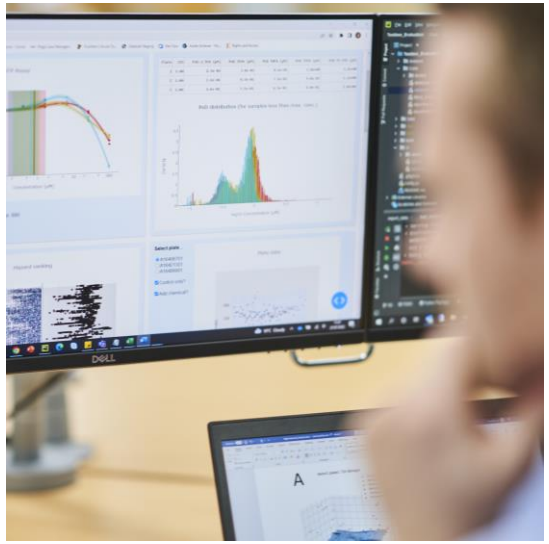
Skin Allergy Risk Assessment Model (SARA): Importance of Chemical Reaction Mechanistic Classification

Nora Aptula



SARA Model – the Journey

2017-2019

A prototype Bayesian statistical model was developed to estimate a no-effect-dose from HRIPT data.

This model was published in Reynolds et al., 2019.

2019-2021

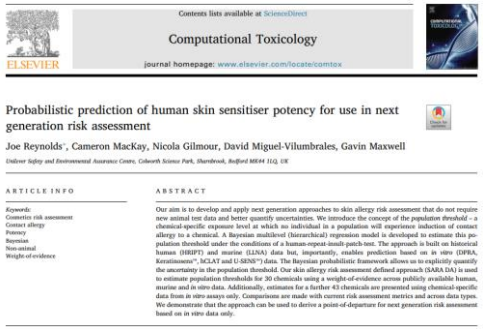
The model and database were revised and expanded. The point of departure became the ED01.

2021-2022

SARA was published within a set of three papers, which explored the model and its use in case study risk assessment scenarios.

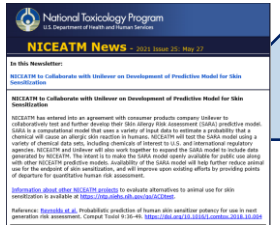
2023 - 2024

Unilever began to develop SARA 2.0, starting from the SARA-ICE database and evaluated the model.



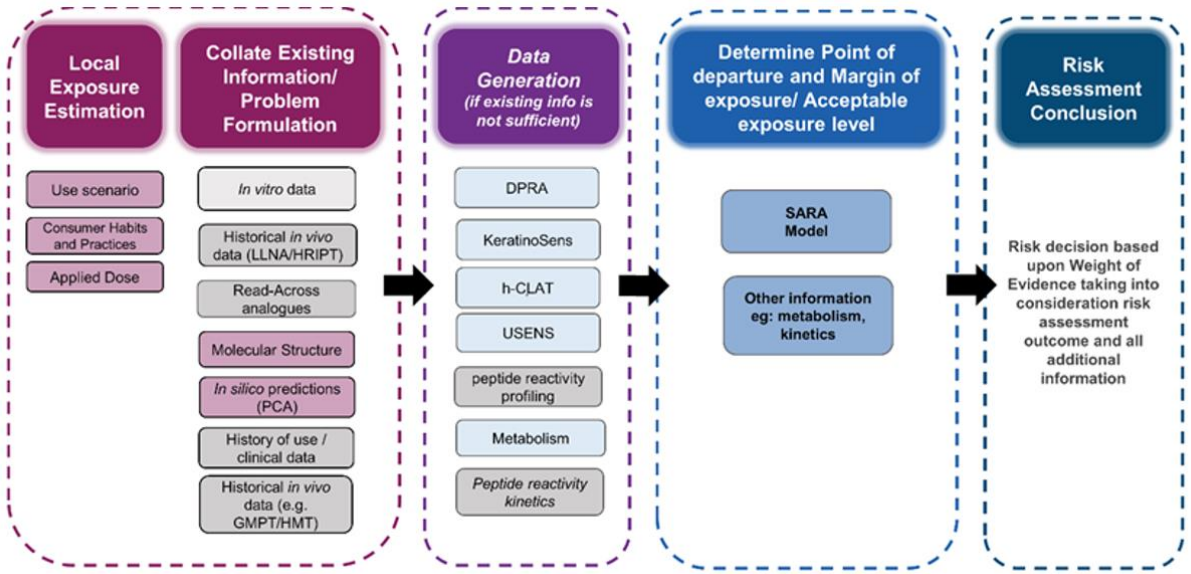
2021 - present

Unilever began working with NICEATM to adapt SARA for regulatory use. The SARA database is merged with the ICE database and the SARA-ICE model is developed. Evaluation of the SARA-ICE DA is ongoing within the OECD DASS expert group.
SARA-ICE is packaged for download for local implementation.



SARA Model (Reynolds et al., 2022)

- **Unilever NGRA framework for Skin Allergy** was 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

