

New Approach Methods (NAMs)-Based Next Generation Risk Assessment (NGRA) for Skin Allergy and Case Study

Dr Jin Li 李津

Unilever's Safety & Environmental Assurance Centre (SEAC)
英国联合利华安全及环境保障中心



Unilever

“科学·创新·发展” - 2022年化妆品评价与科学监管学术研讨会·广州

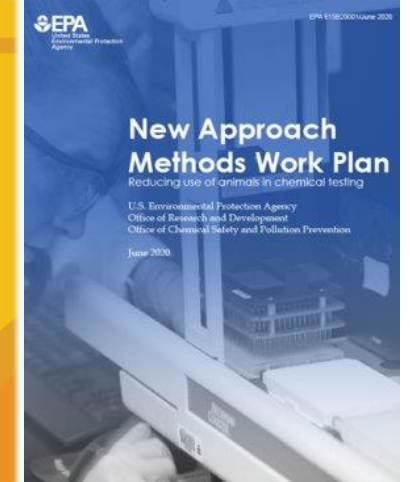
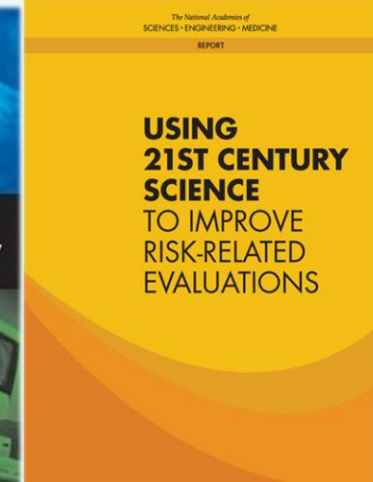
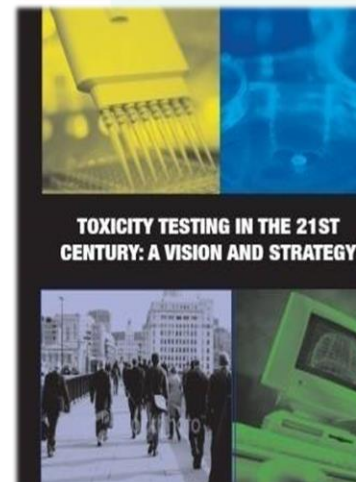
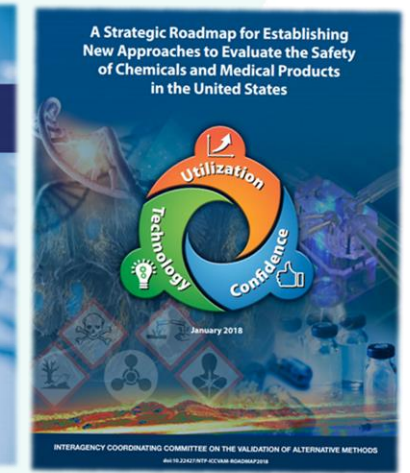
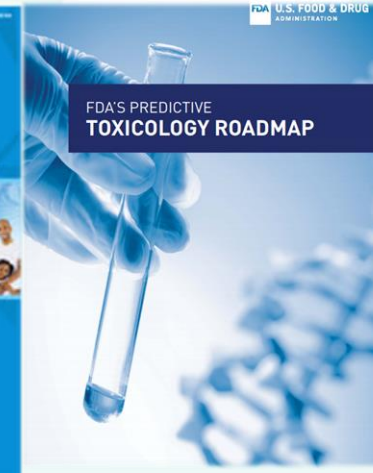
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Assessing ingredient & product safety without animal testing

Next Generation Risk Assessment (NGRA)



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



Principles of Next Generation Risk Assessment from ICCR

Non-animal approaches in Cosmetic Risk Assessment



4 Main overriding principles:

- » The overall goal is a human safety risk assessment
- » The assessment is exposure led
- » The assessment is hypothesis driven
- » The assessment is designed to prevent harm

3 Principles describe how a NGRA should be conducted:

- » Following an appropriate appraisal of existing information
- » Using a tiered and iterative approach
- » Using robust and relevant methods and strategies

2 Principles for documenting NGRA:

- » Sources of uncertainty should be characterized and documented
- » The logic of the approach should be transparently and documented

Dent *et al* (2018), *Computational Toxicology*, **7**, 20-26: <https://doi.org/10.1016/j.comtox.2018.06.001>

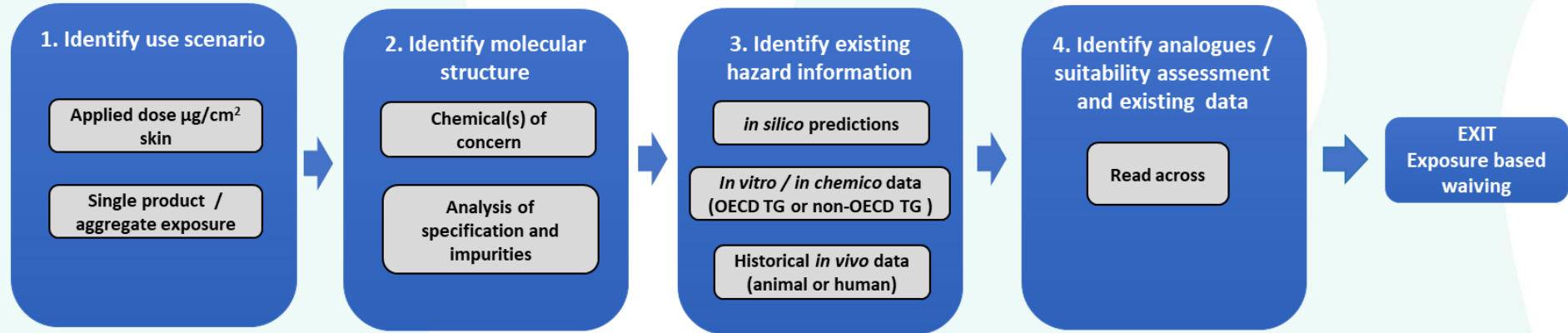
Next Generation Risk Assessment for Skin Allergy



