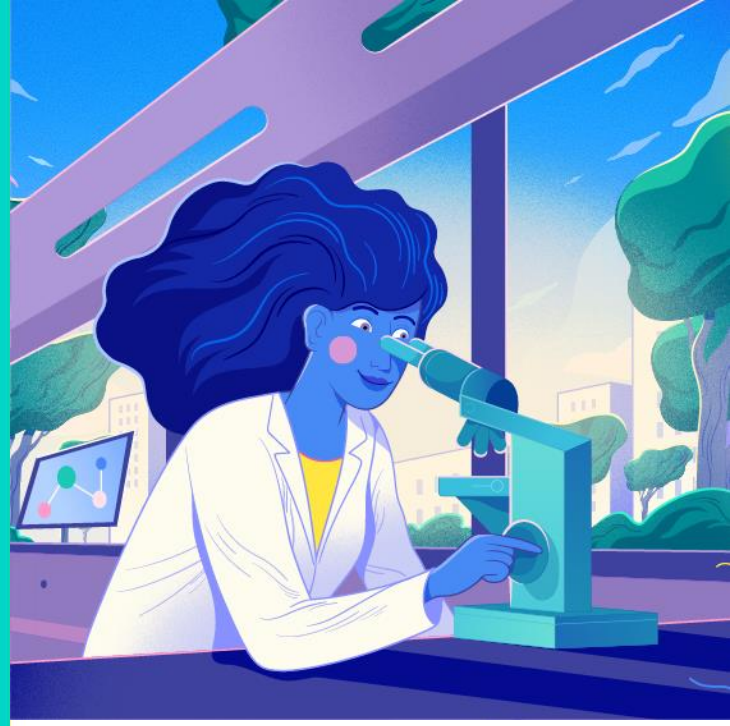
A skin allergy risk assessment (SARA) model – using AOP-aligned NAMs and clinical benchmarks to quantify skin sensitisation risk

Dr Joe Reynolds, SEAC, Unilever
joe.reynolds@unilever.com



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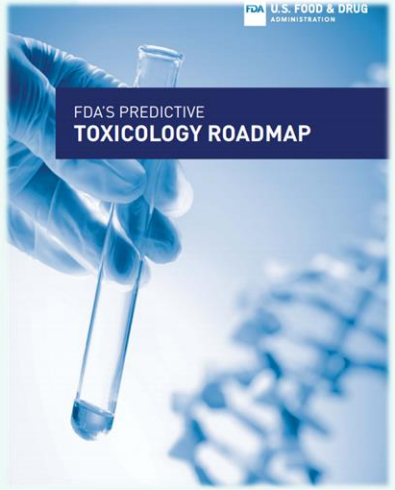
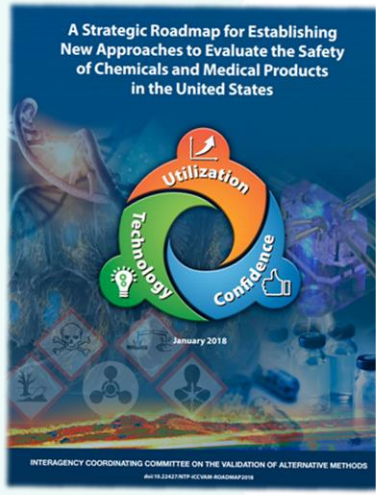
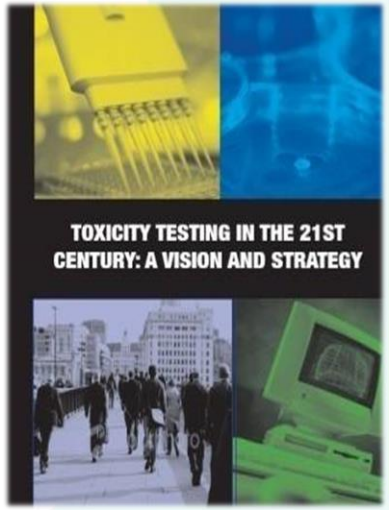
Assessing ingredient & product safety without animal testing

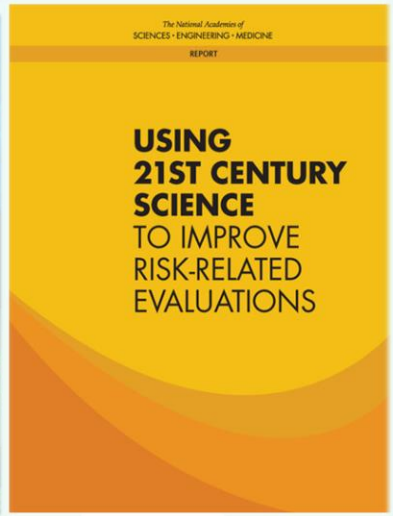
Next Generation Risk Assessment (NGRA)

Is it safe to include x% of chemical y in product z?