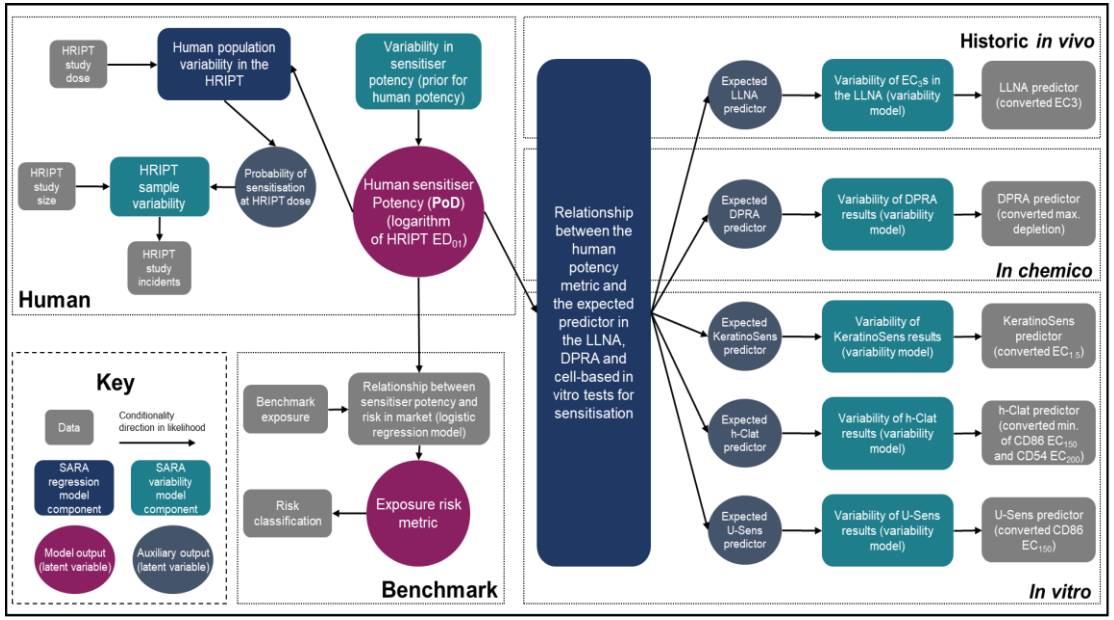


Gilmour et al., 2022: Next generation risk assessment for skin allergy: Decision making using new approach methodologies

The use-case of the SARA Model is to estimate:

1. ED_{01}, for all chemicals in the SARA database

2. probability that a consumer exposure to some chemical is 'low risk', conditional on the available data and the model



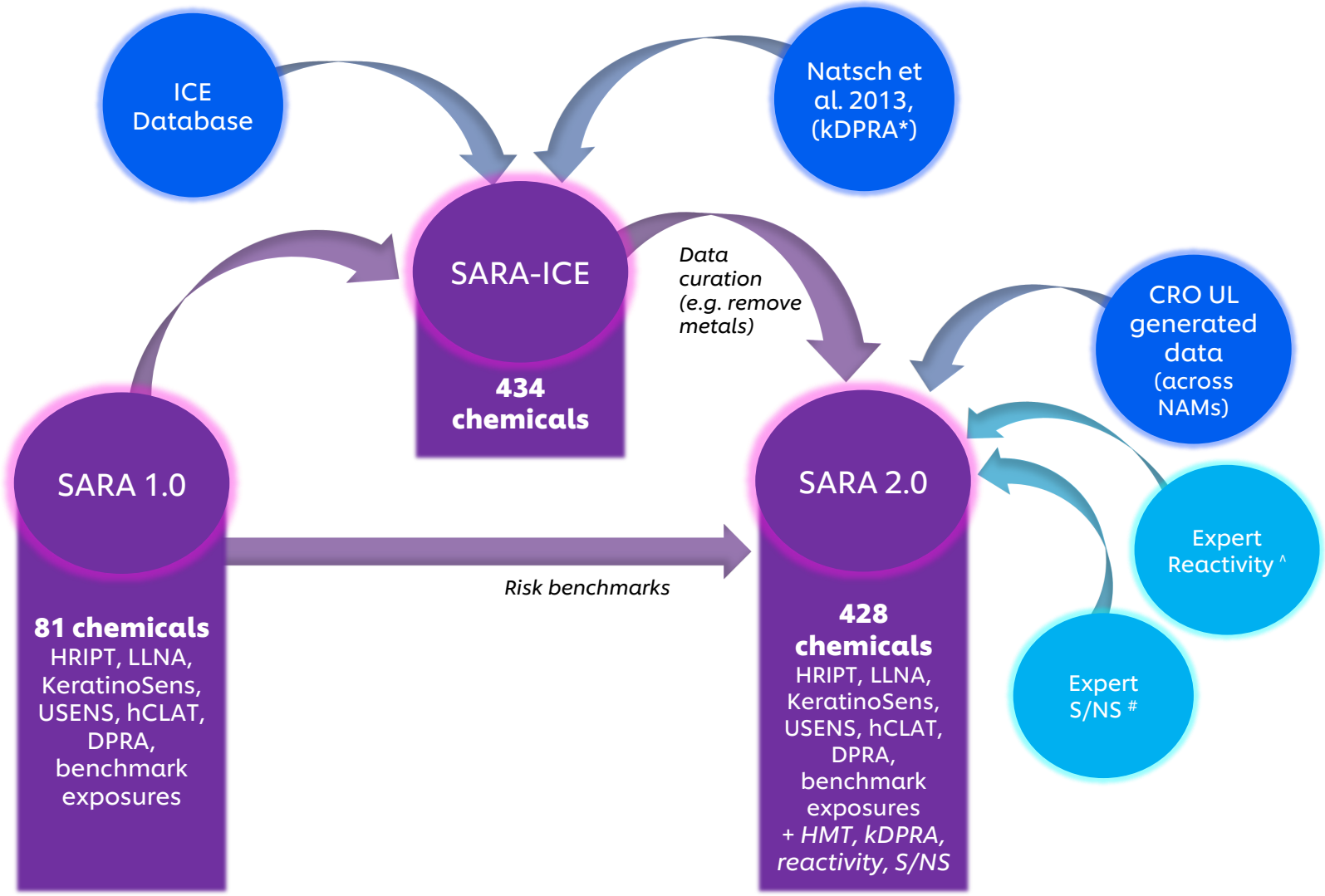
ED_{01} HRIPT induction dose inducing sensitisation in 1% of the population

Reynolds et al., 2022: Decision making in next generation risk assessment for skin allergy: Using historical clinical experience to benchmark risk

SARA 2.0 Model Development Overview

- **An expanded database** on which to estimate model parameters.
- **Incorporation of new inputs**:
  - *In silico*/expert inputs in the form of **reactivity** and **sensitiser/non-sensitiser classifications**.
  - The model now allows **human maximization test (HMT) studies**, in addition to human repeat insult patch test (HRIPT) studies.
  - Reactivity rate estimates from the **kinetic DPRA** can now be used as *in chemico* inputs.
- **Revised model outputs:**
  - The updated model can now provide a **probability that a chemical is a sensitiser** conditional on the data used.
  - The SARA risk metric takes into the account the **probability that a chemical is a non-sensitiser.**
- **Increased speed of operation:**
  - A "SARA-production" version of the model, an approximation of the full model from which potency estimates can be obtained much faster than previously.

