Next Generation Risk Assessment (NGRA) Decision-Making for Skin Allergy

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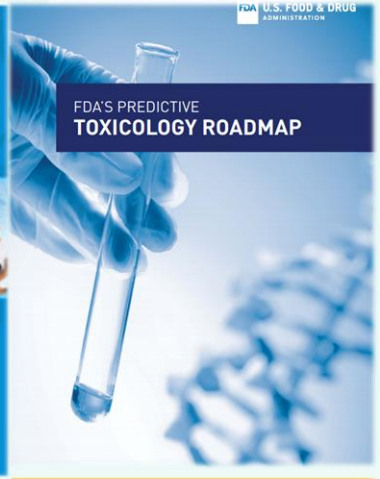
PCPC Safety Seminar 2021

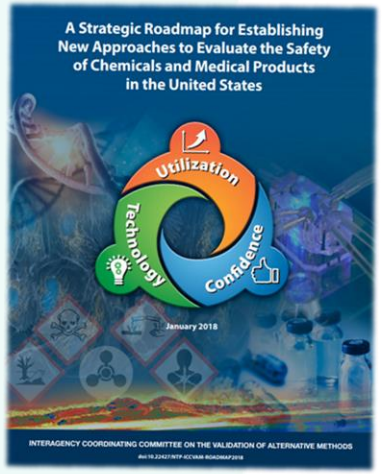
Unilever

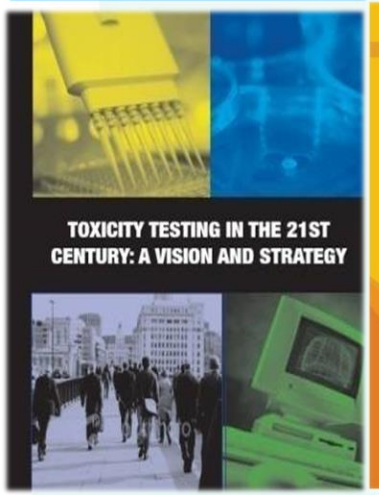
Assessing ingredient & product safety without animal testing

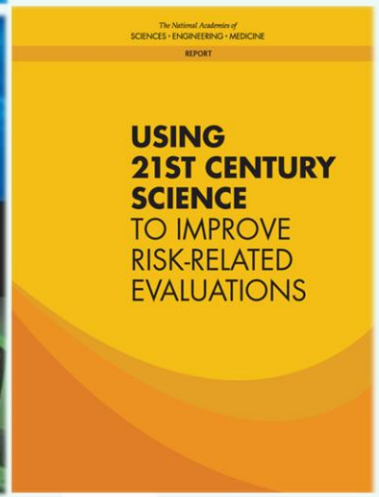
Next Generation Risk Assessment (NGRA)

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









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Principles of Next Generation Risk Assessment from ICCR
Non-animal approaches in Cosmetic Risk Assessment

International Cooperation on Cosmetics Regulation

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

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Next Generation Risk Assessment for Skin Allergy

Cosmetics Europe
the personal care association

Tier 0
Identify use scenario, chemical of concern and existing information

1. Identify use scenario
- Applied dose µg/cm² skin
- Single product / aggregate exposure

2. Identify molecular structure
- Chemical(s) of concern
- Analysis of specification and impurities

3. Identify existing hazard information
- *in silico* predictions
- *In vitro / in chemico* data (OECD TG or non-OECD TG)
- Historical *in vivo* data (animal or human)

4. Identify analogues / suitability assessment and existing data
- Read across

EXIT
Exposure based waiving

Tier 1
Hypothesis generation; how will data be used in risk assessment?

5. Hypothesis generation
- WoE prediction (S / NS) based upon T0 information
- Choice of DA in WoE
- Use of analogues in WoE

EXIT
non-sensitiser

Tier 2
Risk assessment

6. Targeted testing
- Refinement of exposure estimate
- Bioactivation / metabolism data
- *In vitro* hazard data (OECD TG or non-OECD TG)

7. Point of Departure, uncertainty analysis, Margin of safety and final risk assessment
- POD determination
- Characterise uncertainty
- Compare reference dose to consumer exposure

EXIT:
RA + / RA-

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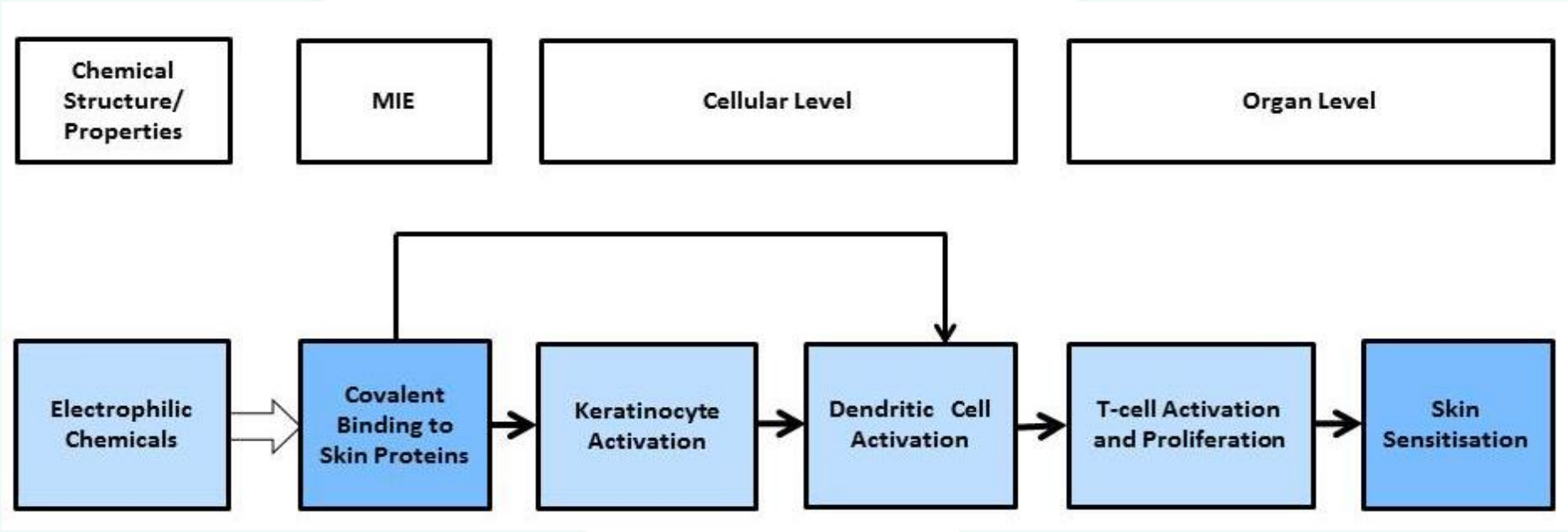
Gilmour et al, (2020),Regulatory Toxicology and Pharmacology, **116:** https://doi.org/10.1016/j.yrtph.2020.104721