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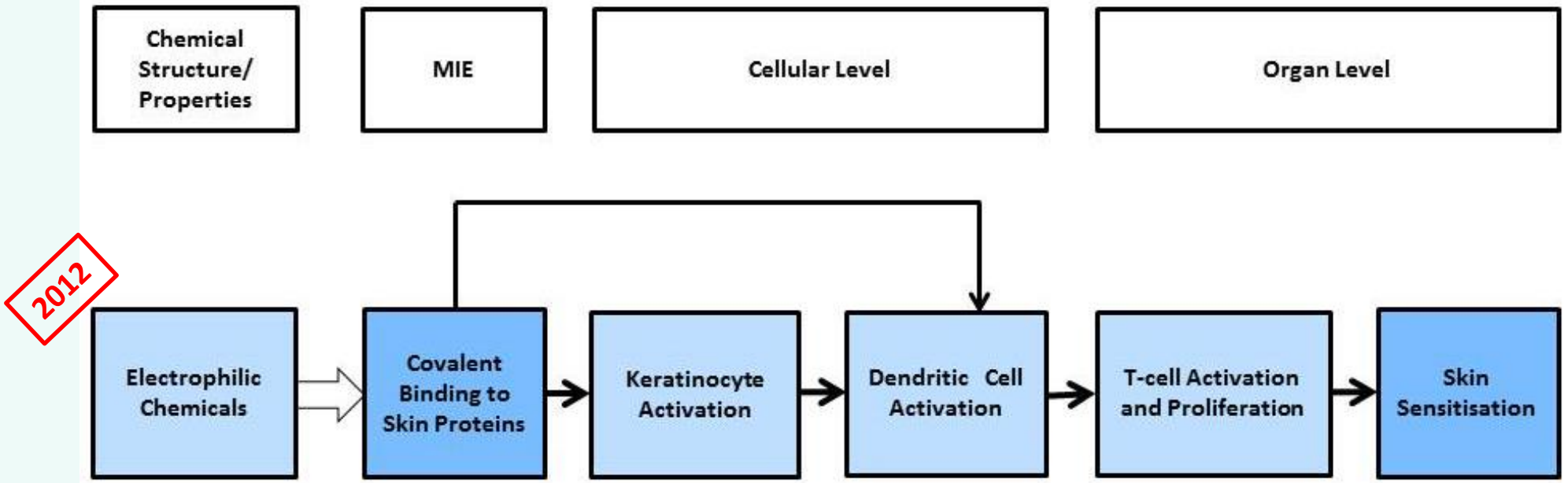
Covalent Protein Binding leading to Skin Sensitisation AOP

https://aopwiki.org/aops/40



Predictive Chemistry

For example:
- DEREK-NEXUS
- OECD QSAR Toolbox
- TIMES
- ToxTree

Protein Reactivity

OECD TG 442C
Includes:
- ADRA
- DPRA
- kDPRA

Keratinocyte Activation

OECD TG 442D
Includes:
- KeratinoSens™
- LuSens

DC Activation

OECD TG 442E
Includes:
- h-CLAT
- IL-8 Luc Assay
- U-Sens™
- GARD

T Cell Proliferation

For Example:
- Human T cell proliferation assays (hTCPA)

Skin Sensitisation

OECD TG 429: mouse local lymph node assay (LLNA) & variants TG442A & 442B

OECD TG 406: Buehler & Guinea Pig Maximisation Test (GPMT)

Human evidence
e.g. Human Repeat Insult Patch Test (HRIPT)

in silico NAM *in chemico/vitro* NAM *in vivo* evidence

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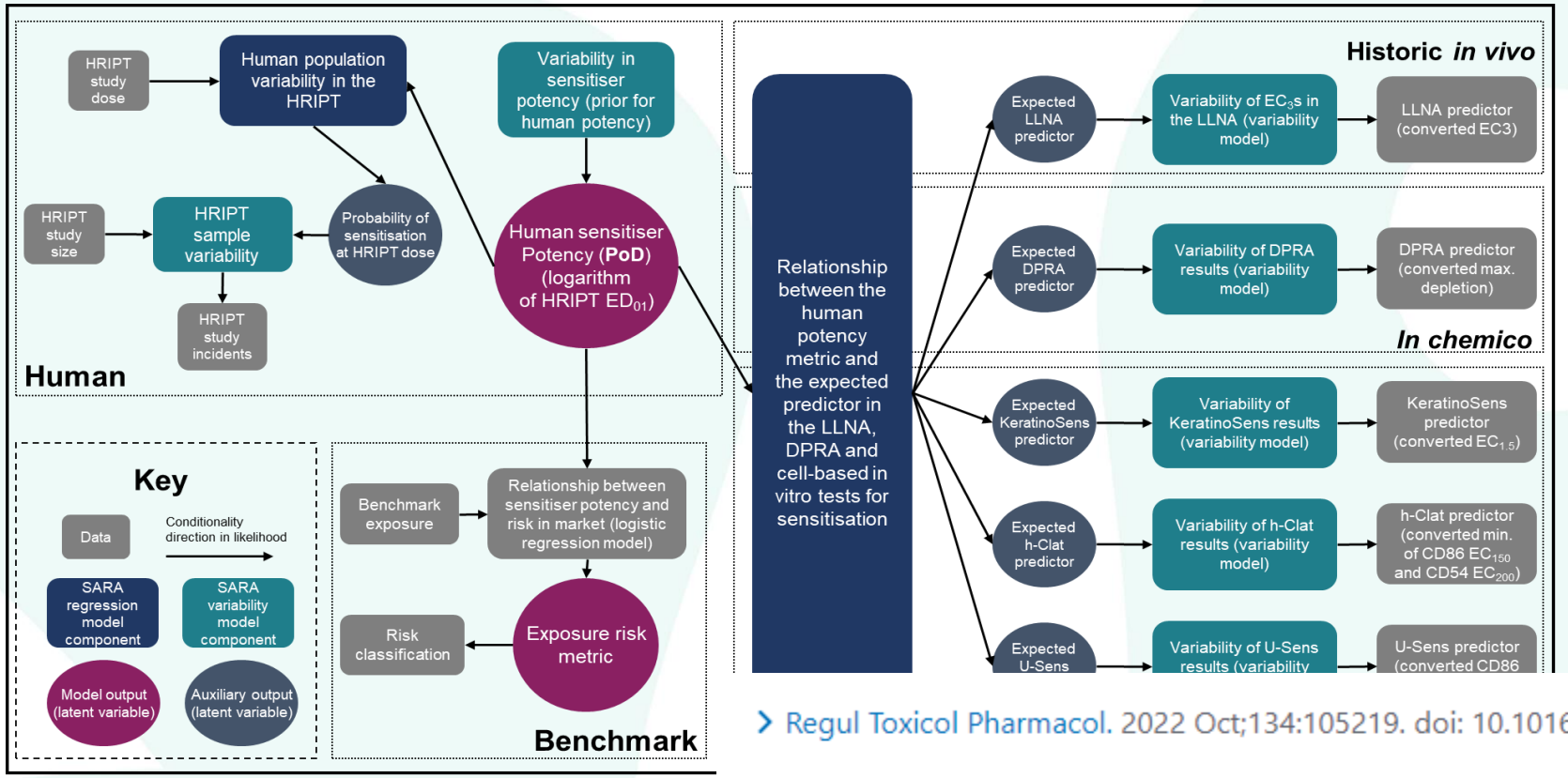
SARA Model



› Regul Toxicol Pharmacol. 2022 Oct;134:105219. doi: 10.1016/j.yrtph.2022.105219. Epub 2022 Jul 12.