Cosmetics Europe
the personal care association

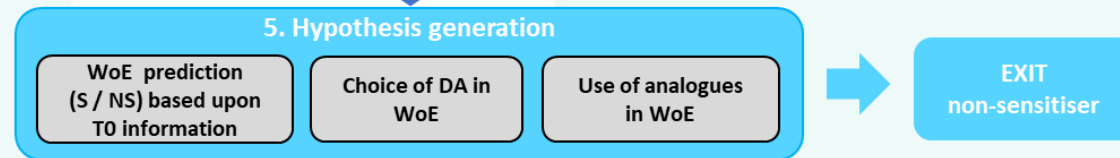
Tier 0

Identify use scenario, chemical of concern and existing information



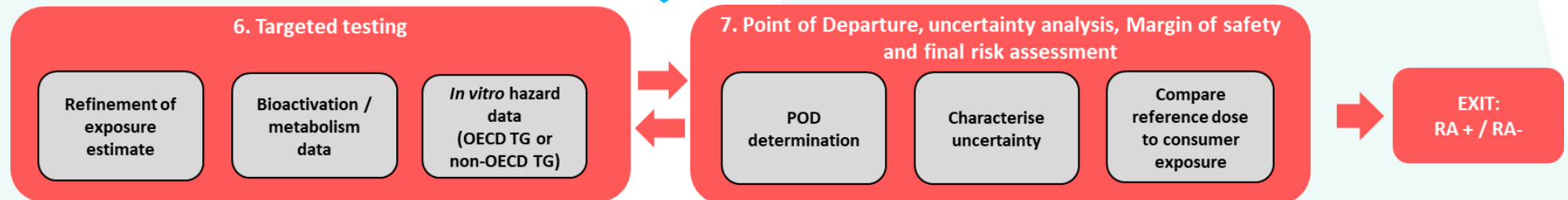
Tier 1

Hypothesis generation; how will data be used in risk assessment?

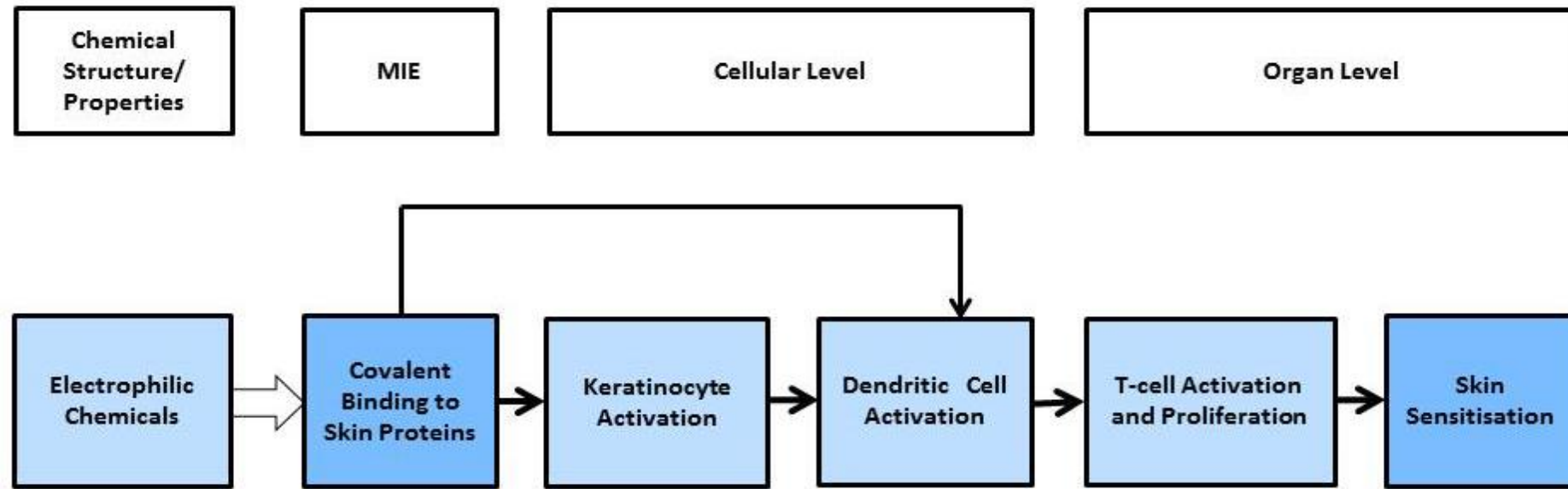


Tier 2

Risk assessment



Skin Sensitisation AOP



Key Event 1 (KE1)

KE2

KE3

KE4

Adverse Outcome (AO)

Predictive Chemistry

For example:

- [DEREK-NEXUS](#)
- [OECD QSAR Toolbox](#)
- [TIMES](#)
- [ToxTree](#)

Protein Reactivity

[OECD TG 442C](#)

Includes:

- ADRA
- ➔ DPRA

Keratinocyte Activation

[OECD TG 442D](#)

Includes:

- ➔ KeratinoSens™
- LuSens

DC Activation

[OECD TG 442E](#)

Includes:

- ➔ h-CLAT
- IL-8 Luc Assay
- ➔ U-Sens™

T Cell Proliferation

For Example:

- Human T cell proliferation assays (hTCPA)

