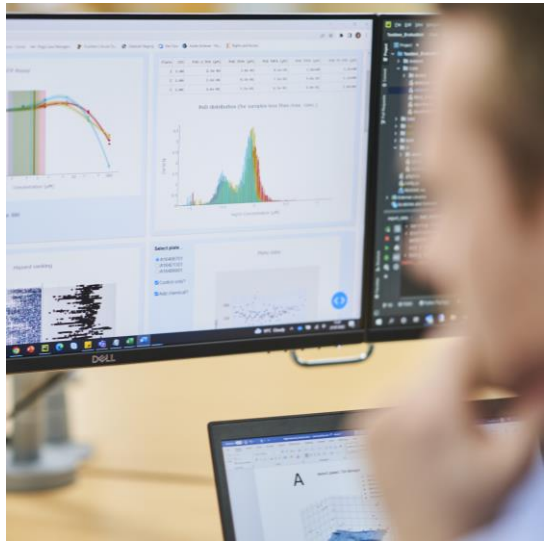
# Incorporating expert knowledge into The Skin Allergy Risk Assessment (SARA) Model

*Georgia Reynolds*



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# SARA Model – The Timeline

**2017-2019**

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

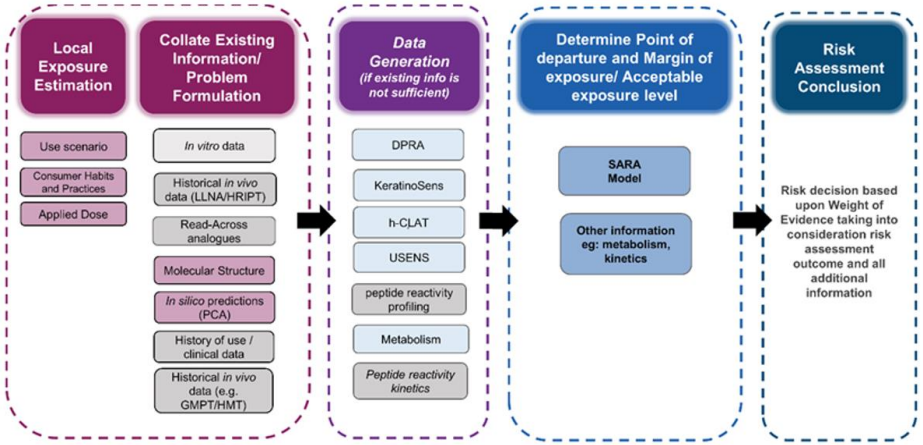
This model was published in Reynolds et al., 2019.

**2019-2021**

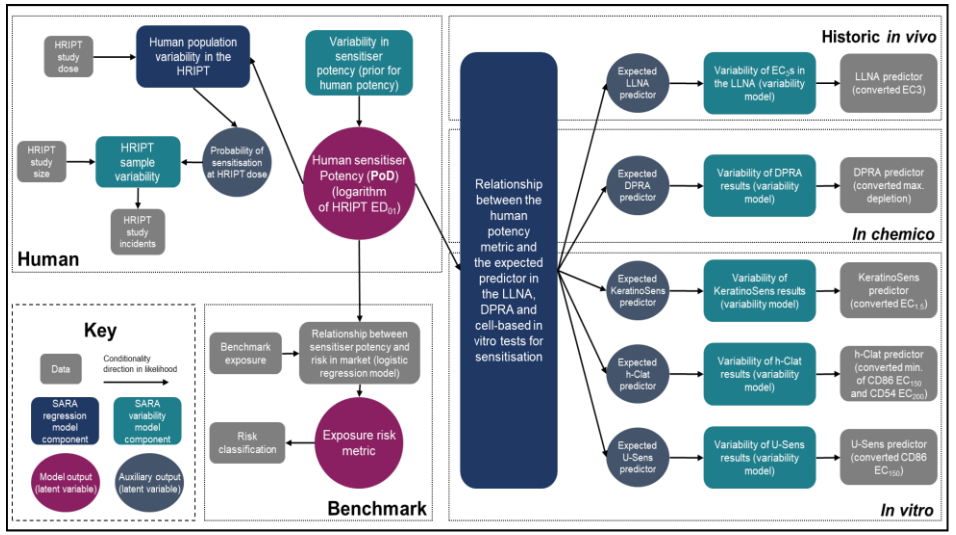
The model and database were revised and expanded. The point of departure became the $ED_{01}$

**2021-2022**

SARA was published within a set of three papers, exploring the model and its use in case study risk assessments.