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

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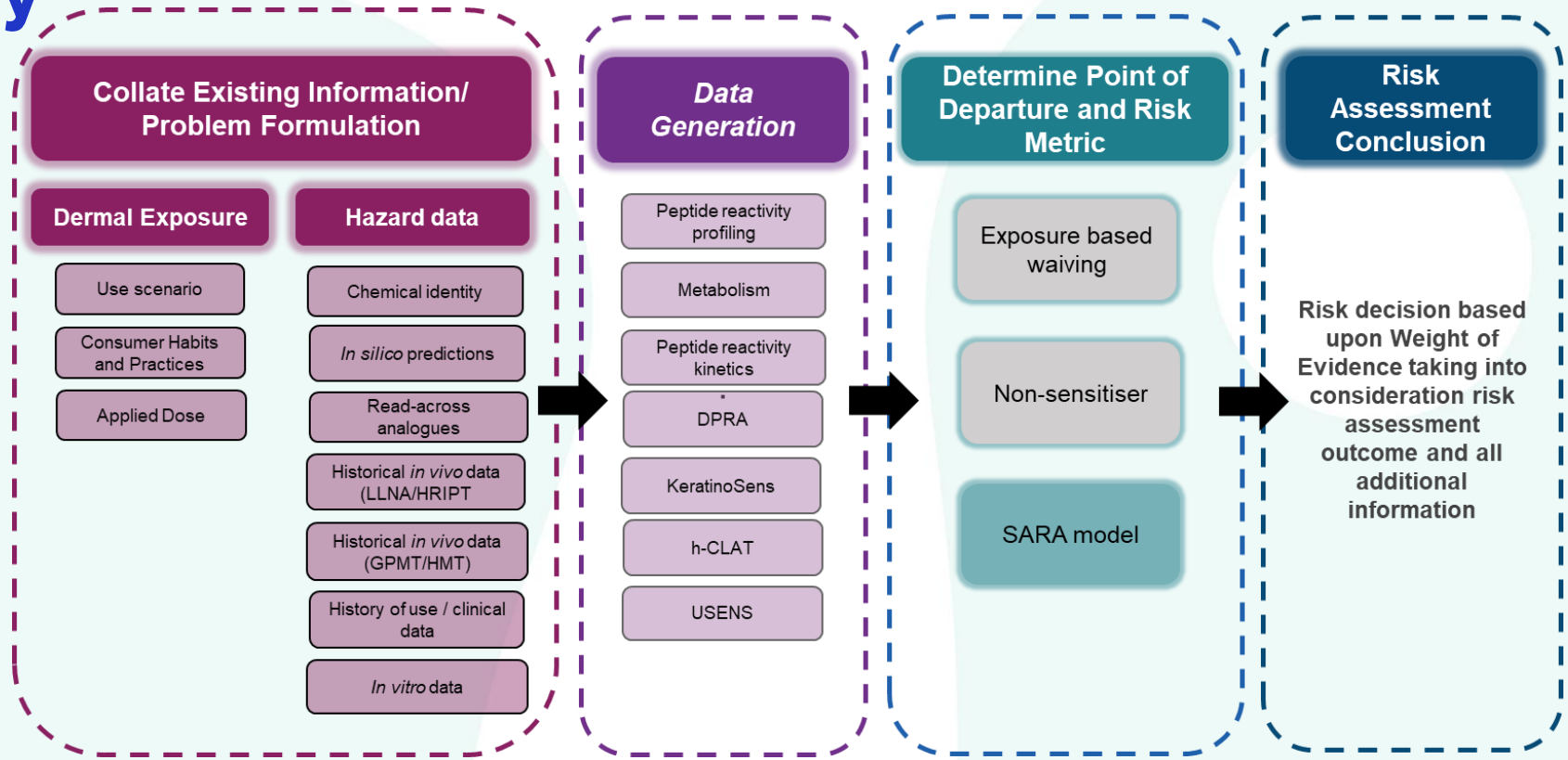
Next Generation Risk Assessment (NGRA) Framework for Skin Allergy



- 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.