Skin Sensitisation

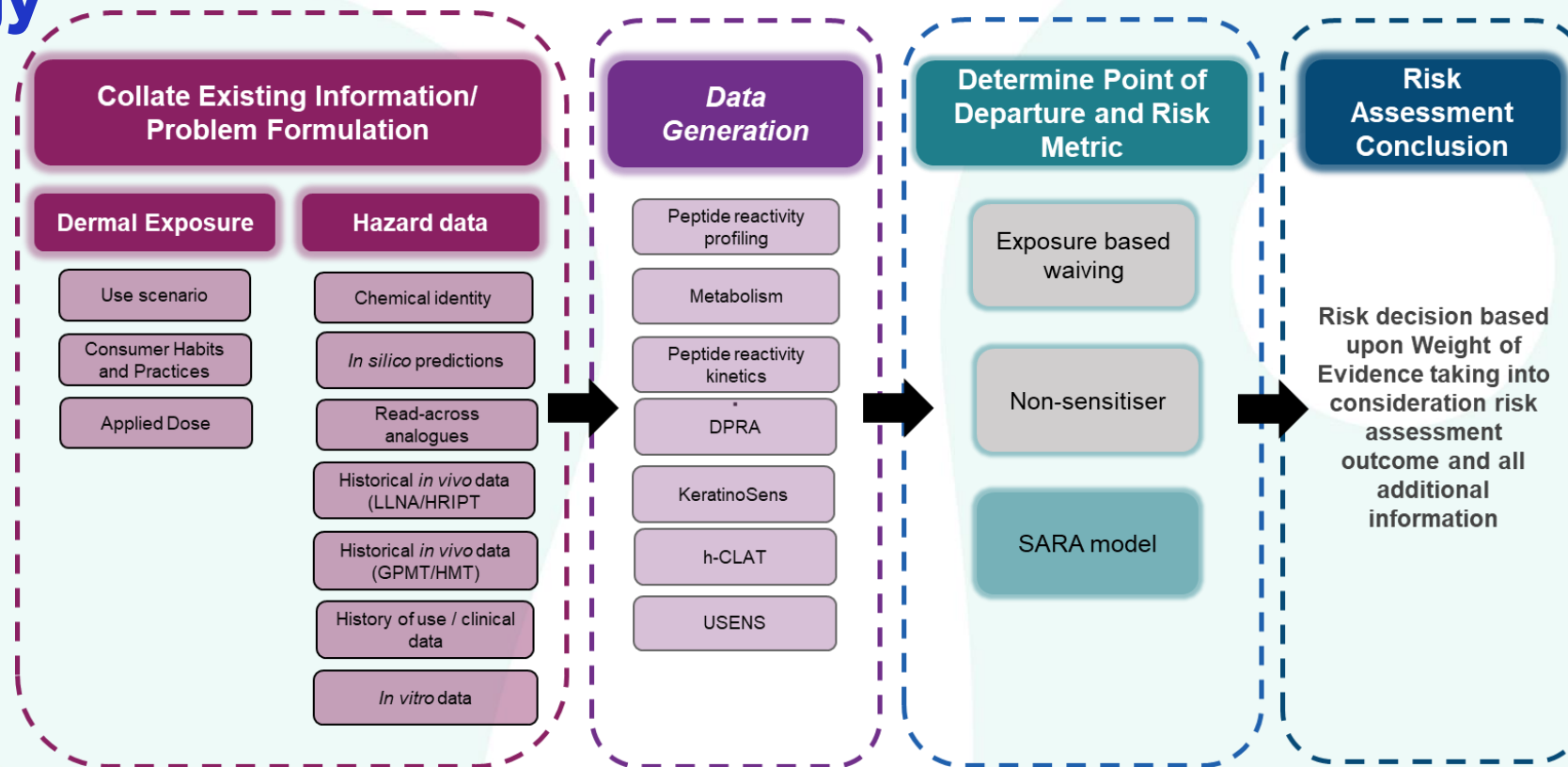
- ➔ [OECD TG 429](#): mouse local lymph node assay (LLNA) & variants [TG442A](#) & [442B](#)
- [OECD TG 406](#): Buehler & Guinea Pig Maximisation Test (GPMT)
- ➔ Human evidence e.g. [Human Repeat Insult Patch Test \(HRIPT\)](#)

in silico NAM

in chemico/vitro NAM

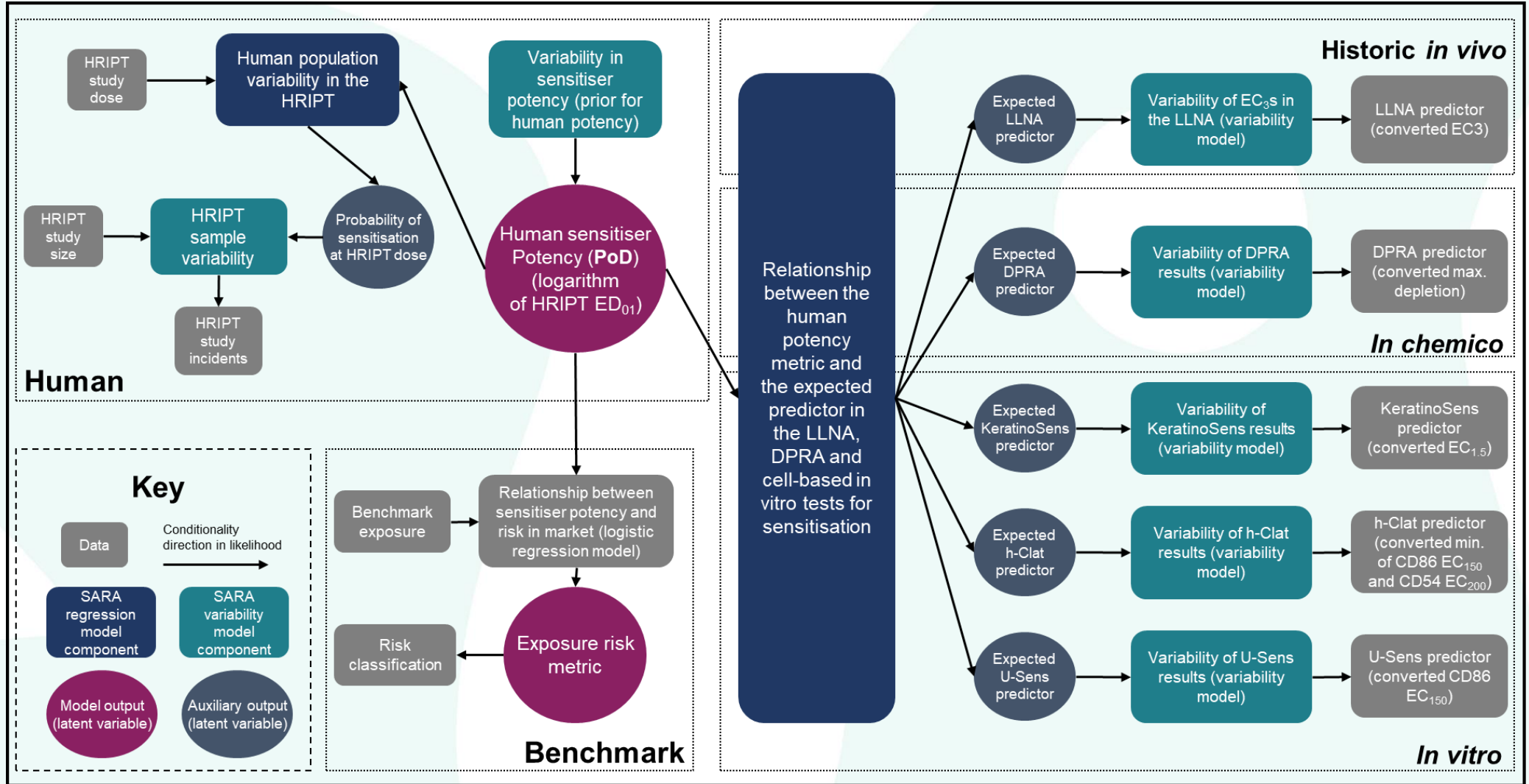
in vivo evidence

Next Generation Risk Assessment (NGRA) Framework for Skin Allergy



- Our NGRA framework for skin allergy is based upon the ICCR principles (Dent *et al* 2018) and the previously published NGRA frameworks for systemic tox {SEURAT-1} (Amaral *et al* 2018) and skin allergy {Cosmetic Europe} (Gilmour *et al* 2020).
- Designed to use a WoE based upon all available information, accommodate range of consumer product exposure scenarios and provide a quantitative point of departure and risk metric → SARA Model.