Decision making in next generation risk assessment for skin allergy: Using historical clinical experience to benchmark risk

J Reynolds, N Gilmour, M T Baltazar, G Reynolds, S Windebank, G Maxwell

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SARA inputs - Historic and new approach methodology (NAM) data

Target of inference: dermally applied dose at which there is a 1% sensitisation rate in a human repeat insult patch test (HRIPT). *Called the* ED_{01}

Historic *in vivo* data:

- HRIPT - N sensitised out of N tested following dermal dose X in µg cm^{-2}
- LLNA - EC_3 (%)

NAM data

- DPRA – percentage depletion of cysteine and lysine peptides
- KeratinoSens™ – $EC_{1.5}$ (µM)
- h-CLAT – CD86 EC_{150} and CD54 EC_{200} (µg cm^{-3})
- U-Sens – CD86 EC_{150} (µg cm^{-3})

Market-relevant data

Benchmark consumer exposures – use levels in products (%) known to be low risk (or not) for induction of sensitisation.

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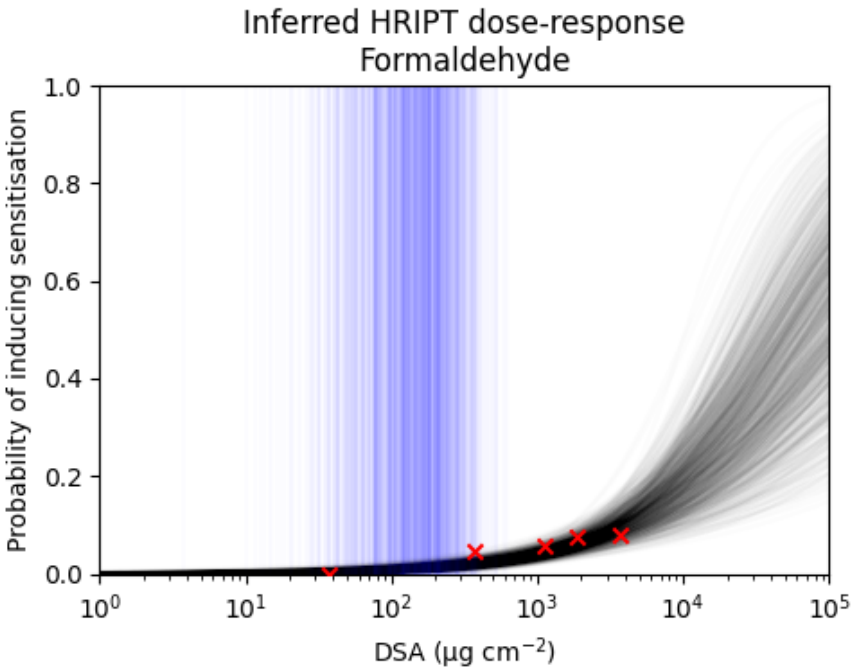
Probabilistic modelling

- SARA model is an example of a Bayesian statistical model
- Model parameters and data are *random variables*
- SARA model is built from a network of conditional probability statements
- The 'fitted' model is the joint distribution of the model parameters conditional on available data

Probability of sensitisation in the HRIPT



- Probability of sensitisation given dermal dose modelled using a logistic function
- Variability in HRIPT studies modelled using a binomial sampling distribution
- Obtain joint distribution of ED_{01} and slope parameter for each chemical
- Partial pooling used to regularise estimates of slope parameters

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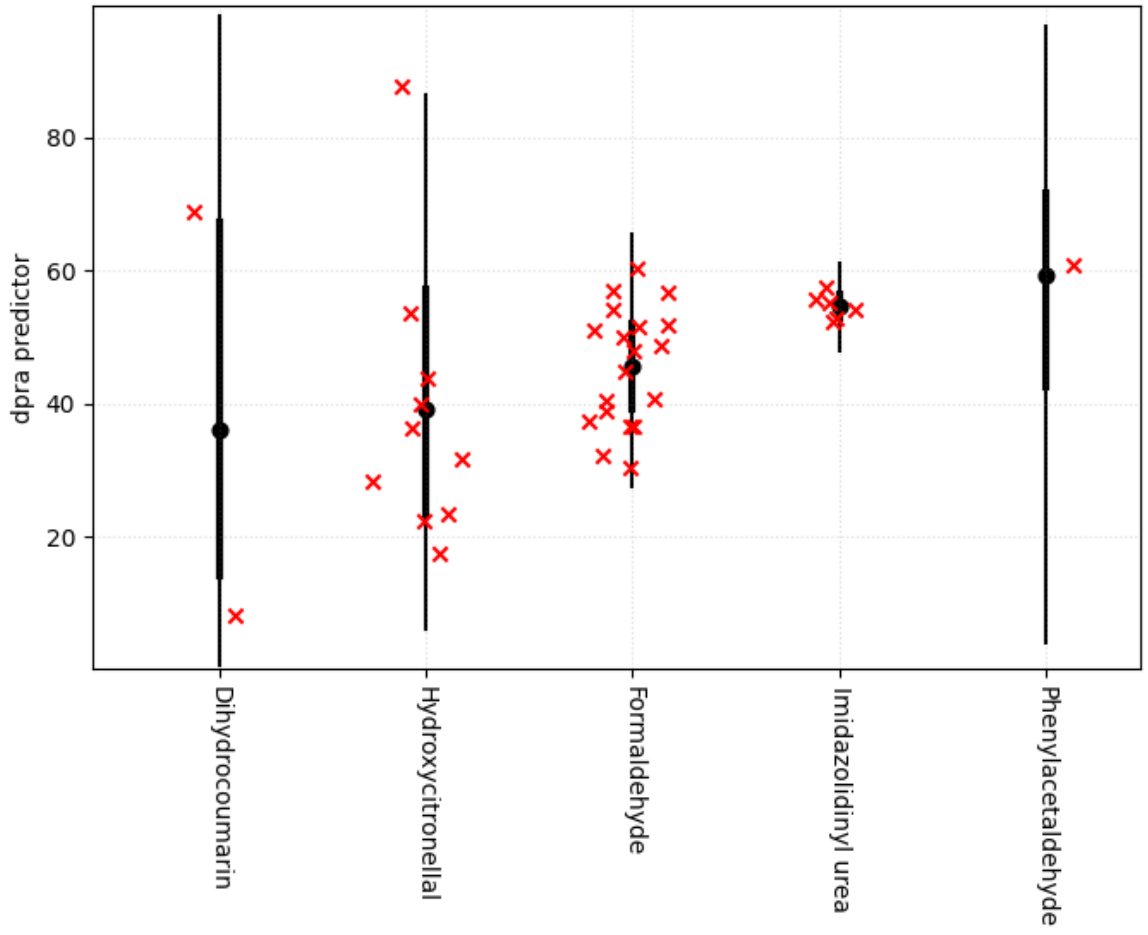
Variability in NAM data