Database Expansion

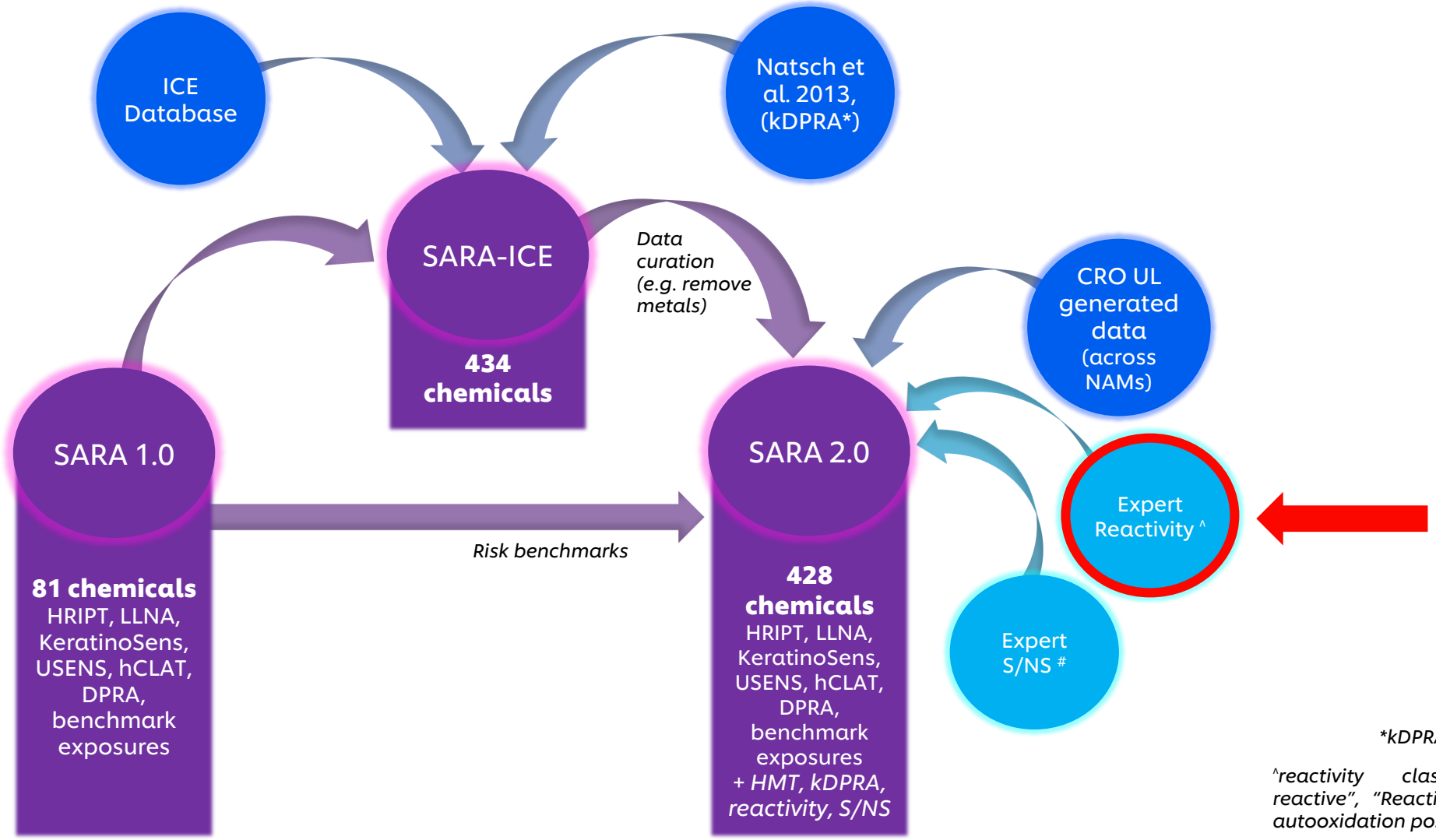


**kDPRA input in log k_{max}*

^reactivity classifications: "Non-reactive", "Reactive", "Non-reactive - autooxidation possible", "HPC")

 # curated sensitiser/non-sensitiser classification

Database Expansion



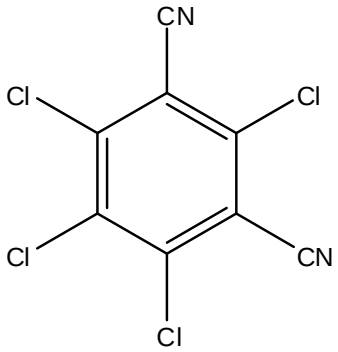
**kDPRA input in log k_{max}*

^reactivity classifications: "Non-reactive", "Reactive", "Non-reactive - autooxidation possible", "HPC")

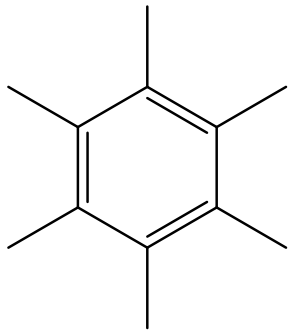
 # curated sensitiser/non-sensitiser classification

Physico-chemical Basis of Skin Sensitisation

- Skin sensitisation potential is dependent on **electrophilic reactivity** of the skin sensitiser or a derivative (produced by metabolism or oxidation)

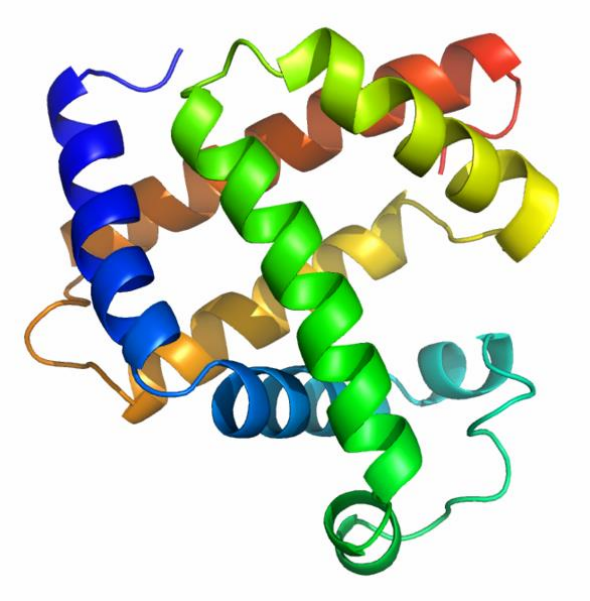


Reactive



Non-reactive

Protein - chemical Reactions



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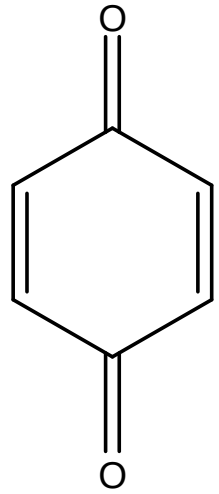