SARA Model

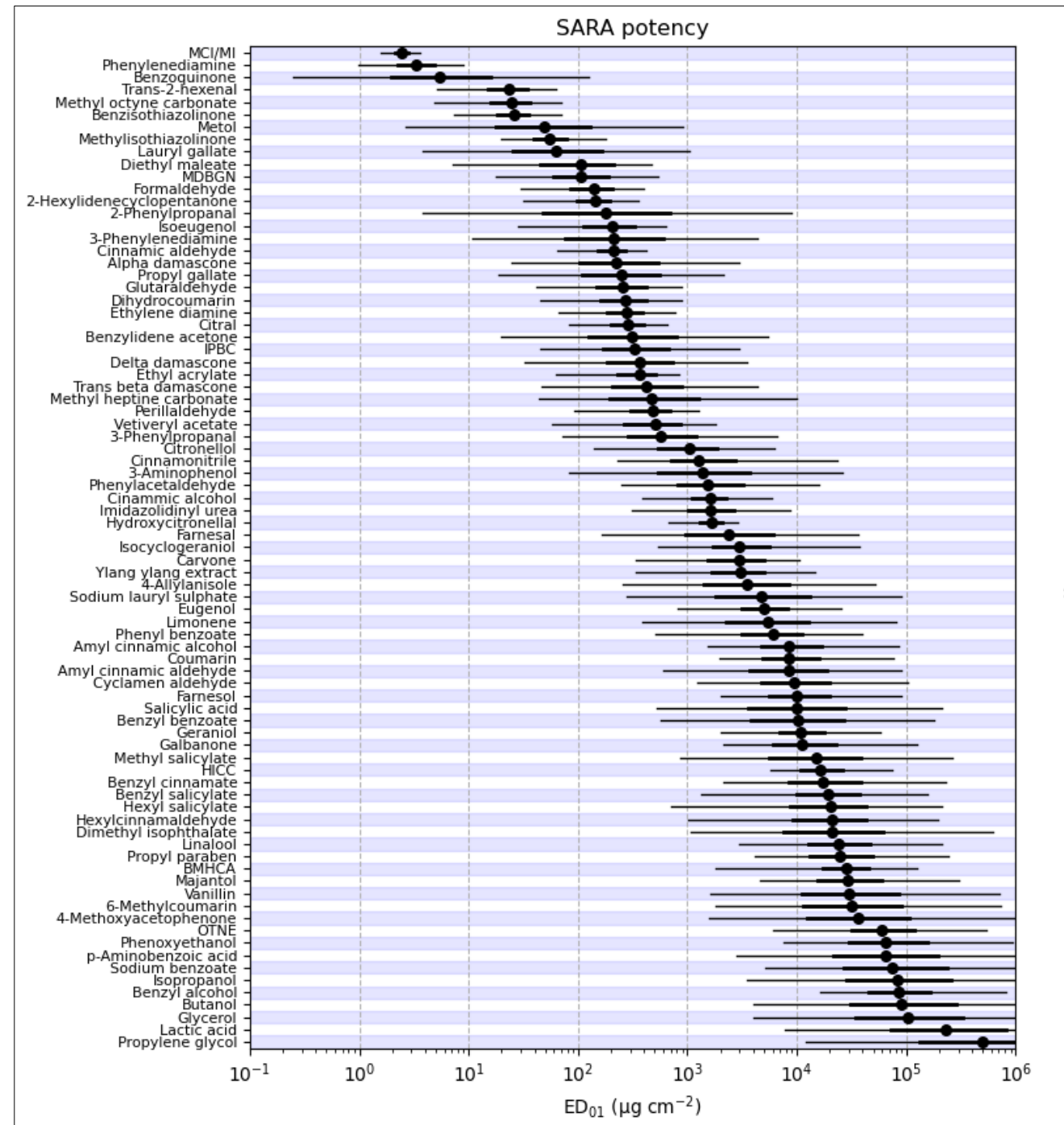


- The SARA model uses Bayesian statistics to infer a probability that a consumer exposure to some chemical can be considered low risk, to inform risk assessment decisions.

- The SARA Model uses a database of public NAM data covering AOP KEs 1-3, and historic LLNA and HRIPT data for the AOP AO.

SARA Defined Approach

- The point of departure (PoD) metric is a dose with a 1% chance of human skin sensitisation (termed ED₀₁).
- The SARA dataset contains 81 chemicals.
- The model accounts for variability in the DPRA, KeratinoSens™, h-CLAT and U-Sens™ and the *in vivo* data.
- The model has been expanded to incorporate benchmark exposure information.