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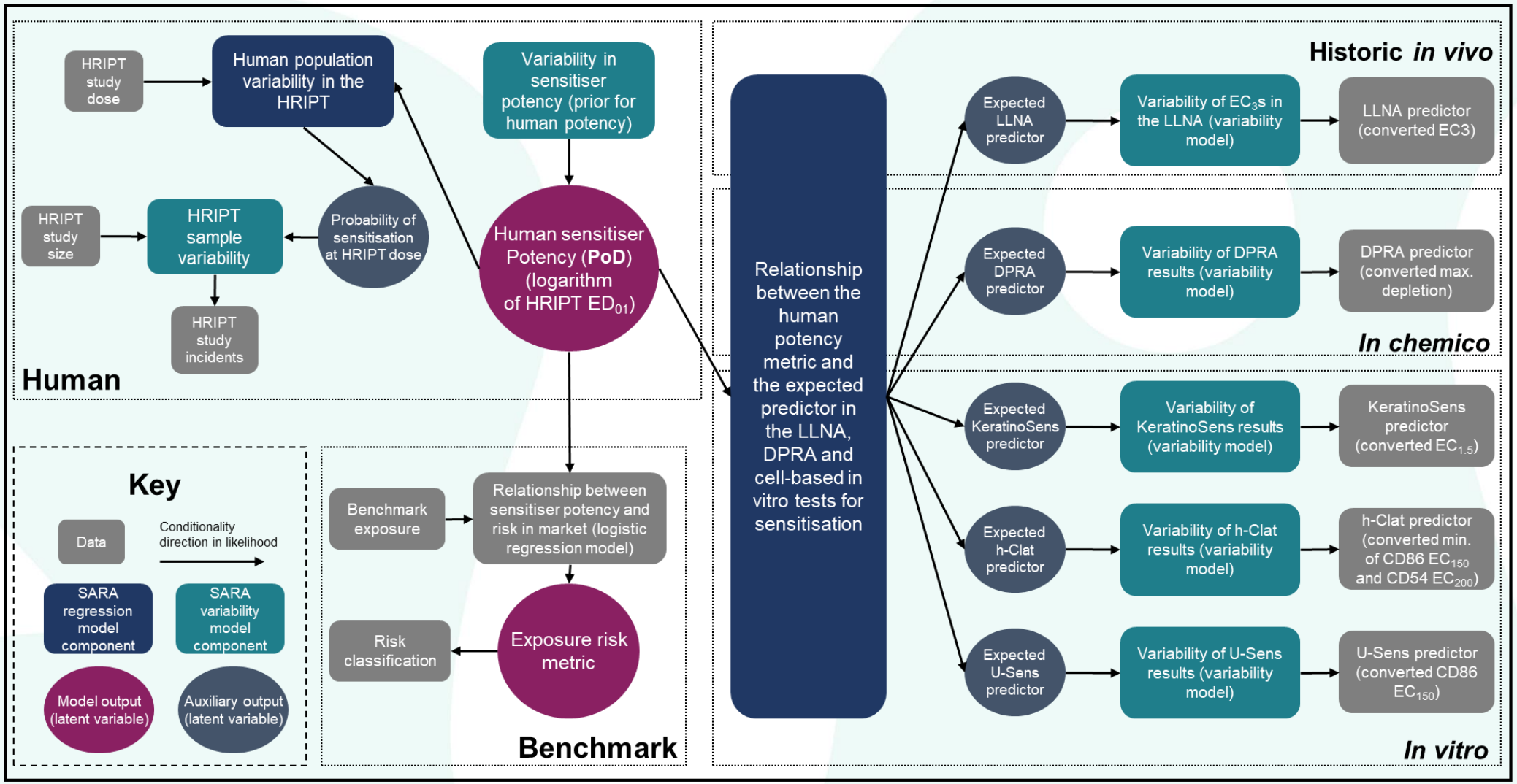
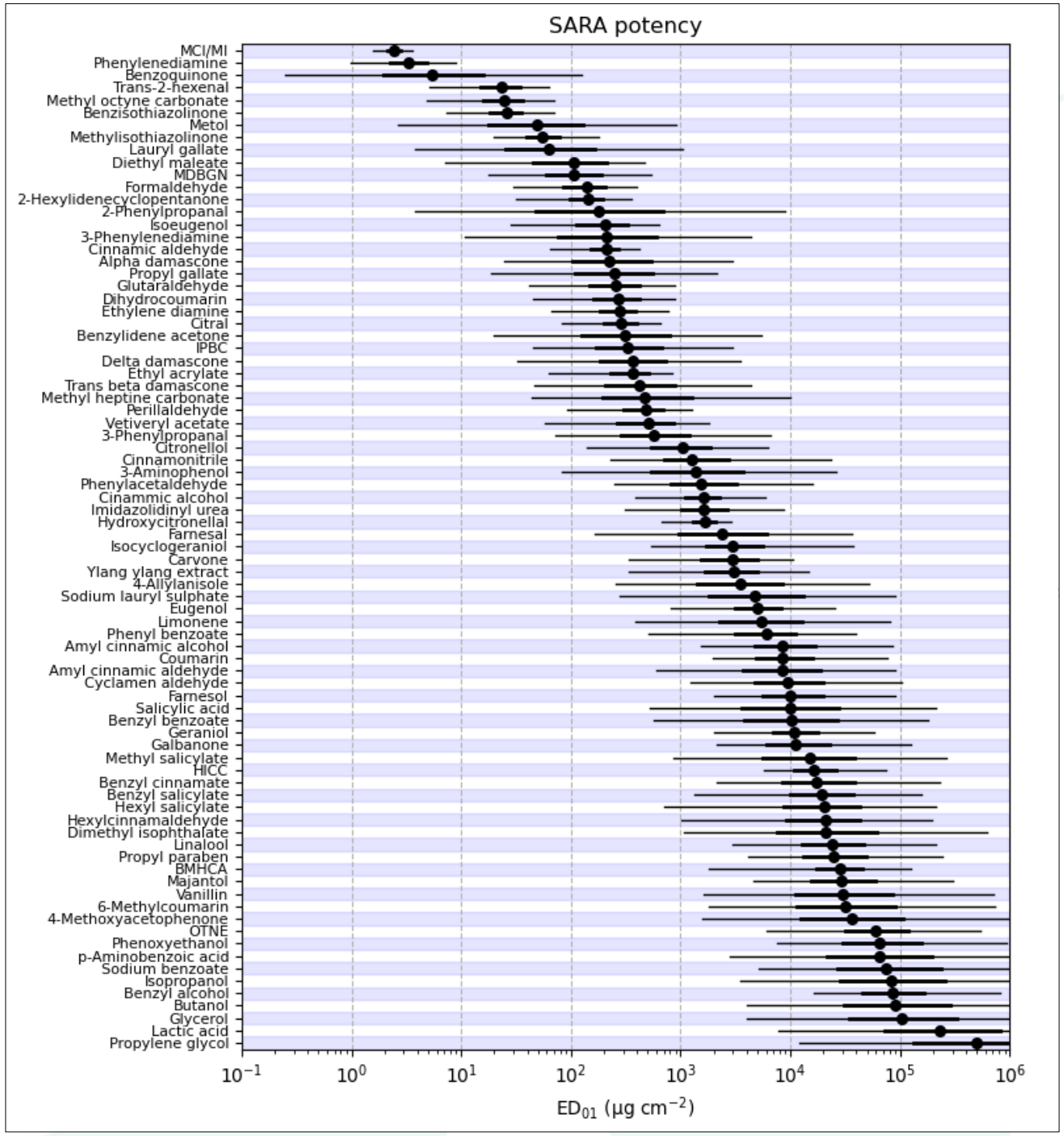
SARA Model