Variability in NAMs modelled within a hierarchical structure:

- Each chemical is assumed to have its own variance
- Variance estimates are regularised using partial pooling
- Allows variance estimates to be made if repeat studies unavailable
- Each chemical has a model parameter for the average result in the NAM

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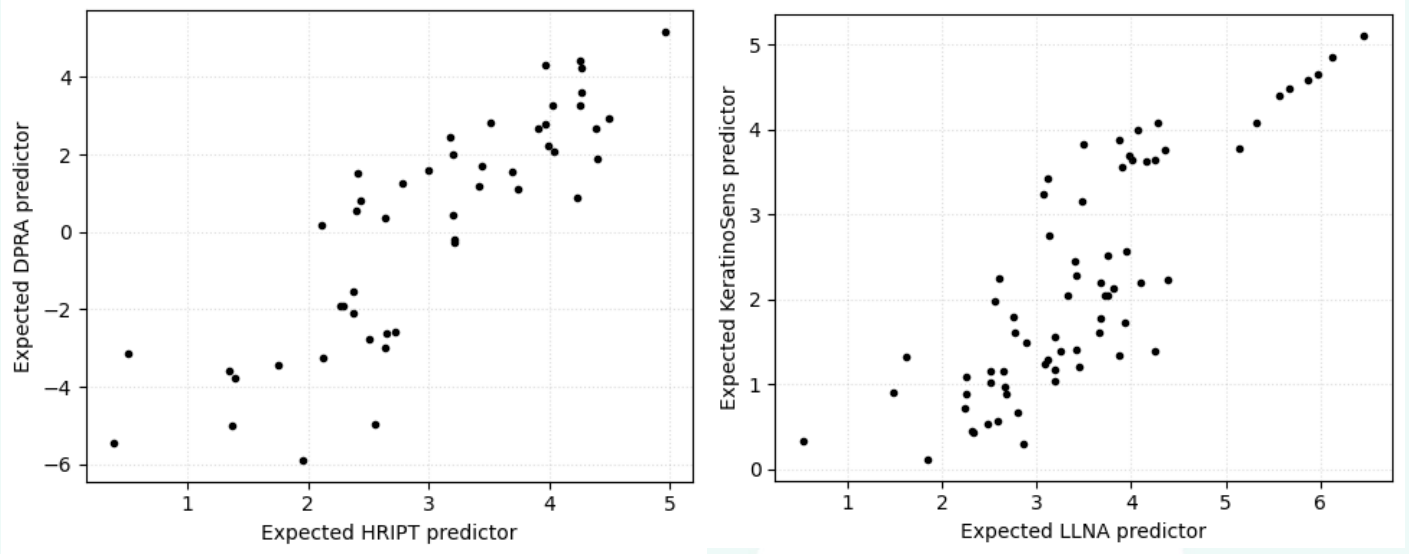
Correlation between NAMs and the ED_{01}



Average result in each NAM (and LLNA) assumed to correlated with HRIPT ED_{01}

NAM results undergo transformation so linearity can be assumed (e.g. logistic transform for DPRA depletion)

Errors modelled using a multivariate Gaussian – accounts for high correlation between NAMs which are measuring similar quantities, e.g. h-CLAT and U-Sens