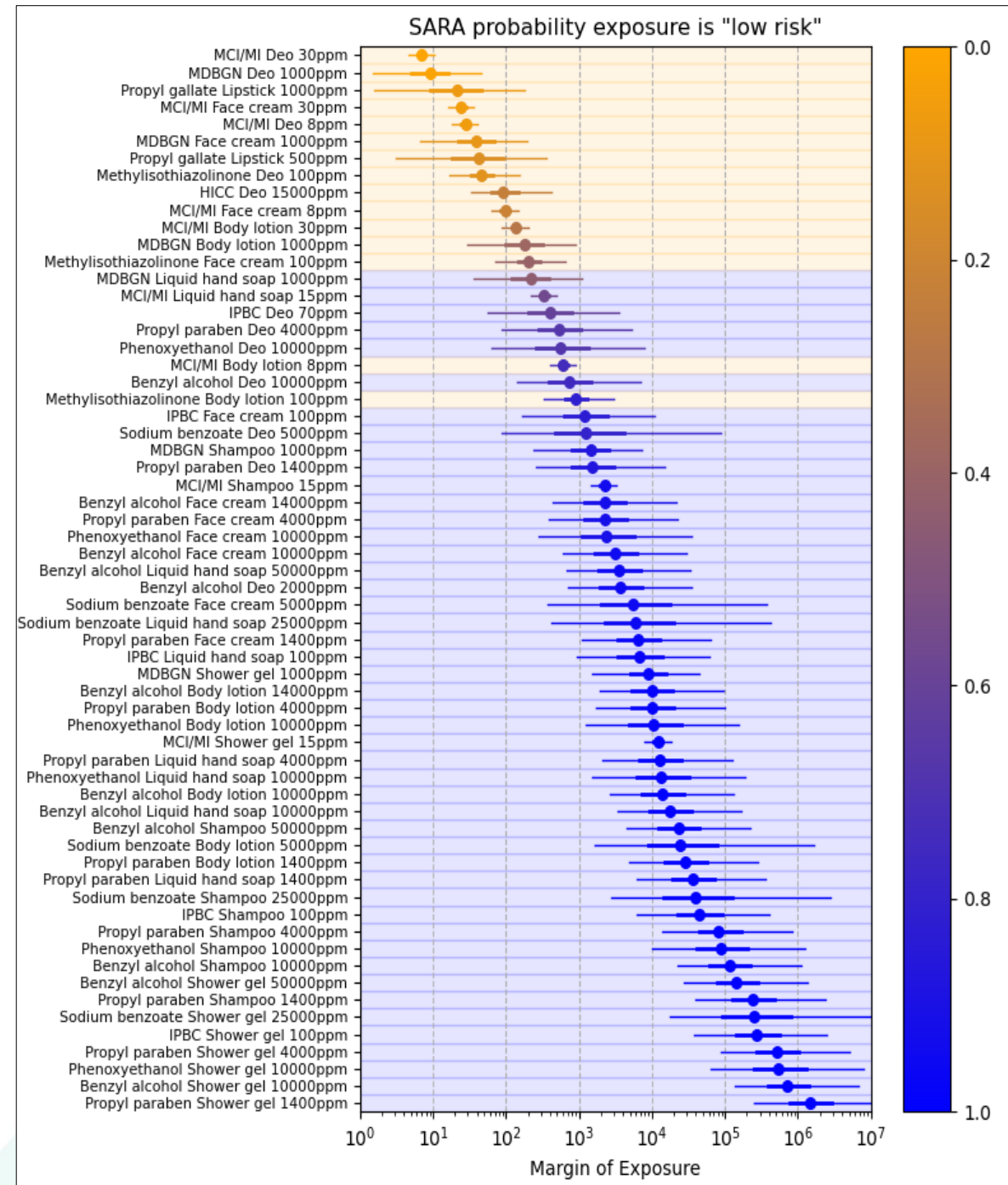
Use of consumer exposure information and clinical evidence to develop skin allergy risk benchmarks

- Traditional risk assessment approaches for skin allergy use safety factors to rescale PoDs to market-equivalent safe doses for comparison against consumer exposure estimates.
- For NGRA, publicly available benchmark exposure information can be used to establish that an exposure is low risk and can be considered safe.
- To apply this concept, we established 62 low or high risk benchmark exposures using 10 human skin allergens (e.g. MCI/MI) with an established history of use in 7 cosmetic product types.

Material	Product type	Use level (ppm)	Consumer exposure to benchmark product (ng cm ⁻²)	Induction risk
MCI/MI	Deo	30	350	HIGH
		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	

Expansion of SARA model to use benchmark exposure information

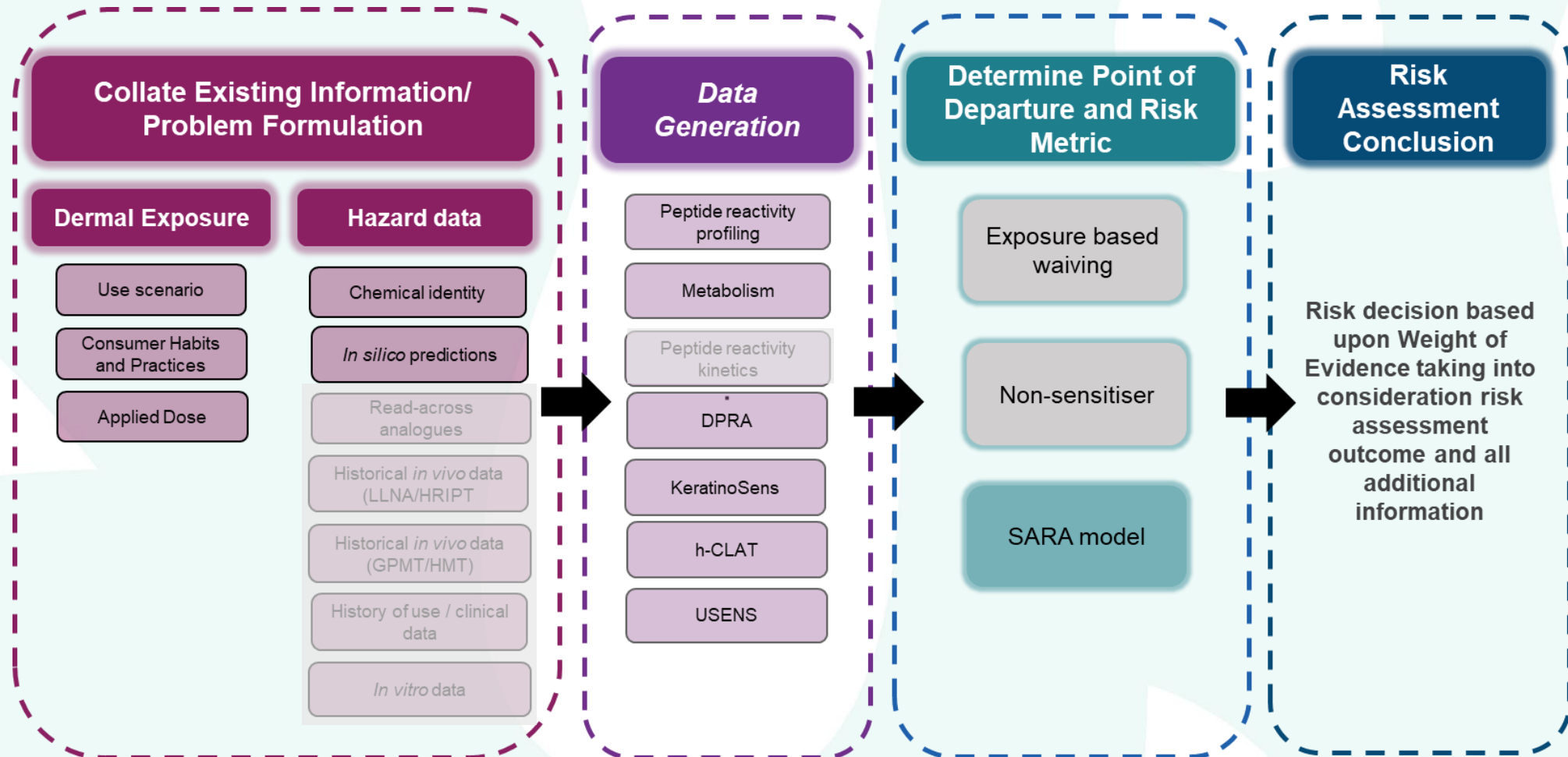
- The SARA model was expanded to incorporate benchmark exposure information as an additional input alongside historic *in vivo* and NAM data.
- After fitting the model, and given some exposure scenario of interest, the model can calculate the *SARA risk metric*, defined as the probability that the exposure is low risk for human skin sensitisation induction.