- 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 ED_{01}).
- 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

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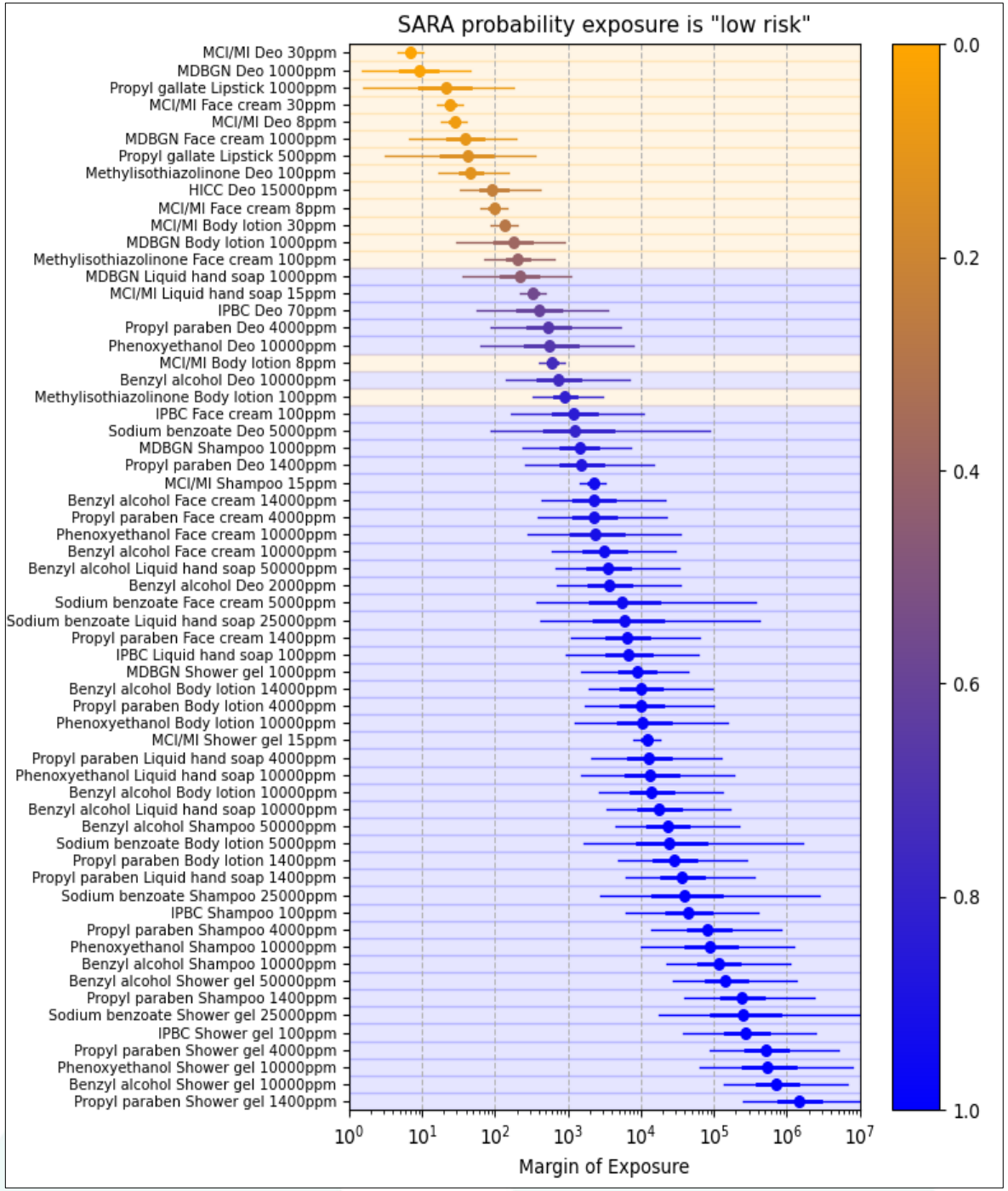
Expansion of SARA model to use benchmark exposure information