**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



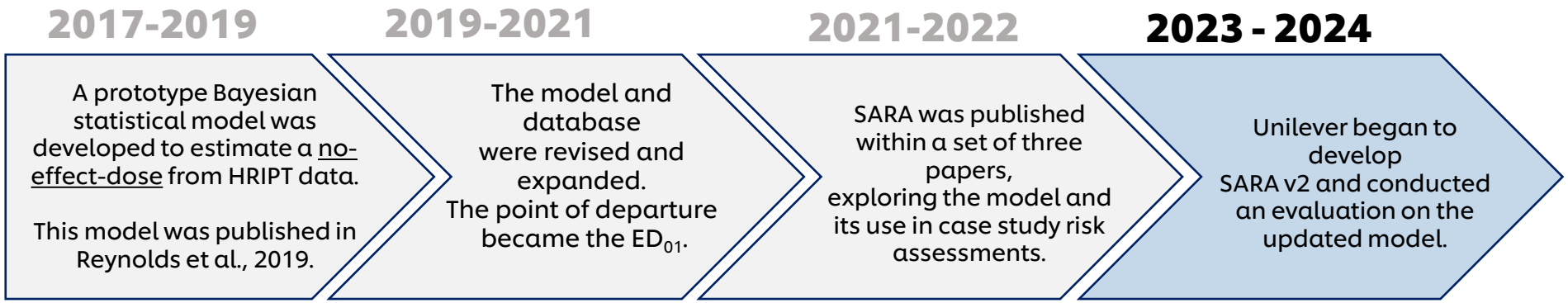

The use-case of the SARA Model is to estimate:

1. **Point of Departure**: An $ED_{01}$, i.e. 1% sensitising dose in a human population for a chemical of interest based upon chemical specific (primarily NAM) data
2. **Risk Metric:** A probability that a consumer exposure to a chemical is 'low risk', conditional on the available data and the model