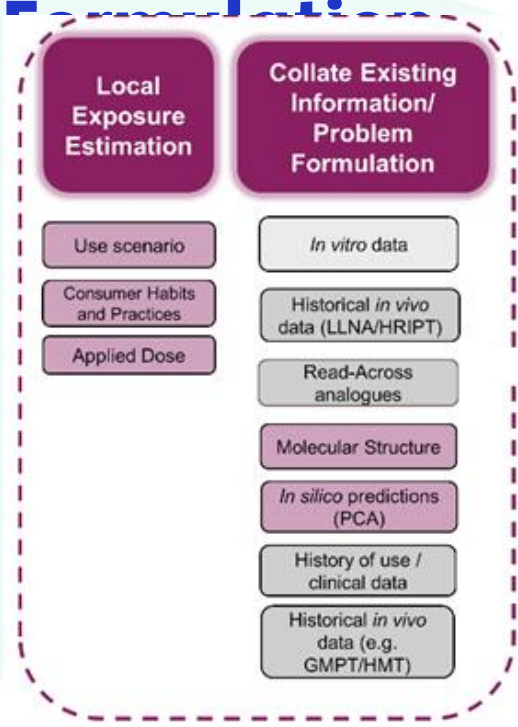
Case Study

Application of NGRA framework for Skin Allergy

This NGRA framework is applied to a hypothetical skin allergy assessment of a consumer product at two exposures - 0.1% coumarin in a face cream and 1% in a deodorant. For the purposes of the case study, *in vivo* data and read-across were not used, and the use of dermal sensitisation threshold (DST) was not appropriate.



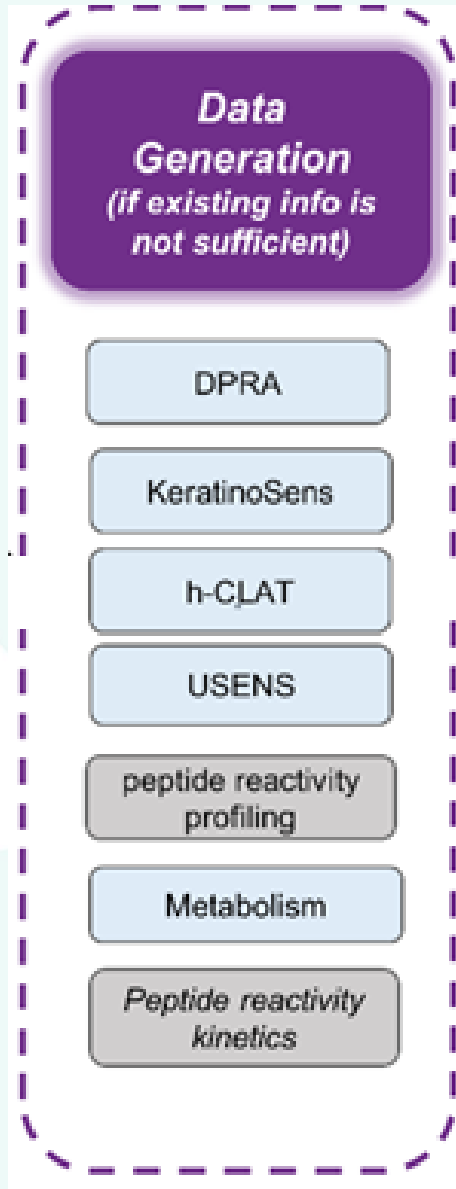
Local exposure + Collate Existing Information/ Problem



Product type	Face cream	Deodorant
Product used per day (90 th percentile) (g/day)	1.54	1.5
Ingredient inclusion level (%)	0.1	1
Skin surface area (face / axilla) (cm ²)	565	200
Leave-on or Rinse-off	Leave-on	Leave-on
Local dermal exposure (µg/cm ²)	2.7	75

- *In silico* chemistry predictions for the sensitiser potential of coumarin: TIMES-SS predicts coumarin and metabolites non-sensitisers; Derek Nexus, ToxTree and OECD QSAR Toolbox all predict sensitiser potential. ToxTree and OECD QSAR Toolbox predicted a Michael Acceptor mechanism. Both direct and indirect (pro-hapten) mechanisms were indicated.
- Meteor Nexus identified hydroxylation as the main route of biotransformation. Most metabolites were predicted to bind to protein, a flag for skin sensitization. 7-OH coumarin was identified as one of the main metabolites in an investigation in human hepatocytes.