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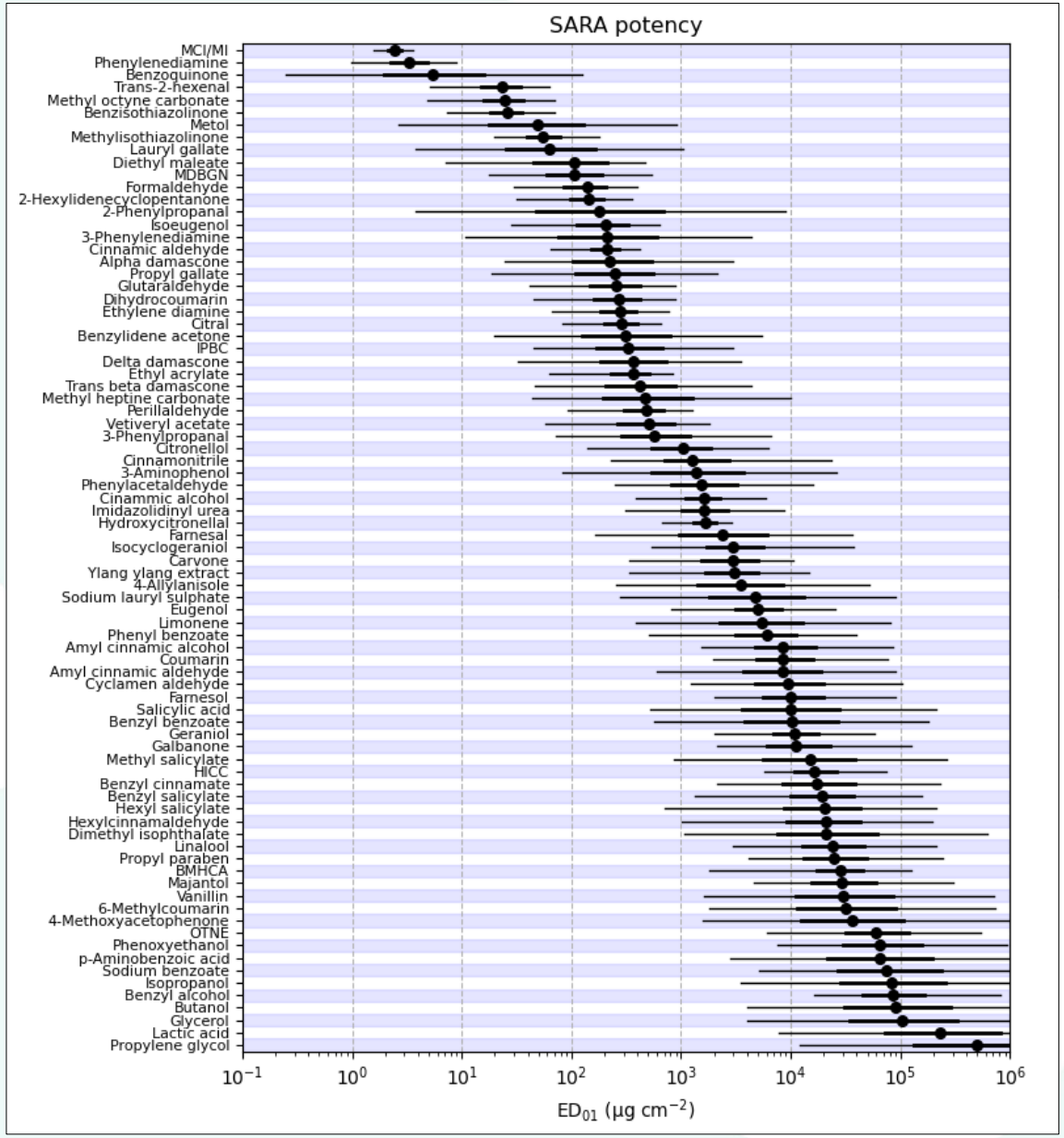
ED_{01} estimates



Obtain distributions for the ED01 for each chemical in the dataset, conditional on all available data

Heterogeneity in data availability results in precision of estimates differing considerably between chemicals

For non-sensitising chemicals, estimates of the ED_{01} largely above what could be physically dosed in the HRIPT

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Benchmark exposures

Material	Product type	Use level (ppm)	Consumer exposure to benchmark product (ng cm^{-2})	Induction risk	Evidence
MCI/MI	Deo	30	350	HIGH	MCI/MI is a broad-spectrum preservative which was first introduced in the 1970's, resulting in an epidemic of contact allergy attributed to its widespread use in leave on cosmetic products at 30ppm, which was reduced to 7.5ppm in leave-on cosmetic products and 15ppm in rinse-off cosmetic products within the European Union (EU) (SCCS, 2009; Thyssen, Johansen, & Menne, 2007) and again in 2014 resulting in MCI/MI being banned from use in in leave on products and restricted to rinse off products (15ppm) (SCCS, 2009). The risk of induction of skin sensitisation from use at both 30ppm and 7.5ppm in leave on products is considered as high risk for induction of skin sensitisation and use at 15ppm in rinse off products is considered as low risk, this is in-line with the conclusions of the SCCS (Fewings & Menne, 1999; SCCS, 2009).
		7.5	87.8	HIGH	
	Face cream	30	100	HIGH	
		7.5	25	HIGH	
	Body lotion	30	18	HIGH	
		7.5	4	HIGH	
	Liquid hand soap	15	7.3	LOW	
	Shampoo	15	1.1	LOW	
	Shower gel	15	0.2	LOW	
MI	Deo	100	1170.5	HIGH	MI was introduced as a stand-alone preservative for use in cosmetic products in 2004, resulting in an epidemic of contact allergy, largely attributed to the presence of MI at 100ppm in cosmetic products and in particular facial product containing MI (SCCS, 2016a; Schwensen et al., 2017; Schwensen et al., 2015, Murad & Marren, 2016; Schwensen et al., 2017; Warshaw et al., 2019). The SCCS concluded in 2014 that MI should be prohibited in leave on products and restricted to 15ppm in rinse off products, this was implemented into regulation from February 2017 (leave on) and January 2018 (rinse off) (2016/1198, 2016; SCCS, 2016a). rates of contact allergy across Europe and other regions have been progressively decreasing since the initial removal from leave on cosmetic products (Kreft & Geier, 2020; Urwin, Craig, Latheef, & Wilkinson, 2017; Uter, Aalto-Korte, et al., 2020, Sukakul, Limphoka, & Boonchai, 2020) but contact allergy to MI is still on the rise in areas where MI use has not yet been regulated (Villarinho, Melo, & Teixeira, 2020). It can be concluded that use of MI at 100ppm in leave on products is high risk for induction of contact allergy. It is not possible to conclude with any certainty whether use of 100ppm MI in rinse off products was high or low risk for induction of skin sensitisation. Thus, the rinse off exposures were classified as unclassifiable. To note, the restriction to 15ppm was intended to prevent elicitation of allergic reactions to these products based upon clinical evidence (SCCS, 2016a; Yazar et al., 2015).
	Face cream	100	272	HIGH	
	Body lotion	100	60	HIGH	
	Liquid hand soap	100	49	UC	
	Shampoo	100	7.4	UC	
	Shower gel	100	1.2	UC	
MDBGN	Deo	1000	11705.4	HIGH	MDBGN was introduced as a preservative in the 1990's and was permitted at levels of up to 1000ppm in both leave on products and rinse off products. Soon after its introduction the prevalence rates of contact allergy in dermatology clinics across Europe began to rise (Wilkinson et al., 2002), resulting in regulatory intervention. In 2005 its use was prohibited in leave on products, and later in 2008 its use was prohibited in rinse off products. (Aakhus & Warshaw, 2011; SCCNFP, 2003; SCCP, 2005; Schwensen et al., 2015). Between 2005 (removal from leave on) and 2008 (time when MDBGN was removed from rinse off products) the prevalence rates of contact allergy were reported to decrease in a number of studies (Schwensen et al., 2015; Svedman et al., 2012; Thyssen et al., 2010) thus it is concluded that exposure of MDBGN from leave on products was responsible for a significant portion of the induction of contact allergy reported and thus be classified as high risk. Since 2008 (removal from rinse off cosmetic products) however, the prevalence rates of contact allergy appear to be subject to fluctuation but no further significant decrease (Deza & Gimenez-Arnau, 2017; Gimenez-Arnau et al., 2017; Schnuch, Schubert, & Geier, 2019; Schwensen et al., 2015), other products have been implicated (Deza & Gimenez-Arnau, 2017; Kamstrup, Bandier, Johansen, & Thyssen, 2017) but on the whole the relatively high rate of contact allergy maintained since 2008 is yet to be fully explained. Given that exposure to MDBGN from rinse off products ceased in 2008 and lack of clear evidence to show further downward trends in contact allergy it is concluded that other exposures are responsible for the ongoing prevalence rates of contact allergy reported and that exposure to MDBGN in rinse off products represents a low risk for
	Face cream	1000	2724	HIGH	
	Body lotion	1000	600	HIGH	
	Liquid hand soap	1000	489	LOW	
	Shampoo	1000	74	LOW	
	Shower gel	1000	12	LOW	