Protein - Nucleophile

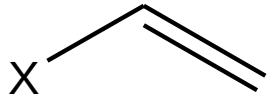
Chemical - Electrophile

Several types of covalent reactions

Sample Protein Reaction Mechanisms

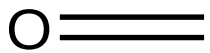
Structural Features

- **Michael acceptors**



X = e.g. -CHO, COR, CN

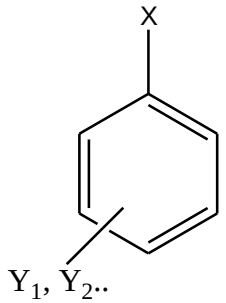
- **Schiff Base formers**



- **S_N2 electrophiles**

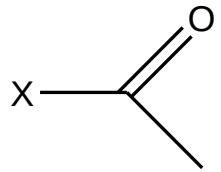
X = e.g. F, Cl, Br, I

- **S_NAr electrophiles**



Y = e.g. $-NO_2$, CN, CHO

- **Acylating agents**



X = e.g. F, Cl, Br, I, $-OC_6H_5$

- **Non-reactive**

no reactive groups

Aptula&Roberts. *Chem. Res. Toxicol.* 2006, **19**, 1097.

Mechanistic Classification of Skin Sensitisers

- Can be done by an expert – following the chemistry rules in this paper

  Aptula, A.O. and Roberts, D.W. (2006) *Chem. Res. Tox.* 19(8), 1097-1105

- Rules from this paper have been coded and implemented into the Toxtree and Toolbox– free tools

- Unfortunately, the in silico tools are not 100% reliable. An expert eye is needed when making a final decision about the mechanistic domain

- "The overall concordance for Cramer classification between Toxtree and expert judgment is 83%, while the concordance between the Toolbox and expert judgment is 77%"

Bhatia et al, (2015) Reg Tox Pharm, 71,52

HPC – High Potency Category Chemicals

- **Principles (structure-based) for identification of HPC chemicals were published by Roberts et al, 2015**

Some examples of HPC rules:

- 1. Compounds used as protein derivatisation agents
- 2a. Quinones, di-imines and quinone-imines
- 5b. Anhydrides, i.e. compounds with the substructure –CO.O.CO–, should be assigned HPC if the log P value is greater than 1

- **These were encoded and available in several in silico tools (e.g. TIMES, DEREK)**

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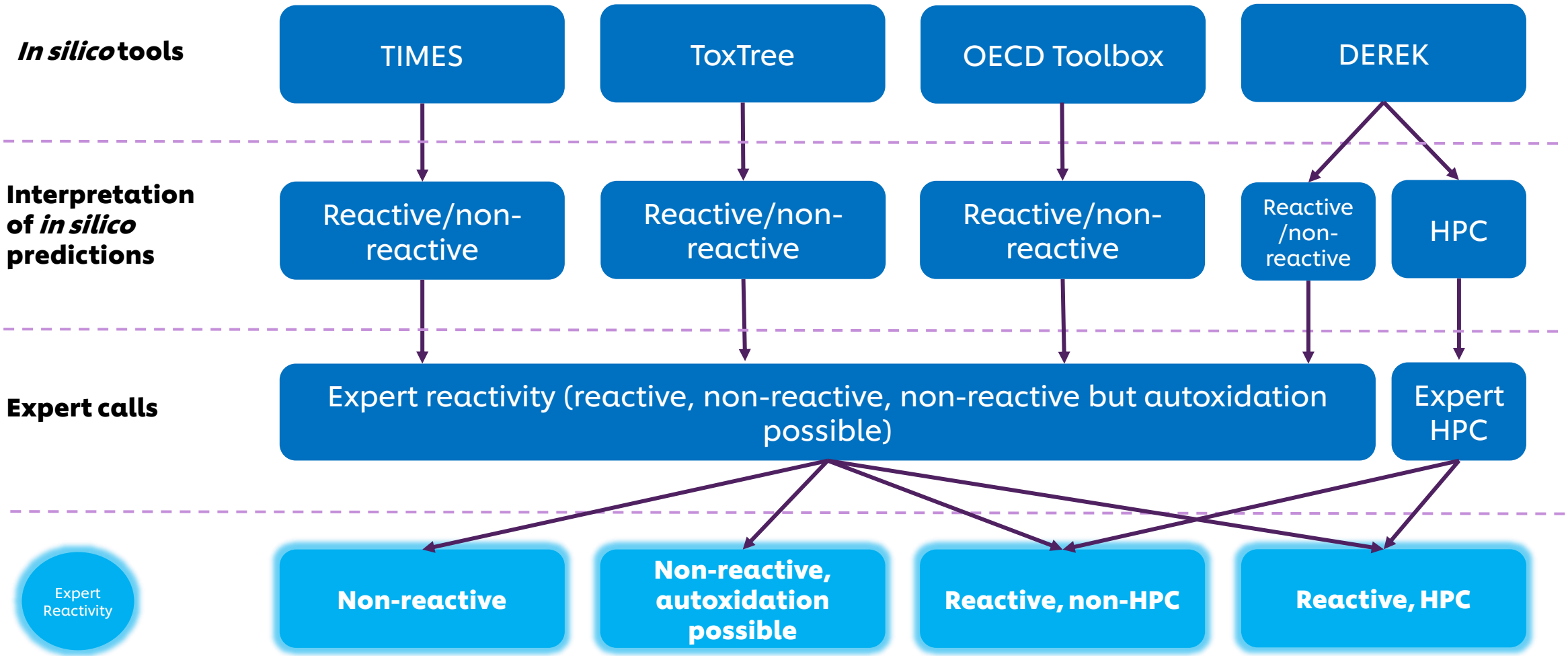
Roberts at al. Regulatory Toxicology and Pharmacology 72 (2015) 683–693