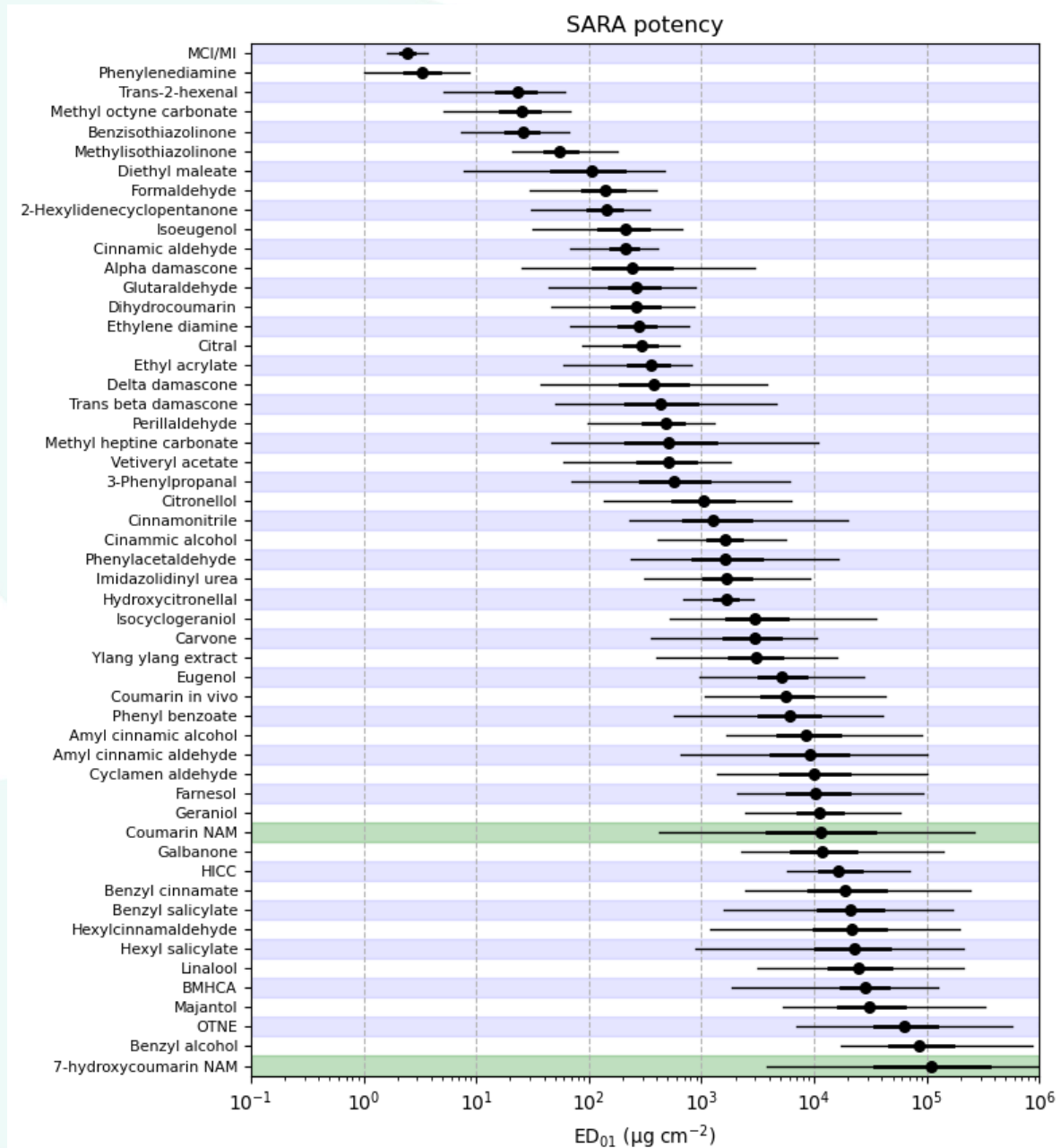
Data Generation



	DPRA (TG442C)		KeratinoSens™ (TG 442D)	h-CLAT (TG 442E)		U-SENS™ (TG 442E)
	%cys depl.	%lys depl.	EC1.5 (µM)	CD86 (EC200 µg/mL)	CD54 (EC150 µg/mL)	CD86 (EC150 µg/mL)
Coumarin	1.3	0	187.5	<178	>637	95.5
7-OH Coumarin	0*	0	>2000	>566	>566	182

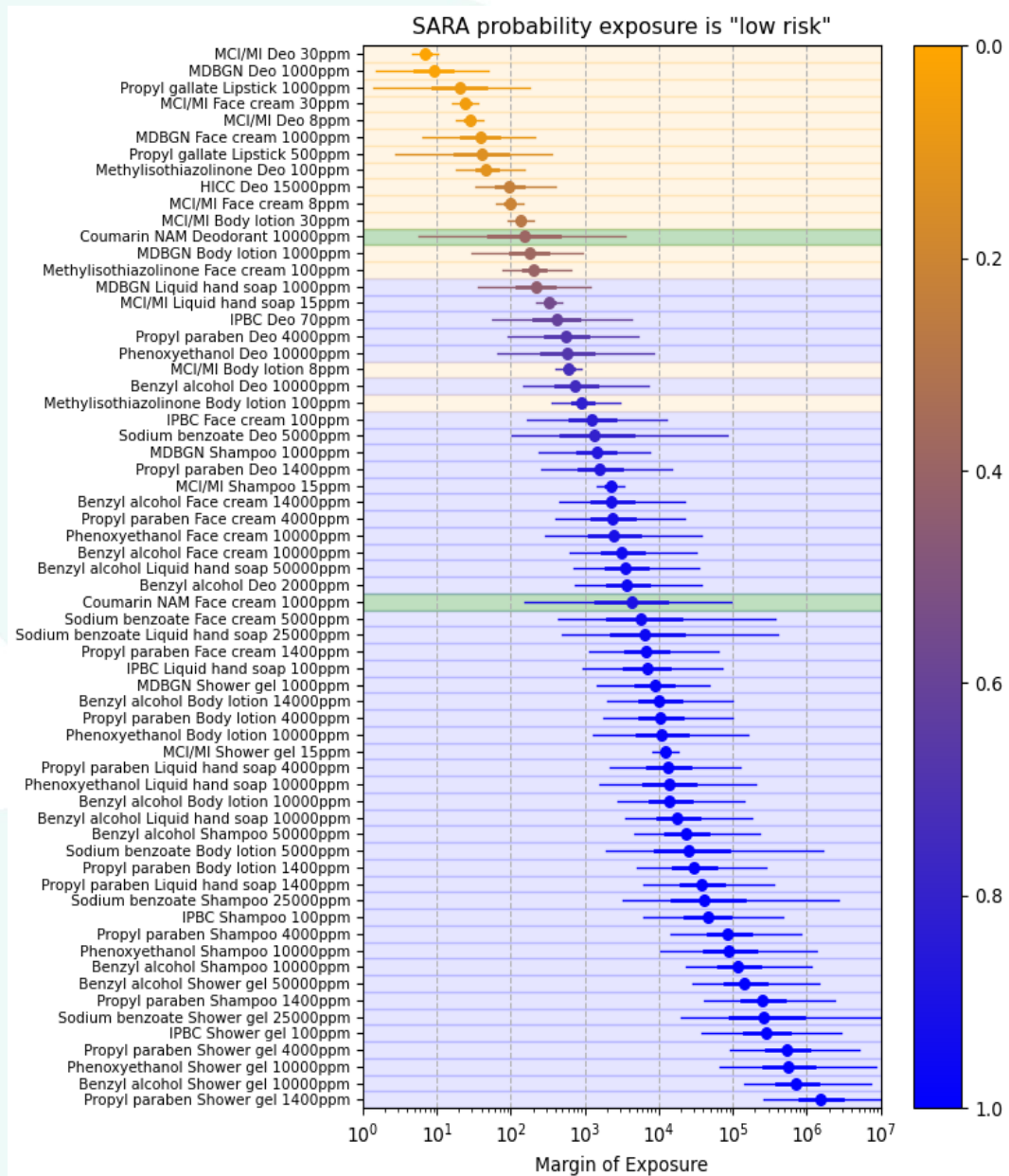
- Coumarin was positive in all tests, except for DPRA where peptide depletion was too low to meet positive threshold.
- 7-OH coumarin was negative in KeratinoSens™ & h-CLAT, positive in USENS™, inconclusive in DPRA. *Peptide profiling was completed which identified cysteine depletion to be caused by dimerization and therefore the DPRA value was adjusted.