- 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

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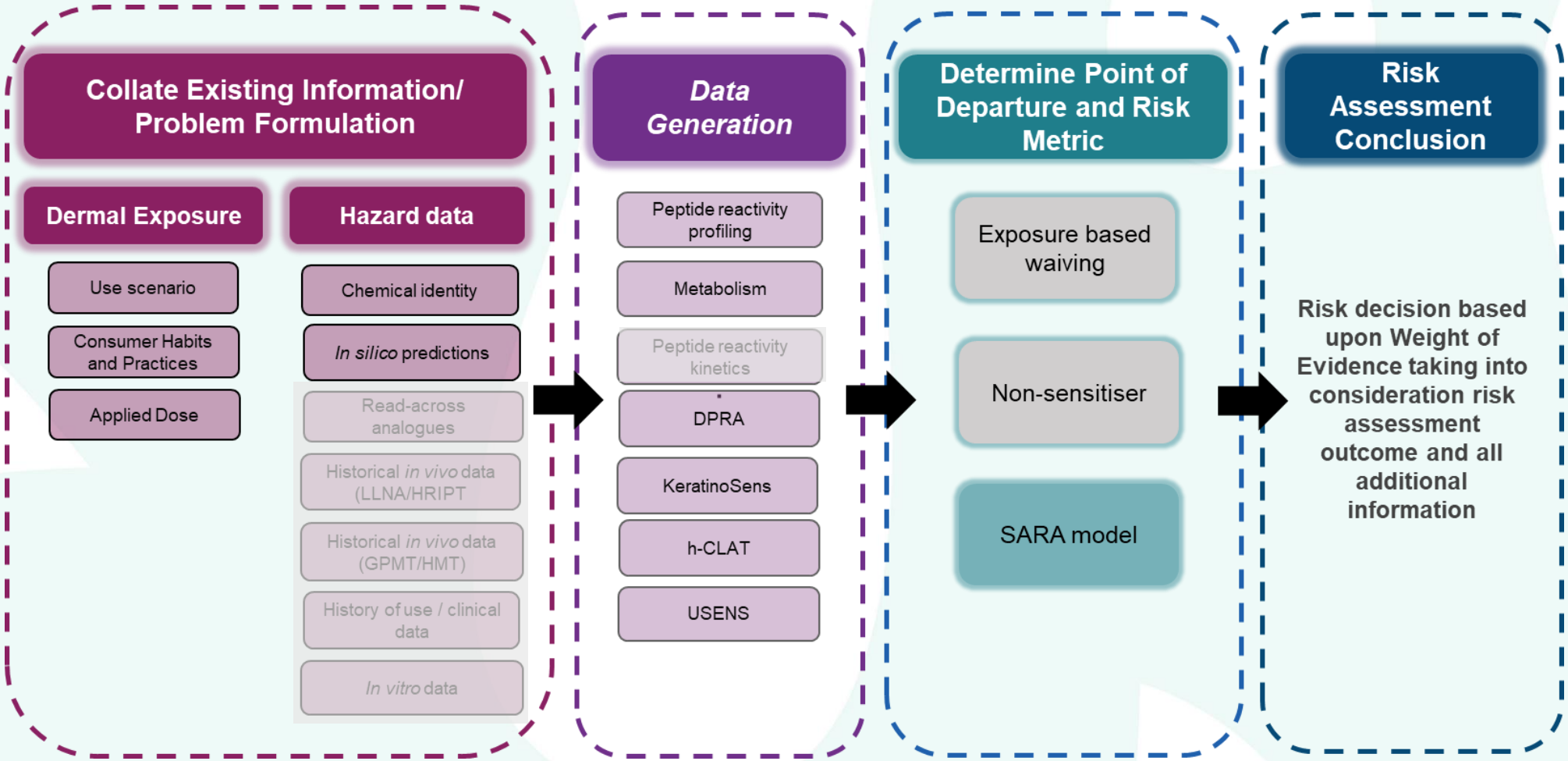
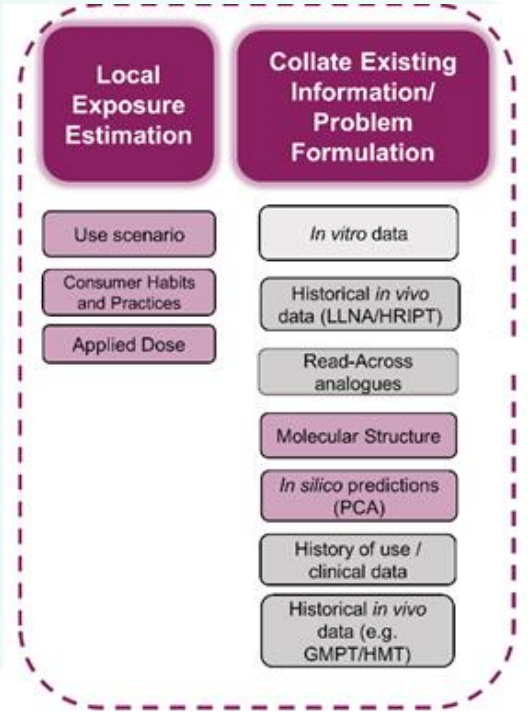
Application of NGRA framework for Skin Allergy

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 Formulation



Product type	Face cream	Deodorant
Product used per day (90th 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.