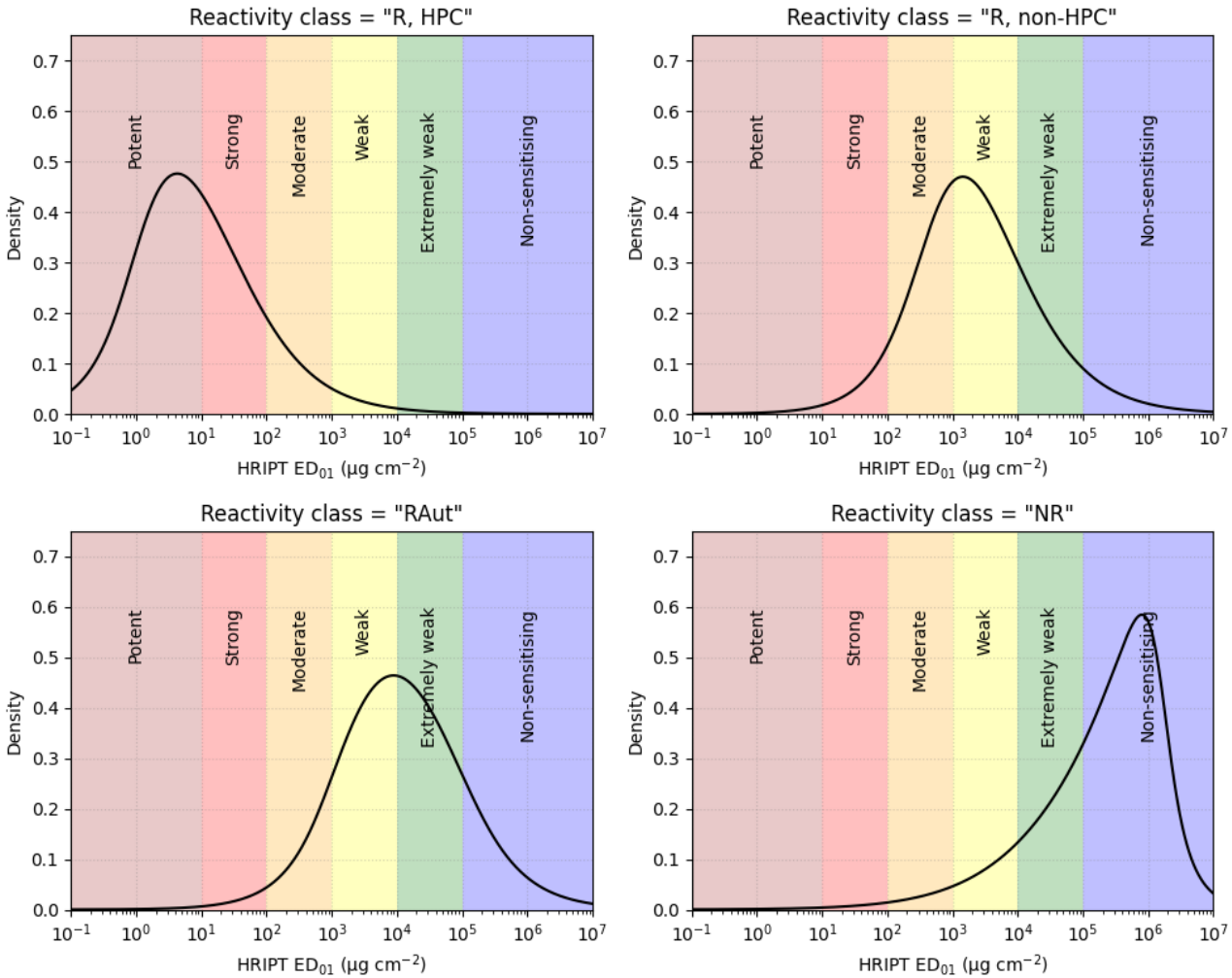
Determining expert reactivity classifications for SARA 2.0



HPC – high potency chemical

Addition of reactivity classifications to inform SARA 2.0 priors

- Each chemical in the database now has a **reactivity classification**.
- Consensus reactivity classifications are based upon outputs of ***in silico*** **tools and are expert curated.**
- Possible classifications are "**Reactive, HPC**", "**Reactive, non-HPC**", "**Non-reactive, but autooxidation possible**" and "**Non-reactive**".
- The model learns an adaptive prior distribution for each of the four reactivity classifications.
- The reactivity prior distributions align well with the six potency classes defined by Gerberick et al., 2001.



Conclusions

- SARA 2.0 now incorporates additional input information, including reactivity classifications.
- The reactivity prior distributions align well with the six potency classes defined by Gerberick et al., 2001.
- Performance using reactivity classifications only, against benchmark exposure classifications, shows a higher average high/low risk classification rate with fewer incorrect classifications made, versus a QRA approach using dermal sensitisation thresholds.
- Publication to summarise updates to the model to follow.

Thank you

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Gilmour *et al* 2022 case study scenarios re-visited

	0.1% Lactic acid in shampoo	2% Lactic acid in face cream	2% geraniol in face cream	0.2% formaldehyde in face cream
Exposure				
Expected outcome	Low risk	Low risk	Low risk	High risk

SARA (Reynolds et al., 2022; Gilmour et al., 2022)

0.1% Lactic acid in shampoo

Chem prediction: non-reactive
NAM Data: not available
SARA prediction: not possible, apply QRA

NESIL/SAF = AEL = 900/300= 30

AEL:CEL= 3 / 0.77 = 3.9

Risk outcome low risk

2% Lactic acid in face cream

Chem prediction: non-reactive
NAM Data: negative
SARA prediction: NAM data

Chemical	ED_{01} 2.5th (µg cm^{-2})	ED_{01} 50th (µg cm^{-2})	ED_{01} 97.5th (µg cm^{-2})
Lactic Acid	7,100	310,000	25,000,000

P exposure (low risk) **0.9**

Risk outcome low risk

2% geraniol in face cream

Chem prediction: reactive (auto)
NAM data: mixed
SARA prediction: NAM data

Chemical	ED_{01} 2.5th (µg cm^{-2})	ED_{01} 50th (µg cm^{-2})	ED_{01} 97.5th (µg cm^{-2})
Geraniol	180	4500	96,000