Determine Point of Departure (PoD) using SARA Model



- The generated DPRA, KeratinoSens™, hCLAT and USens™ data were used as inputs into the SARA Model to define a human relevant PoD (ED₀₁ i.e the 1% sensitising dose for a HRIPT population).
- For coumarin, the expected SARA Model derived ED₀₁ is 11,000µgcm⁻², whilst for 7-OH coumarin the expected ED₀₁ is 110,000µgcm⁻² i.e. 7-OH coumarin is estimated to be 10-fold less potent than coumarin).
- Therefore, a risk assessment based on coumarin potency data only would be conservative.

Determine Margin of Exposure (MoE)



- The MoE was calculated from the ED₀₁ for coumarin and the dermal exposures for each product type using the SARA Model.
- The median MoE for face cream exposure ranks with the low-risk benchmarks whilst the median MoE for the deodorant exposure ranks with the high-risk benchmarks.
- The SARA DA probability that the exposure is low risk is calculated to be 0.90 for the face cream dermal exposure and 0.39 for the deodorant dermal exposure.
- **Coumarin exposure at 0.1% in a face cream is low risk for skin sensitisation whereas coumarin exposure at 1% in a deodorant is high risk**

NICEATM-Unilever CRADA



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>

NICEATM Team

Nicole Kleinstreuer

Judy Strickland

Dori Germolec

Dave Allen

Jim Truax

Unilever Team

Georgia Reynolds

Nicola Gilmour

Joe Reynolds

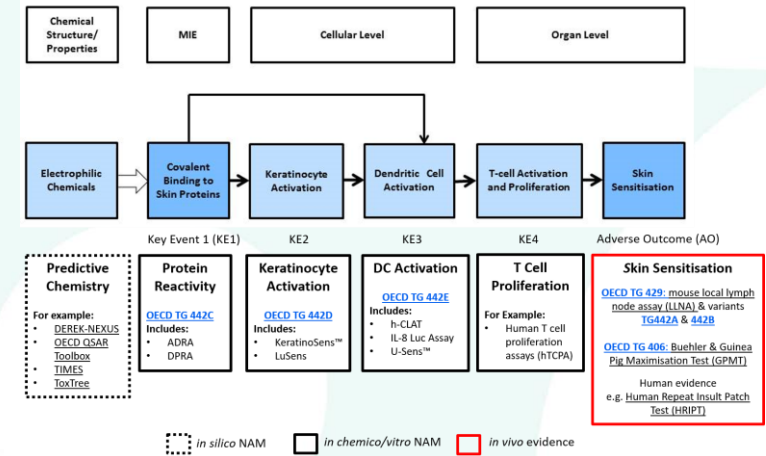
Gavin Maxwell



Unilever

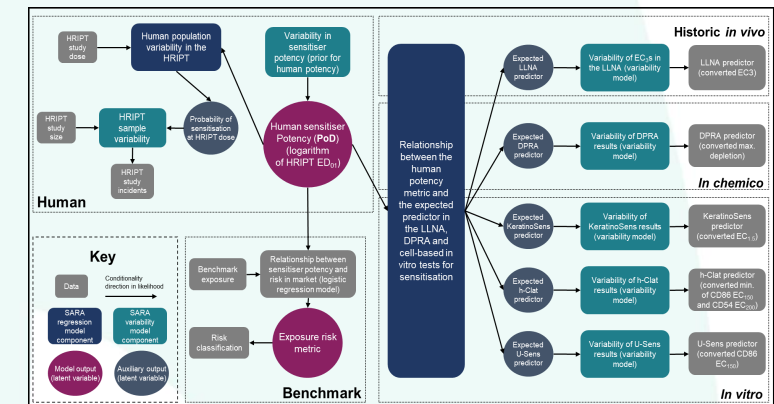
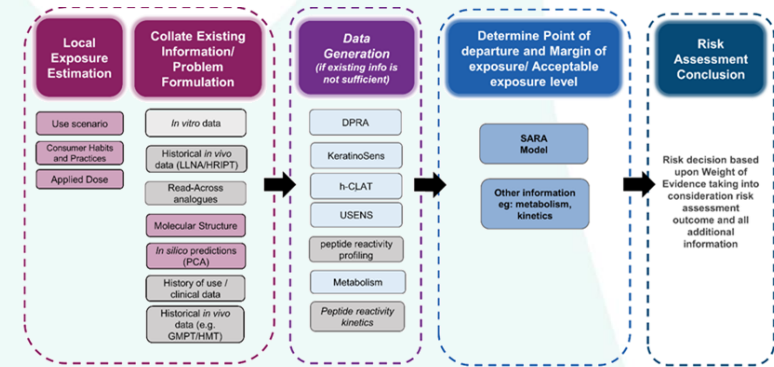
Conclusions

- Significant progress has been made in the last decade to apply non-animal experimental data using Defined Approaches & tiered frameworks.
- Bayesian DAs enable experimental data variability to be modelled and uncertainty in PoDs & risk metrics to be factored into decision-making.



Next Steps

- SARA DA & Skin Allergy Risk Benchmarks manuscripts submitted for publication.
- NICEATM collaboration established to test SARA, expand the approach and make it publicly available.
- In-house work ongoing to explore new SARA inputs & expand the database, including risk benchmarks.



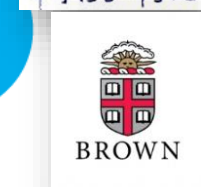
Scientific partnership 科学合作



tt21c.org

GLOBAL PRODUCT SAFETY COLLABORATION

全球产品安全合作 替代方面的合作



联合利华安全及环境保障中心 - 英国



中国消费者产品安全合作中心 - 上海

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Thank you!

谢谢!