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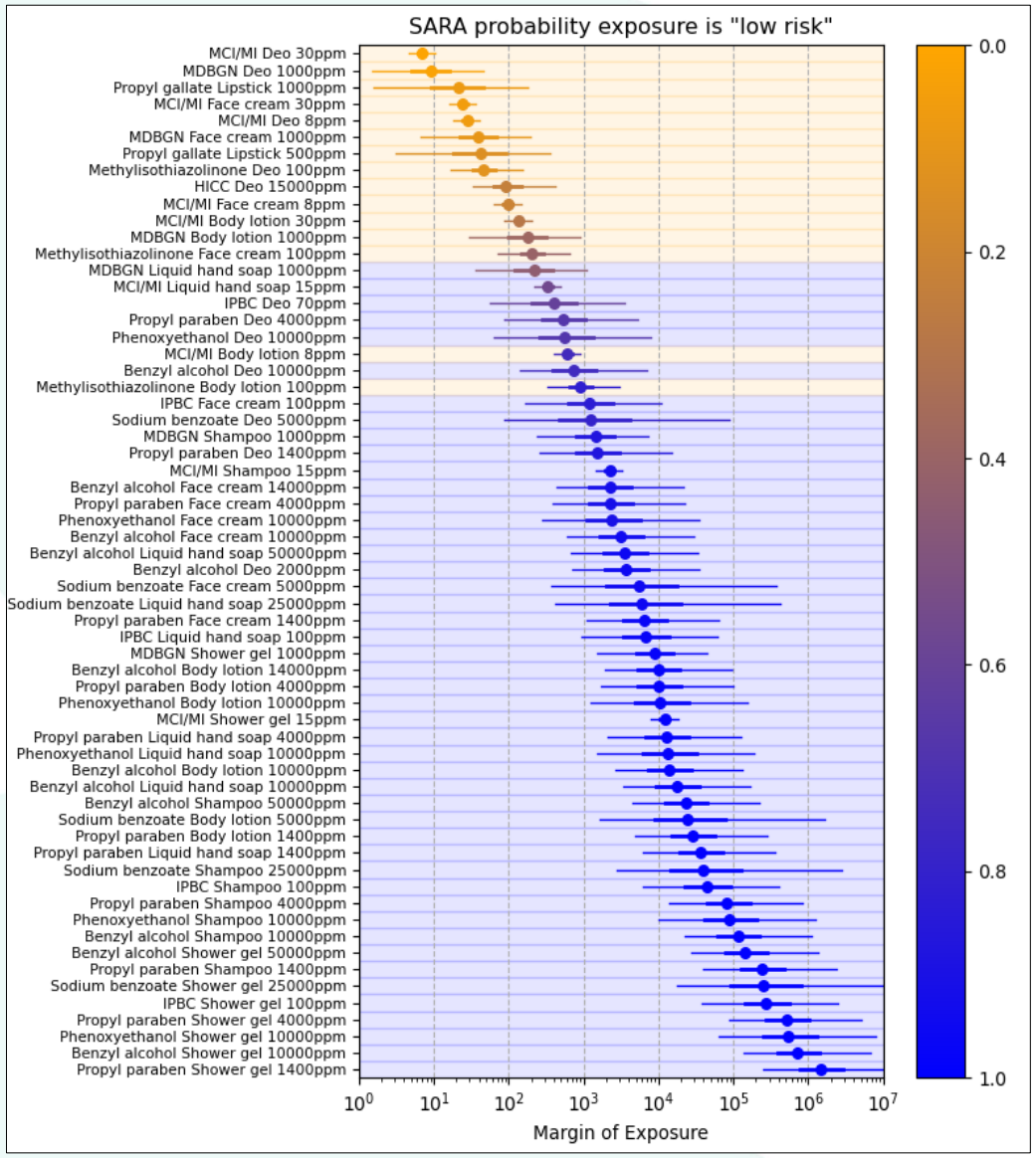
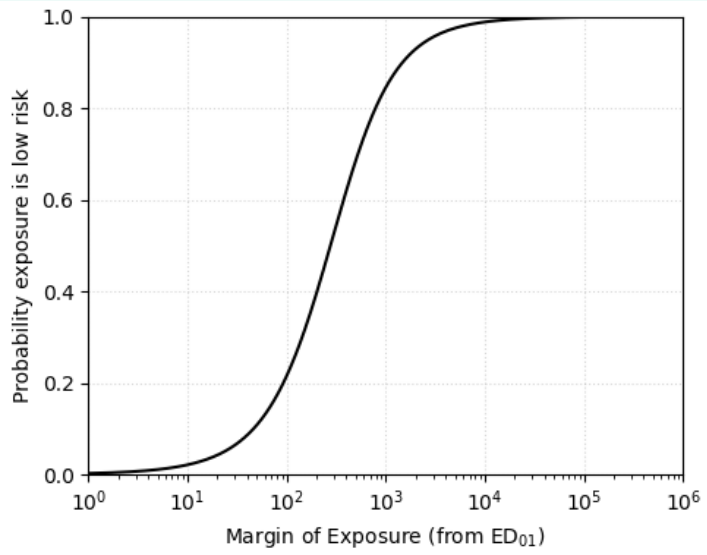
Benchmark exposures – mapping margins of exposure to risk classifications