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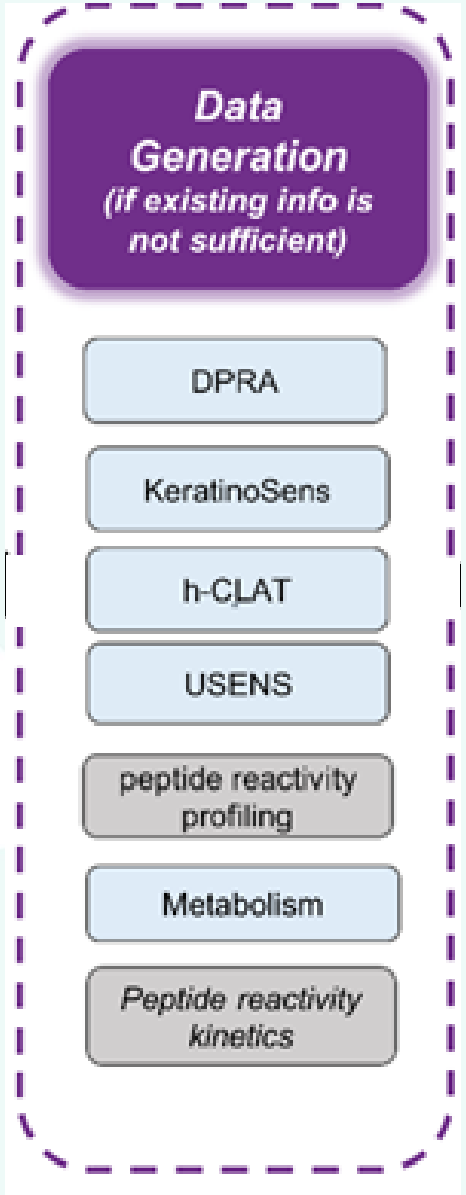
Data Generation



	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.

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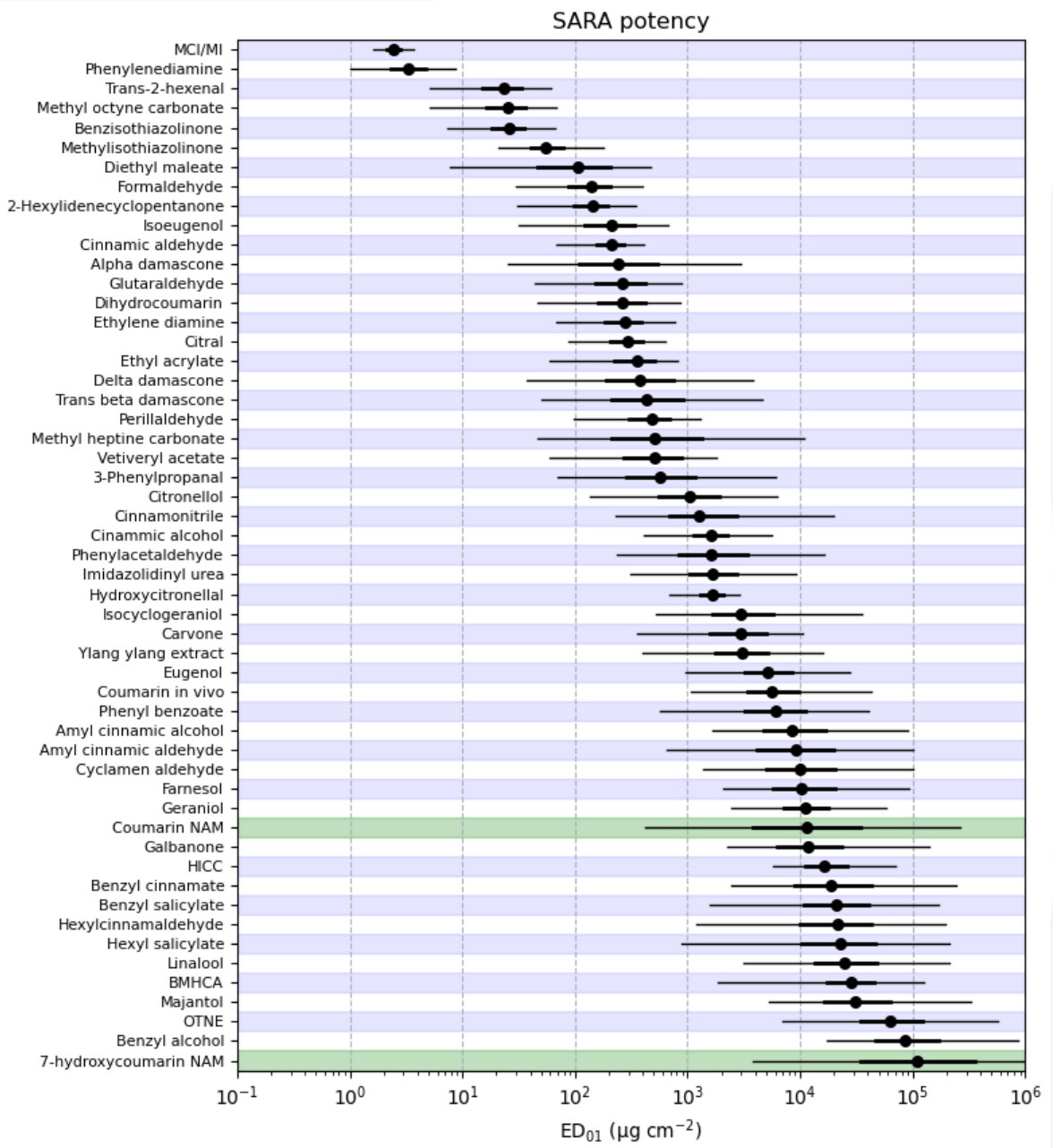
Determine Point of Departure (PoD) using SARA Model