P exposure (low risk) **0.95**

Risk outcome low risk

0.2% formaldehyde in face cream

Chem prediction: reactive
NAM data: positive
SARA prediction: NAM data

Chemical	ED01 2.5th (µg cm^{2})	ED01 50th (µg cm^{2})	ED01 97.5th (µg cm^{2})
Formaldehyde	25	550	12,000

P exposure (low risk) **0.33**

Risk outcome high risk

SARA (updated)

0.1% Lactic acid in shampoo

Chem prediction: non-reactive
NAM Data: not available
SARA prediction: reactivity info

Chemical	ED_{01} 2.5th (µg cm^{-2})	ED_{01} 50th (µg cm^{-2})	ED_{01} 97.5th (µg cm^{-2})
Lactic Acid	31,000	590,000	21,000,000

P(NS) = 0.63
P exposure (low risk) = **0.97**

Risk outcome low risk

2% Lactic acid in face cream

Chem prediction: non-reactive
NAM Data: negative
SARA prediction: reactivity info / NAM

Chemical	ED_{01} 2.5th (µg cm^{-2})	ED_{01} 50th (µg cm^{-2})	ED_{01} 97.5th (µg cm^{-2})
Lactic Acid	31,000	590,000	21,000,000

P(NS) = 0.91
P exposure (low risk) **~1**

Risk outcome low risk

2% geraniol in face cream

Chem prediction: reactive (auto)
NAM data: mixed
SARA prediction: reactivity info/NAM data

Chemical	ED_{01} 2.5th (µg cm^{-2})	ED_{01} 50th (µg cm^{-2})	ED_{01} 97.5th (µg cm^{-2})
Geraniol	390	7,800	160,000

P(S) = 0.93
P exposure (low risk) = **0.994**

Risk outcome low risk

0.2% formaldehyde in face cream

Chem prediction: reactive
NAM data: positive
SARA prediction: reactivity info/NAM data

Chemical	ED_{01} 2.5th (µg cm^{-2})	ED_{01} 50th (µg cm^{-2})	ED_{01} 97.5th (µg cm^{-2})
Formaldehyde	0.76	18	540

P(S) ~1.
P exposure (low risk) = **0.008**.

Risk outcome high risk

Uses of Mechanistic Classification

- It is used as an input into the SARA model
- Which Dermal Sensitisation Threshold (DST) will be appropriate to use
- It does NOT automatically mean that the chemical is a sensitiser, it means that it HAS the potential to bind to a protein by this specific mechanism

Evaluation Conclusions

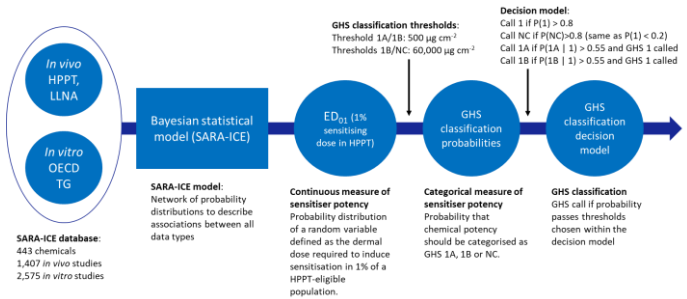
- SARA 2.0 incorporates additional input information including reactivity classifications, HMT data and kinetic DPRA
- SARA 2.0 has an additional output, the likelihood that a chemical is a sensitiser
  - the uncertainty in sensitiser/non-sensitiser classification for a chemical is now factored into the calculation of the SARA 2.0 risk metric
- A SARA-production model has been developed which allows ED_{01} estimates for novel datasets to be generated in a matter of seconds rather than hours
- A decision model is proposed to translate the risk metric into classifications of “low risk”, “high risk” or “inconclusive”.
- The case study scenarios published in Gilmour et al., 2022 were re-run using SARA 2.0 and the desired risk assessment conclusion was reached with higher confidence for all case studies
- SARA 2.0, with the proposed decision model, is more conservative than QRA for reactive chemicals and less conservative for non-reactive chemicals

SARA 2.0 outperforms SARA 1.0 on every metric considered

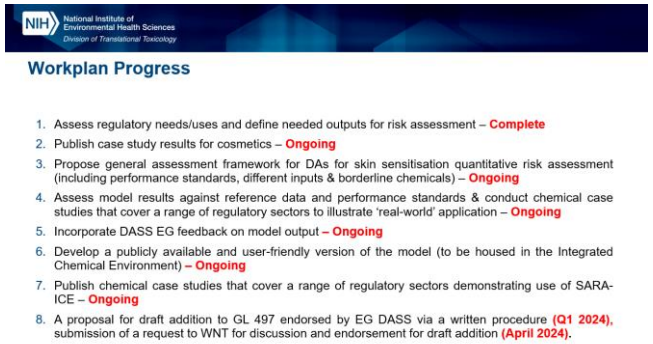
SARA-ICE Model Development

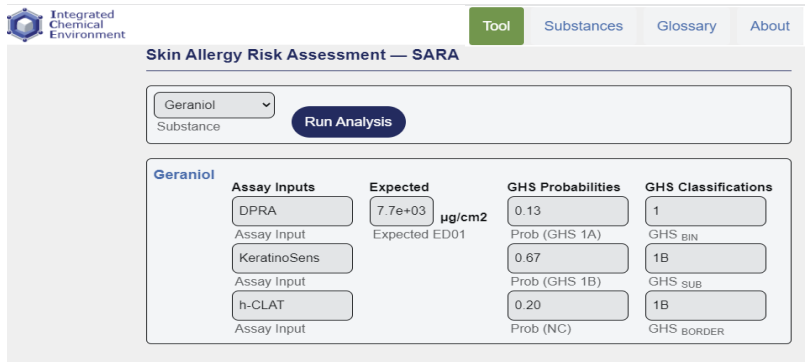
- Development of the SARA-ICE DA in collaboration with NICEATM to create a version of the model which meets the needs of wider industry for risk assessment and regulatory applications

- **Key differentiating features include;**
  - **an expanded database (SARA 1.0 and ICE data)**
  - **removal of risk benchmarks**
  - **GHS Classification (binary / potency subcategories)**



- Significant progress made in feasibility study for OECD DASS TG 497
- Development of an open access user interface
- EPA risk assessment community are early adopters of the approach for fragrance chemical risk assessment

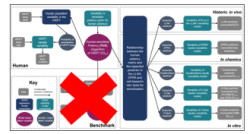




Database
Aim to expand the core dataset underpinning the model using data in the ICE database (relaxing the constraint that chemicals be limited to cosmetic ingredients).