A set of benchmark consumer exposures have been defined and categorised as low or high risk for induction of skin sensitisation

Margins of exposure from the ED_{01} are regressed against the classification

Allows prediction of the classification using the margin of exposure when the true risk status is unknown



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Evaluation of the SARA model

- Limited set of benchmark exposures means truly independent test set unavailable
- Use of a “leave-one-chemical-out” cross validation strategy
- Predict benchmark risk using
  a) NAM data only
  b) Historic in vivo data only
  c) All available data

Chemical	Product	Use level	Exposure (µg/cm2)	Risk class	Prob. low risk in vivo	Prob. low risk all data	Prob. low risk NAM	AEL:CEL
MDBGN	Shower gel	1000ppm	0.012	0	0.98	0.92	0.85	35
MDBGN	Shampoo	1000ppm	0.074	0	0.89	0.69	0.56	5.7
MDBGN	Liquid hand soap	1000ppm	0.49	0	0.66	0.32	0.23	2.6
MDBGN	Body lotion	1000ppm	0.60	1	0.62	0.28	0.20	2.1
MDBGN	Face cream	1000ppm	2.7	1	0.36	0.10	0.06	0.46
MDBGN	Deo	1000ppm	12	1	0.16	0.03	0.02	0.036
Propyl gallate	Lipstick	500ppm	5.9	1	0.22	0.26	0.37	0.19
Propyl gallate	Lipstick	1000ppm	12	1	0.15	0.16	0.25	0.093

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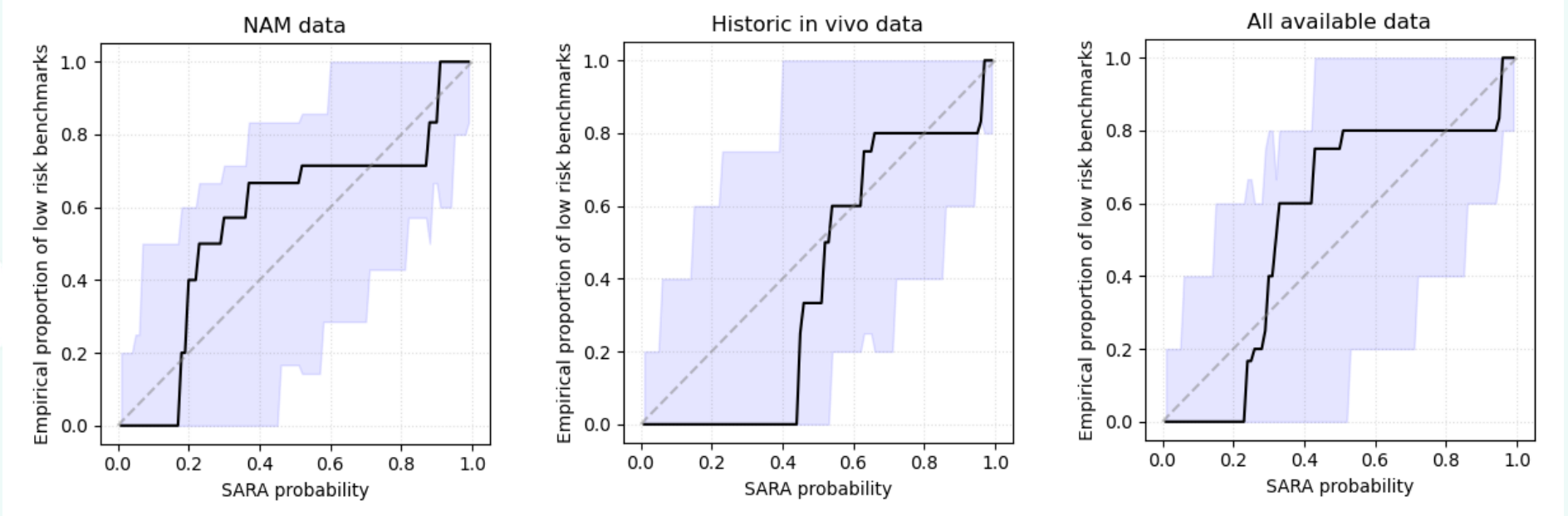
Calibration of the risk metric

- Demonstrate probability predictions can be assumed calibrated, i.e. at 95% confidence level, around 95% of predictions correct



Conclusions

- Probabilistic model constructed to quantify associations (with explicit representation of the uncertainty) between historic *in vivo* data and NAM data relevant for skin sensitisation
- Takes into account variability in all data sources
- Provides a hazard-based output (ED_{01}) and a risk-based output if considering some exposure scenario (probability exposure is low risk for induction of skin sensitisation)
- Evaluated with respect to calibration of the risk metric

