approaches (DAs) to predict the probability of human skin sensitisation occurring following a given product exposure, with explicit uncertainty.

The first computational model is a probabilistic, weight of evidence (WoE) approach that predicts the outcome of a Human Repeat Insult Patch Test (HRIPT) following exposure to the chemical of interest. The human potency model is a high-dimensional probability distribution constructed using skin sensitisation-relevant *in vivo* [HRIPT and mouse Local Lymph Node Assay (LLNA)], *in vitro* [Direct Peptide Reactivity Assay (DPRA), human Cell Line Activation Test (hCLAT), KeratinoSens, SENS-IS and U-SENS] or *in silico* (DEREK-NEXUS) hazard information. The WoE model output can be expressed as the probability of observing one or more incidences of inducing skin allergy following exposure to a chemical under the conditions of the HRIPT and can therefore be used for risk assessment decision-making. Depending on this initial human potency model prediction, a second model-based approach can be used for risk extrapolation from a HRIPT exposure to a product exposure scenario by applying skin exposure and Toxicokinetic models that use consumer exposure, skin penetration and protein reactivity data [1, 2].

Introduction

Toxicokinetic-toxicodynamic (TKTD) modelling of the key events captured in the Skin Sensitisation AOP has been central to our NexGen Risk Assessment (NGRA) approach for Skin Allergy [1] over the past five years. However, evaluation of our TKTD model highlighted uncertainty in a thresholded, TD model output for decision-making due to the current lack of sensitiser-specific data for benchmarking TD model assumptions & predictions.

Folllowing this insight, we have taken a data-driven approach to predicting human sensitiser potency and paired this with TK modelling for extrapolation to exposure scenarios of interest. Thereby creating a tiered NGRA approach for Skin Allergy, which catalysed by a recent Cosmetics Europe (CE) workshop, we have since evaluated using six ingredients across two product types using data from the CE Skin Tolerance database [3].

Step 1. Initial estimates of external exposure to skin via shampoo & face cream products

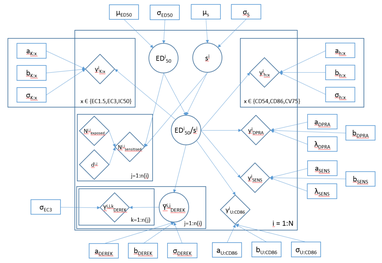
Parameter	Shampoo	Face cream
Amount of product used per day (**g/day**)	10.46	1.54
Retention factor	0.1	1
Skin surface area (**cm²**)	1440	565
Amount of product in contact with skin (**mg**)	104.6	1536
Percentage ingredient in product (**%**)	0.2	0.2
Amount of ingredient in contact with skin (**µg**)	209	3072
Local dermal exposure (**µg/cm²**)	0.145	5

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

Step 2. Expert assessment of protein reactivity mechanism & read-across candidates

	Ingredient	Reactivity Domain	Read-Across candidates
1	DNCB	SNAr	DNFB; Citramalic acid
2	PTD	Pro-MA	1,4-Phenylenediamine; 2,5-Diaminotulene; 1,4-Diamino-2-nitrobenzene
3	Eugenol	Pro-MA	6-Methyleugenol; Phenol, 2-methoxy-5-methyl-4-(2-propenyl)-
4	Resorcinol	Pro-MA	3-Aminophenol; 3-Hydroxy-4-methylaniline
5	Propyl Paraben	Pro-MA	Methyl-4-hydroxybenzoate
6	Lactic acid	Non-reactive	Tartaric acid; Citramalic acid

Step 3. Use Weight of Evidence (WoE) human potency model to make an initial prediction of the dose response in a Human Repeat Insult Patch Test (HRIPT) using available *in vivo*, *in vitro* and *in silico* information.