Integrated Chemical Environment

Risk benchmarking
Drop the risk benchmarking component of the model – the current set of benchmarks are limited to use of consumer goods. Use the model for human potency estimation for quantitative risk assessment.



GHS classification
Add functionality to predict GHS classification (estimated as a class probability) to communicate uncertainty in classification.

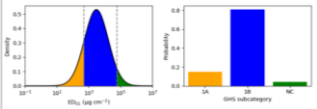


Figure (a) Example estimate of ED_{01} distribution with overlay of GHS subcategories 1A, 1B and NC defined thresholds, (b) probability of each GHS subcategory from ED_{01} distribution

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Overview SARA-ICE

	SARA prototype (Reynolds et al. 2019)	SARA 1.0 (Reynolds et al. 2022)	SARA 2.0	SARA-ICE
Database	30 chemicals	81 chemicals	428 chemicals	434 Chemicals, >4000 studies
			LLNA, KeratinoSens, USENS, hCLAT, DPRA, kDPRA (log kmax), Reactivity (NR, RAut, R, HPC), Human data (HRIPT & HMT)	
Assay Inputs	HRIPT, LLNA, DPRA, KeratinoSens, hCLAT, USENS	HRIPT, LLNA, DPRA, KeratinoSens, hCLAT, USENS	Binary + confidence chemical exposure risk	v1 + kDPRA (log kmax), Human max. test (HMT), cytotoxicity concentrations from KeratinoSens, hCLAT, USENS
Probability of Sensitiser	Assumes sensitiser	Assumes sensitiser	ED01 (1% sensitising dose for a HRIPT exposure scenario)	+ GHS NC / 1
Production Model	N/A	N/A	S/NS	Faster production model (to be hosted on ICE)
Probability of GHS Cat.	N/A	N/A	Probability exposure is low risk/probability exposure is high risk. Low risk/high risk/inconclusive calls	Probability of GHS Cat., *binary or 1A, 1B, NC
Risk Model	N/A	Probability exposure is low risk	Faster, approximated production model	N/A

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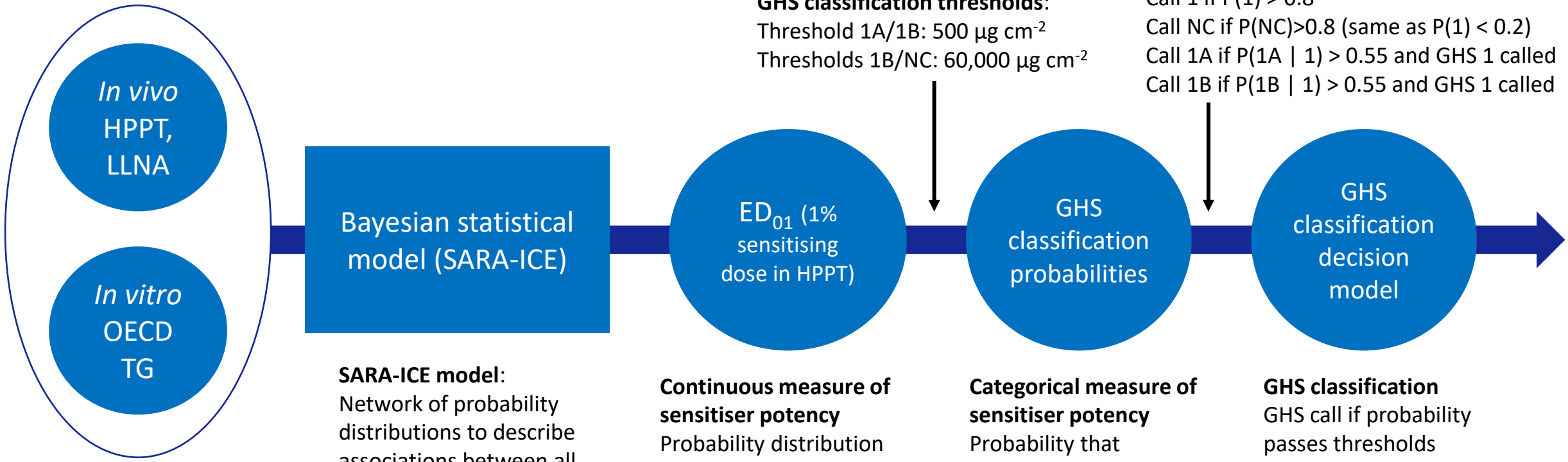
SARA-ICE DA: Skin Allergy Risk Assessment - Integrated Chemical Environment Defined Approach



GHS classification thresholds:
Threshold 1A/1B: 500 µg cm^{-2}
Thresholds 1B/NC: 60,000 µg cm^{-2}

Decision model:
Call 1 if P(1) > 0.8
Call NC if P(NC)>0.8 (same as P(1) < 0.2)
Call 1A if P(1A | 1) > 0.55 and GHS 1 called
Call 1B if P(1B | 1) > 0.55 and GHS 1 called

SARA-ICE database:
443 chemicals
1,407 *in vivo* studies
2,575 *in vitro* studies