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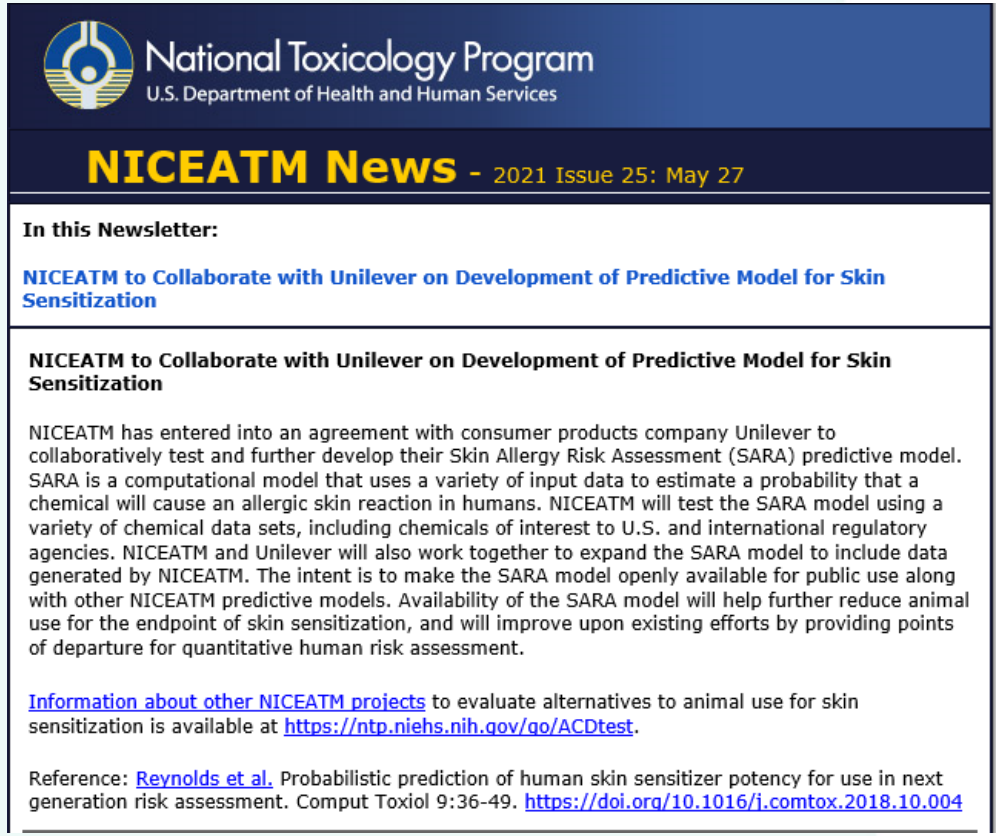
Next steps

- Include me-too assays for key events 1 and 2, e.g. kinetic DPRA and Lu-Sens assays
- Expand the number of benchmark exposures – work with dermatology clinics to identify further product-chemical combinations that considered low / high risk for induction of skin sensitisation based on market experience
- Explore more novel NAMs as predictors for skin sensitisation potency, e.g. potential to induce oxidative stress
- Include in silico reactivity predictions derived from chemical structure



National Toxicology Program
U.S. Department of Health and Human Services

NICEATM News - 2021 Issue 25: May 27

In this Newsletter:

NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization

NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization

NICEATM has entered into an agreement with consumer products company Unilever to collaboratively test and further develop their Skin Allergy Risk Assessment (SARA) predictive model. SARA is a computational model that uses a variety of input data to estimate a probability that a chemical will cause an allergic skin reaction in humans. NICEATM will test the SARA model using a variety of chemical data sets, including chemicals of interest to U.S. and international regulatory agencies. NICEATM and Unilever will also work together to expand the SARA model to include data generated by NICEATM. The intent is to make the SARA model openly available for public use along with other NICEATM predictive models. Availability of the SARA model will help further reduce animal use for the endpoint of skin sensitization, and will improve upon existing efforts by providing points of departure for quantitative human risk assessment.

Information about other NICEATM projects to evaluate alternatives to animal use for skin sensitization is available at https://ntp.niehs.nih.gov/go/ACDtest.

Reference: Reynolds et al. Probabilistic prediction of human skin sensitizer potency for use in next generation risk assessment. Comput Toxiol 9:36-49. https://doi.org/10.1016/j.comtox.2018.10.004

Unilever are working with NICEATM to develop a publicly available version of the SARA model

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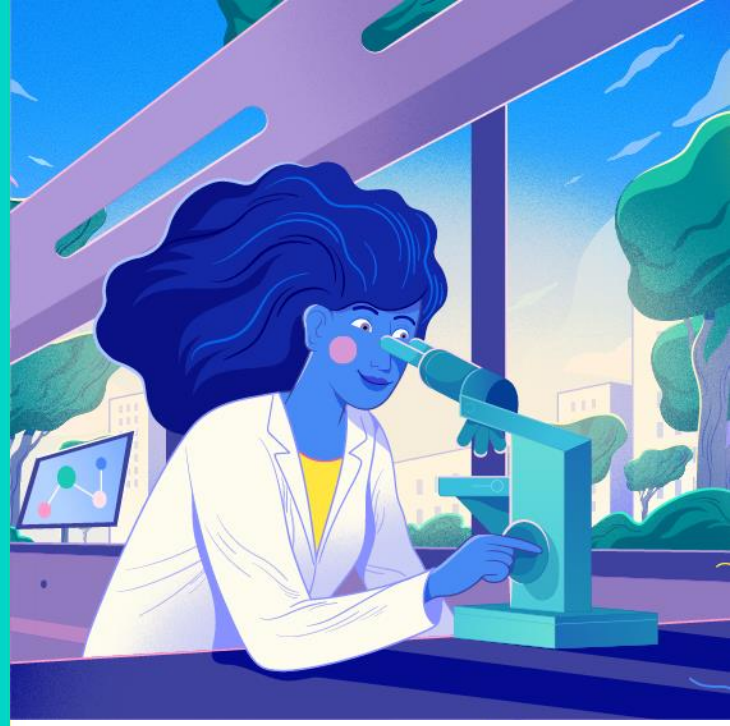
Acknowledgements

Unilever Skin Allergy team: Maja Aleksic, Nora Aptula, Maria Baltazar, Catherine Barratt, Richard Cubberley, Matt Dent, Nicola Gilmour, Cameron MacKay, Sue Martin, Alistair Middleton, Beate Nicol, Ruth Pendlington, Sam Piechota, Katarzyna Przybylak, Ramya Rajagopal, Georgia Reynolds, Ouarda Saib, Sandrine Spriggs, Charlotte Thorpe, Carl Westmoreland, Sam Windebank, Gavin Maxwell

Our collaborators – past and present

Joe.reynolds@unilever.com



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