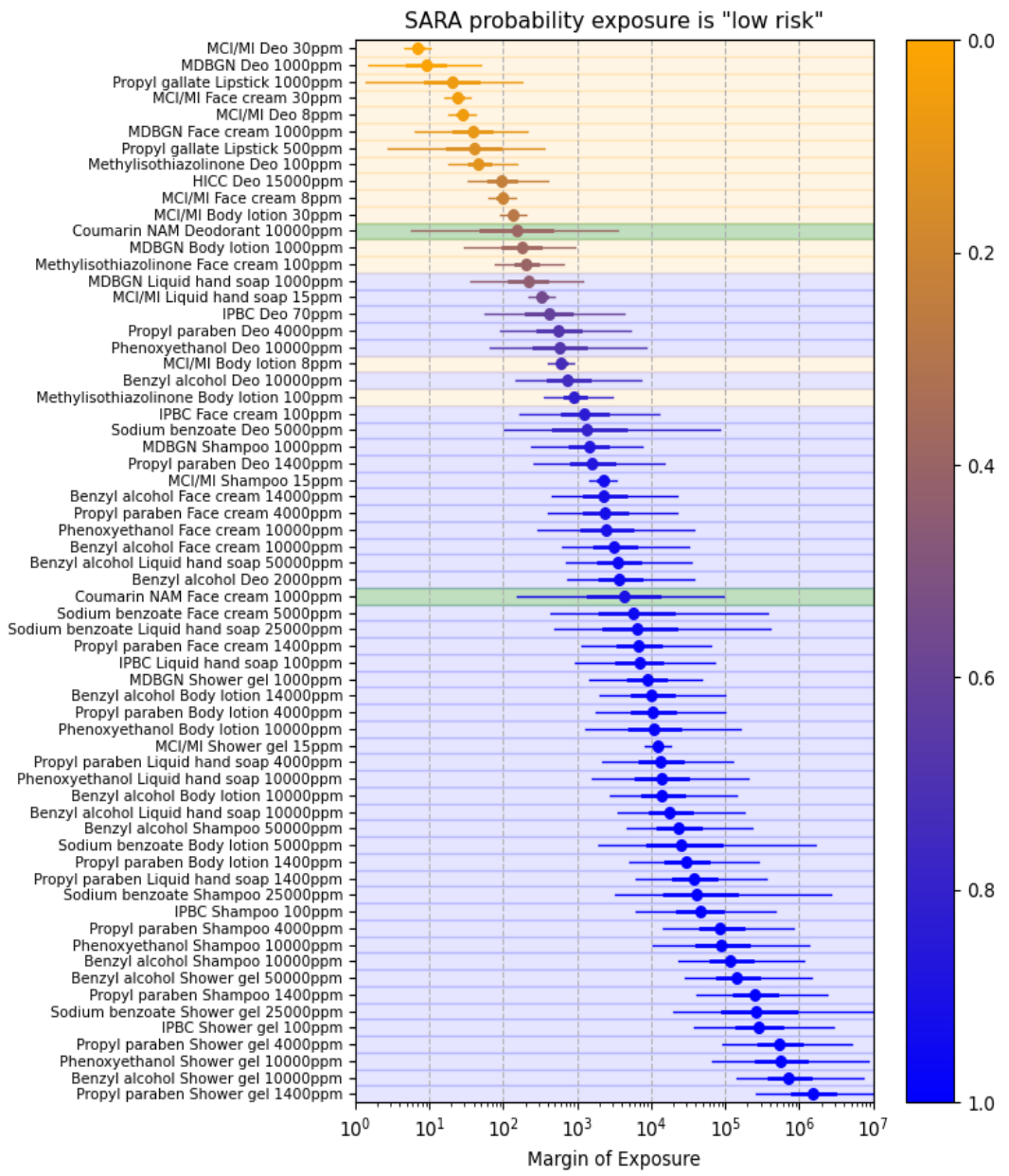


- The generated DPRA, KeratinoSens™, hCLAT and USens™ data were used as inputs into the SARA Model to define a human relevant PoD (ED_{01} i.e the 1% sensitising dose for a HRIPT population).

- For coumarin, the expected SARA Model derived ED_{01} is 11,000µgcm^{-2}, whilst for 7-OH coumarin the expected ED_{01} 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 ED_{01} 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**