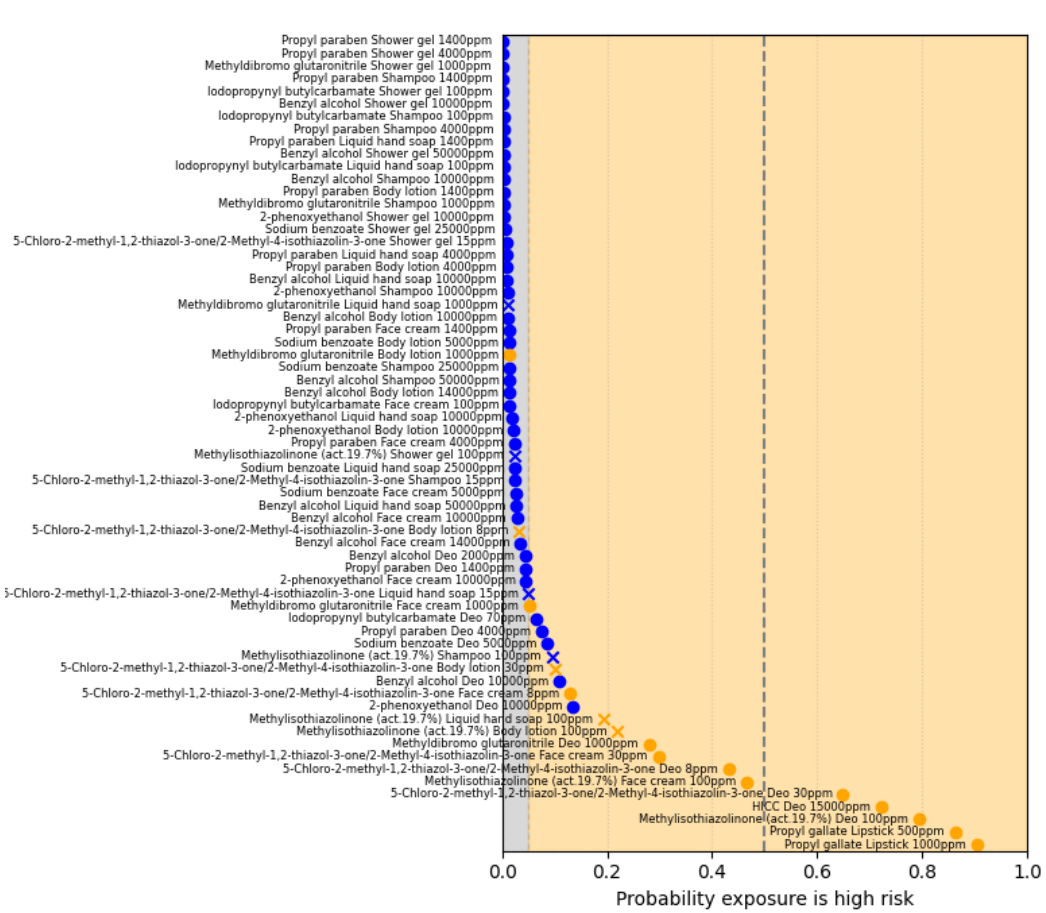
SARA-ICE model:
Network of probability distributions to describe associations between all data types

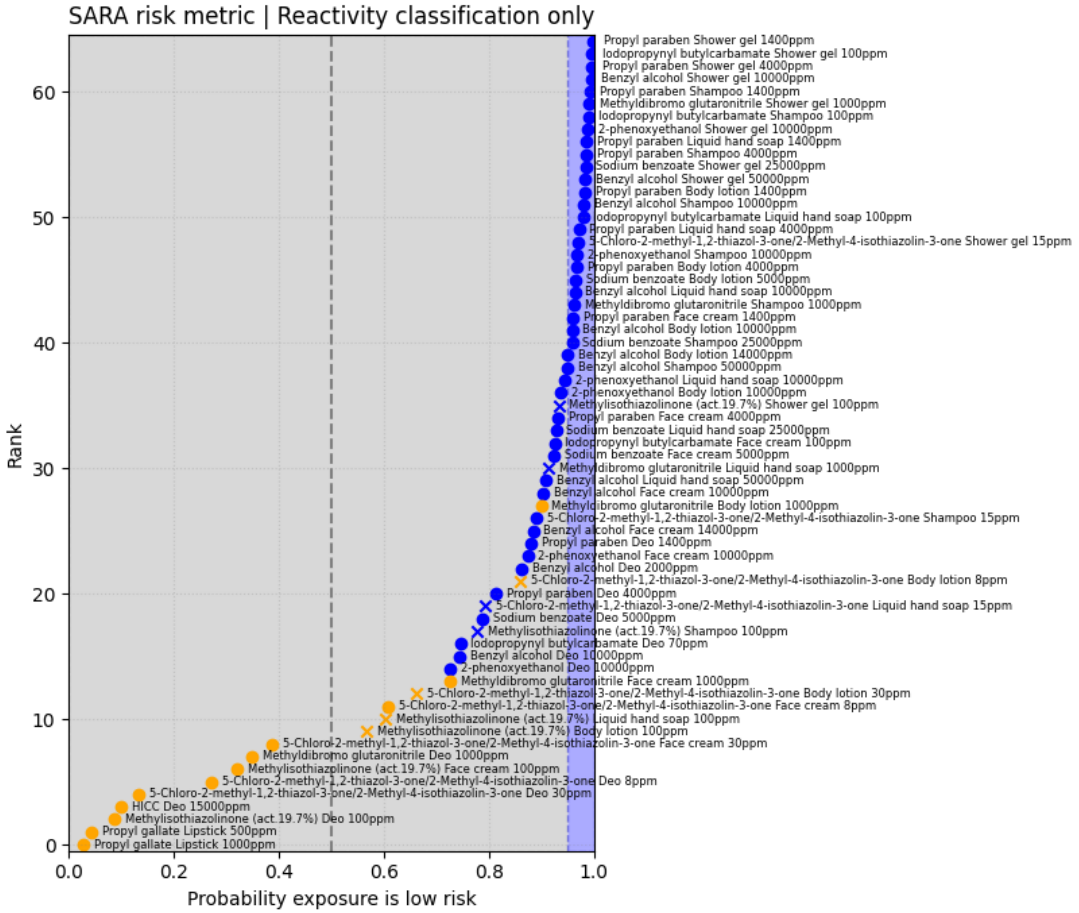
Continuous measure of sensitiser potency
Probability distribution of a random variable defined as the dermal dose required to induce sensitisation in 1% of a HPPT-eligible population.

Categorical measure of sensitiser potency
Probability that chemical potency should be categorised as GHS 1A, 1B or NC.

GHS classification
GHS call if probability passes thresholds chosen within the decision model

SARA 2.0 performance against benchmark exposure classifications – reactivity information only





Input combination	Low-risk classification rate	High-risk classification rate	Average classification rate	Number of inconclusive classifications	Number of incorrect classifications
QRA | DST	20 / 49, 41%	14 / 16, 88%	64%	15 / 65, 23%	16 / 50, 32%
SARA | Reactivity information only	26 / 49, 53%	14 / 16, 88%	70%	18 / 65, 28%	7 / 47, 15%