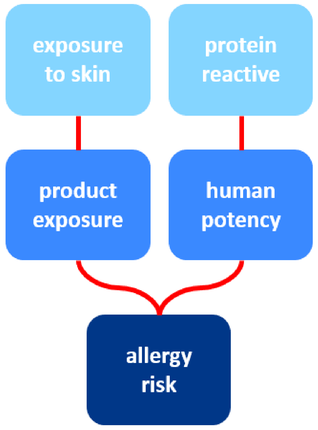


Human potency model (schematic above) is a probability distribution describing data from the following sources:

- HRIPT (dose, cohort size, number sensitised)
- DPRA (cys/lys depletion)
- KeratinoSens ($EC_{1.5}$, EC_3, IC_{50})
- hClat (CD54 EC_{200}, CD86 EC_{150}, CV75)
- U-SENS (CD86)
- SENS-IS (Categorical potency)
- DEREK-NEXUS (read-across EC3s based on Tanimoto distance)

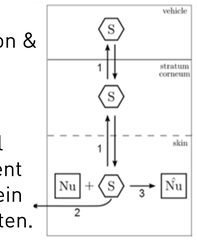
Data for all chemicals are stored within a matrix. The model does not need all the data for a particular chemical to make a prediction.

The model is able to make a prediction of sensitiser potency (with uncertainty) in a HRIPT based on the available information. HRIPT data removed for case study ingredients.



Step 5. Use probabilistic external exposure data & applied dose modelling alongside internal exposure data & toxicokinetic modelling to reduce uncertainty when extrapolating from human potency model to predict allergy risk for a consumer exposure.

TK model: 1) diffusion & partitioning into the stratum corneum & skin; 2) sensitiser clearance by dermal capillaries; 3) covalent modification of protein nucleophiles by hapten.



Step 4. Human potency prediction of Allergy Risk

To accommodate additional sources of uncertainty (application frequency & duration, exposure site & skin conditions) we assume the market exposure has an equivalent sensitisation risk to a HRIPT performed at a dose 10 fold higher than the consumer exposure level. **Probability of exceeding reference skin sensitisation induction rates shown below:**

Shampoo

	reference skin sensitisation induction rates: > 1 in 10,000	> 1 in 100,000	> 1 in 1 million	> 1 in 10 million	> 1 in 100 million	> 1 in 1 billion
DNCB	1.00	1.00	1.00	1.00	1.00	1.00
PTD	0.55	0.91	0.99	1.00	1.00	1.00
Eugenol	0.00	0.00	0.04	0.25	0.62	0.89
Resorcinol	0.00	0.00	0.00	0.01	0.09	0.33
Propyl Paraben	0.00	0.00	0.04	0.28	0.66	0.91
Lactic Acid	0.00	0.00	0.00	0.00	0.00	0.00

Face cream

	reference skin sensitisation induction rates: > 1 in 10,000	> 1 in 100,000	> 1 in 1 million	> 1 in 10 million	> 1 in 100 million	> 1 in 1 billion
DNCB	1.00	1.00	1.00	1.00	1.00	1.00
PTD	0.98	1.00	1.00	1.00	1.00	1.00
Eugenol	0.03	0.25	0.66	0.92	0.99	1.00
Resorcinol	0.00	0.01	0.12	0.42	0.74	0.92
Propyl Paraben	0.04	0.28	0.70	0.94	0.99	1.00
Lactic Acid	0.00	0.00	0.00	0.00	0.01	0.06

Key
$p < 0.05$
$0.05 < p < 0.95$
$p > 0.95$

Conclusions

- The output of our NGRA for Skin Allergy (i.e. decision heat map) enables a risk assessment decision to be made using probability of skin sensitisation induction allergy risk metric.
- NGRA for Skin Allergy can also be used to make sensitiser/non-sensitiser prediction by applying expert judgement applied to continuous measure of risk (i.e. some probabilities of sensitisation are effectively zero)
- Our human potency model uses all available data (i.e. non-concordant data = greater uncertainty) and make a prediction with incomplete datasets (i.e. ⩾1 data type needed for prediction)
- Expert-derived read-across candidates (and associated *in vivo* and/or *in vitro* datasets) can be used to inform a NGRA for Skin Allergy prediction but were considered out of scope, however DEREK-NEXUS is used.
- Simple deterministic product exposure assessment (+ conservative assumptions) can be used to make an initial NGRA for Skin Allergy prediction that can be further refined using applied dose & toxicokinetic modelling as necessary.

Next Steps

- Develop an approach to accommodate expert-driven read-across candidates as a human potency model input
- Continue to benchmark the performance of our human potency model and NGRA approach for Skin Allergy using well-characterised ingredients

References

[1] MacKay C. *et al.* 2013. ALTEX.**40**.473-86
[2] Davies *et al.* 2011. Toxicological. Sci. **119**. P301-318
[3] Hoffmann S. *et al.* 2018. Critical Rev. in Toxicol.
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