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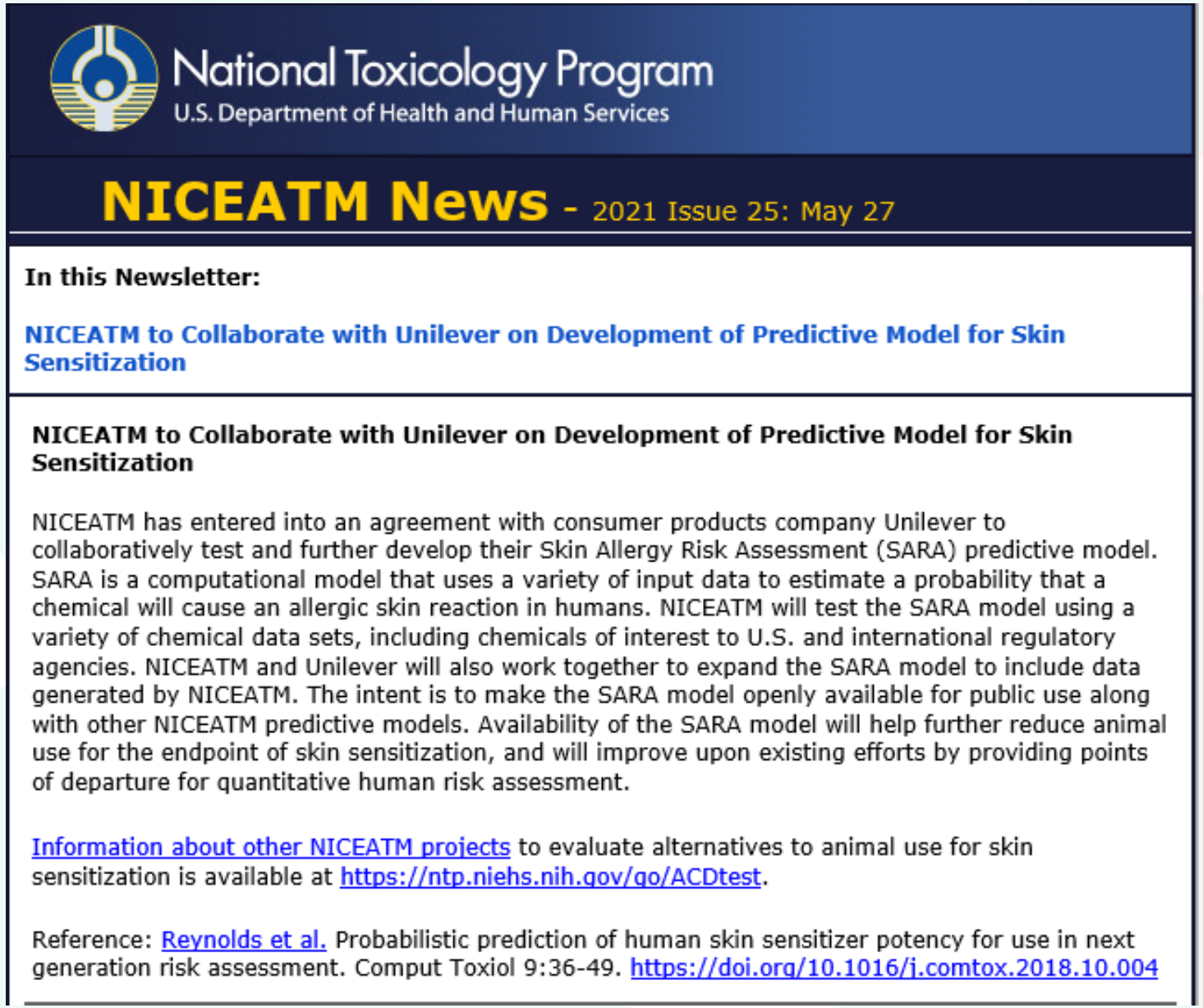
NICEATM-Unilever CRADA



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

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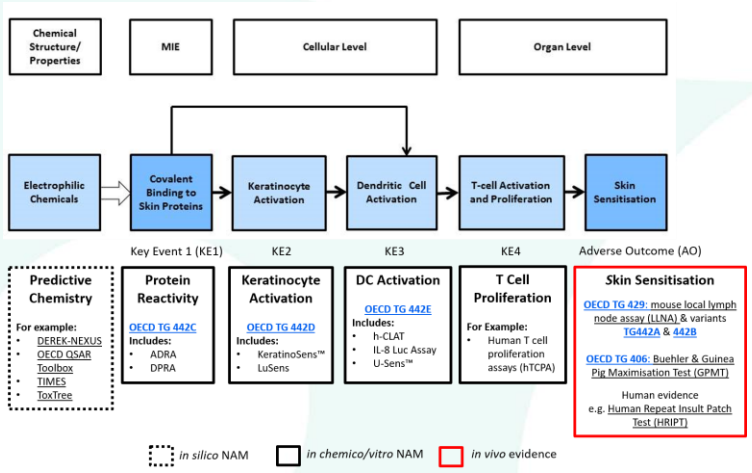
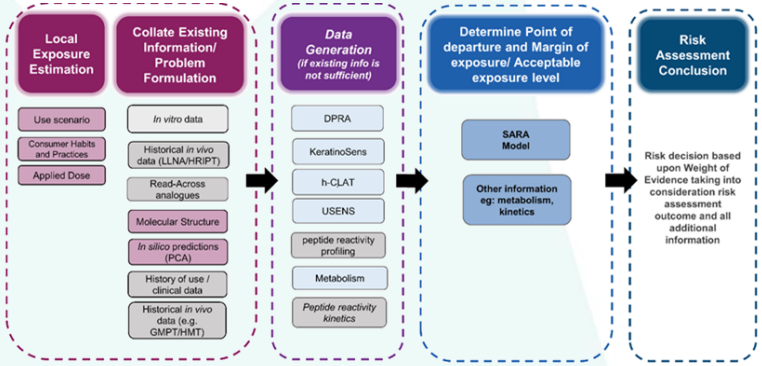
Conclusions

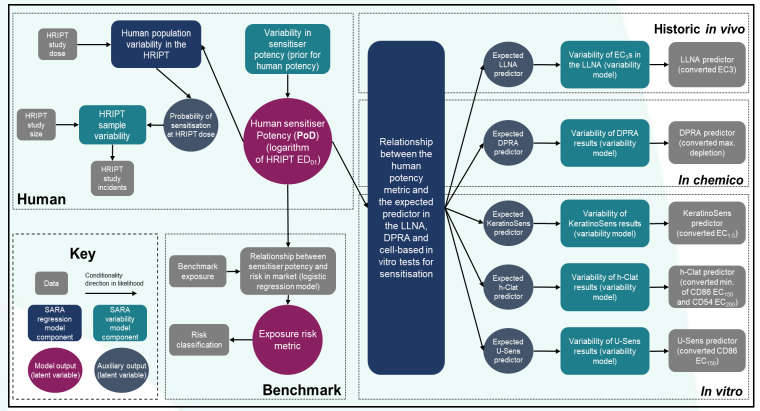
- Significant progress has been made in the last decade to apply non-animal experimental data using Defined Approaches & tiered frameworks.
- Bayesian DAs enable experimental data variability to be modelled and uncertainty in PoDs & risk metrics to be factored into decision-making.

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.







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