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

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

# SARA Model v2 – 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.

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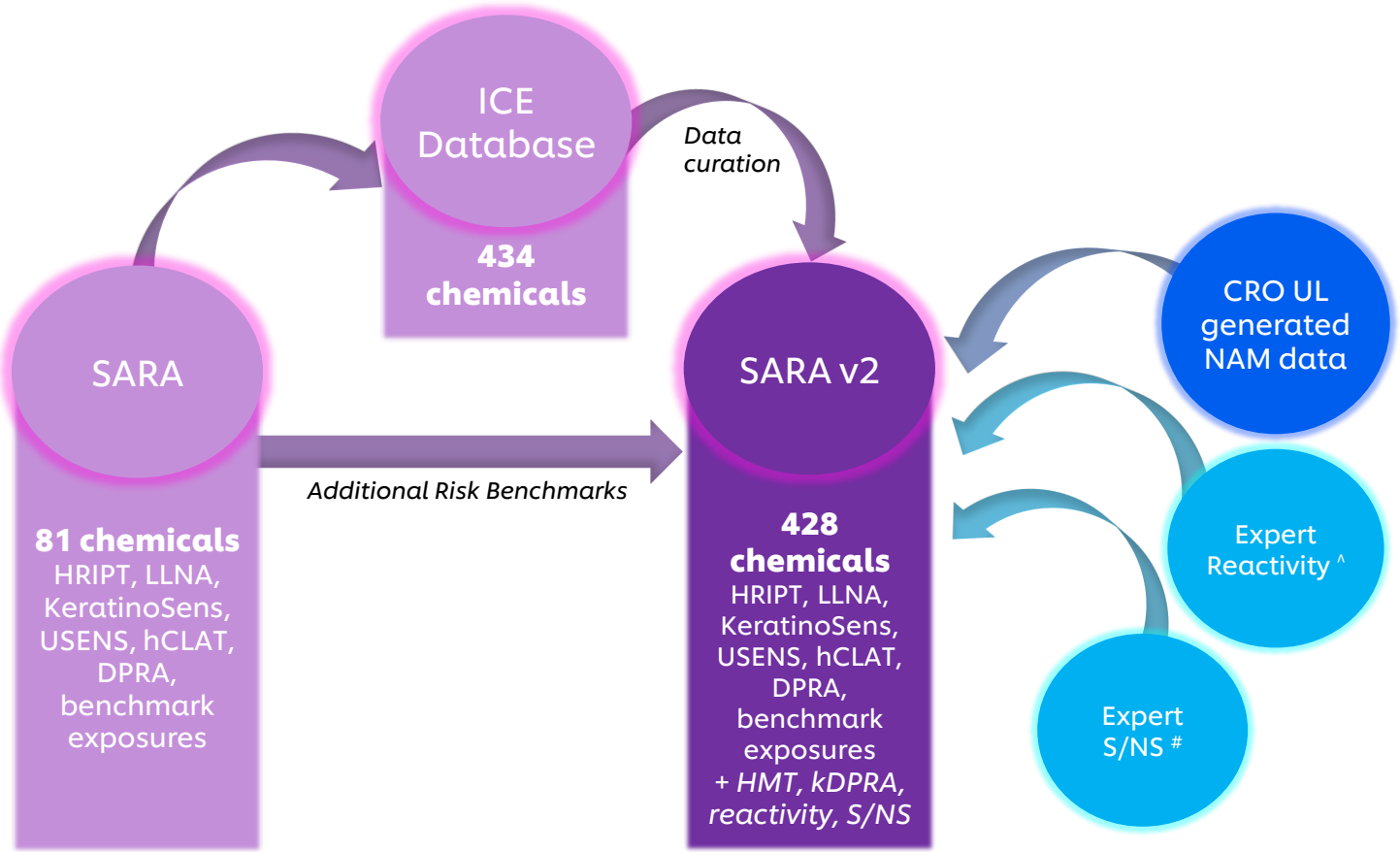
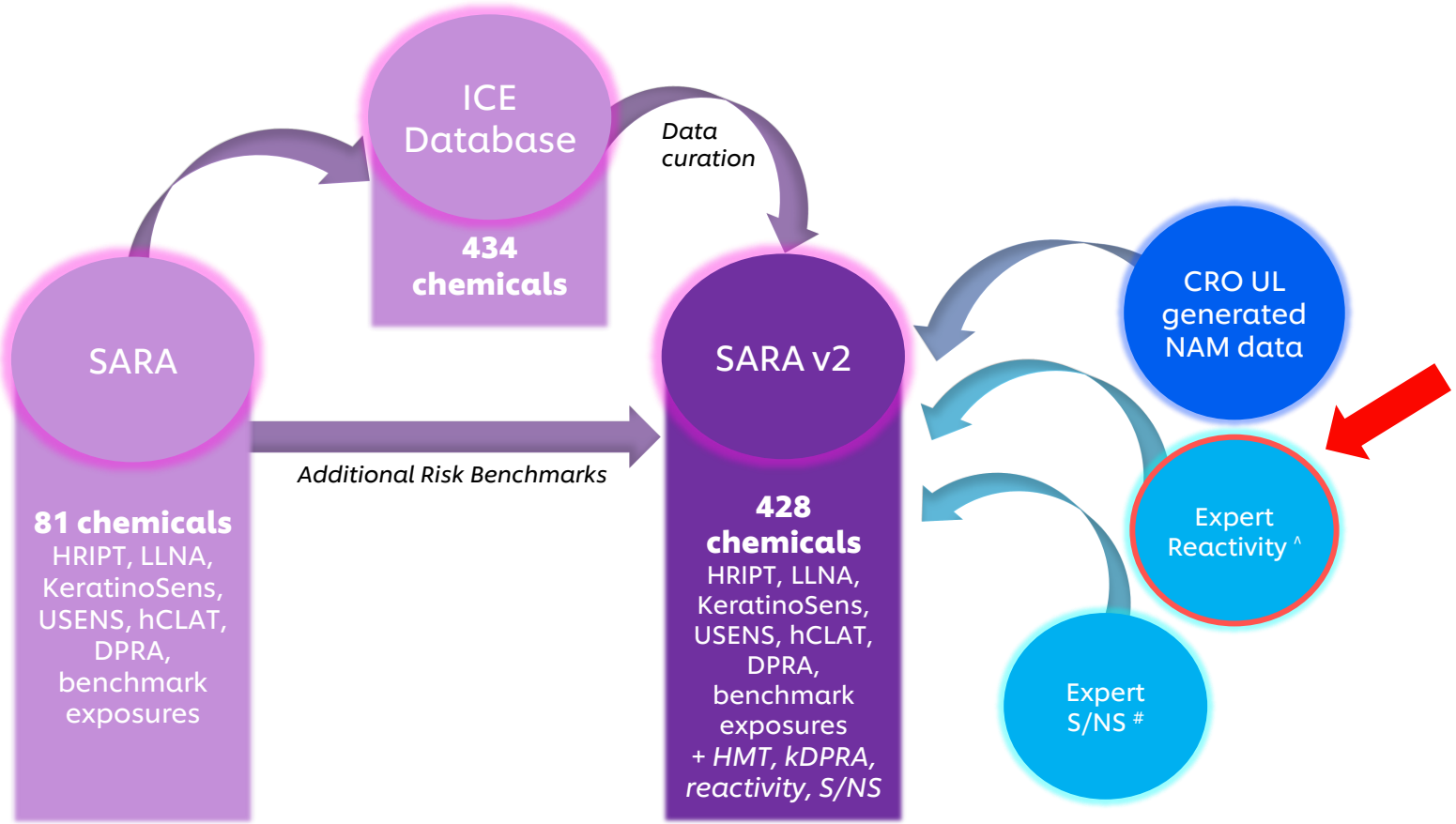
# Database expansion




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

*# curated sensitiser/non-sensitiser classification*

# Mechanistic Classification of Skin Sensitisers




Can be done by an expert – following the chemistry rules in *Aptula and Roberts, 2006*.

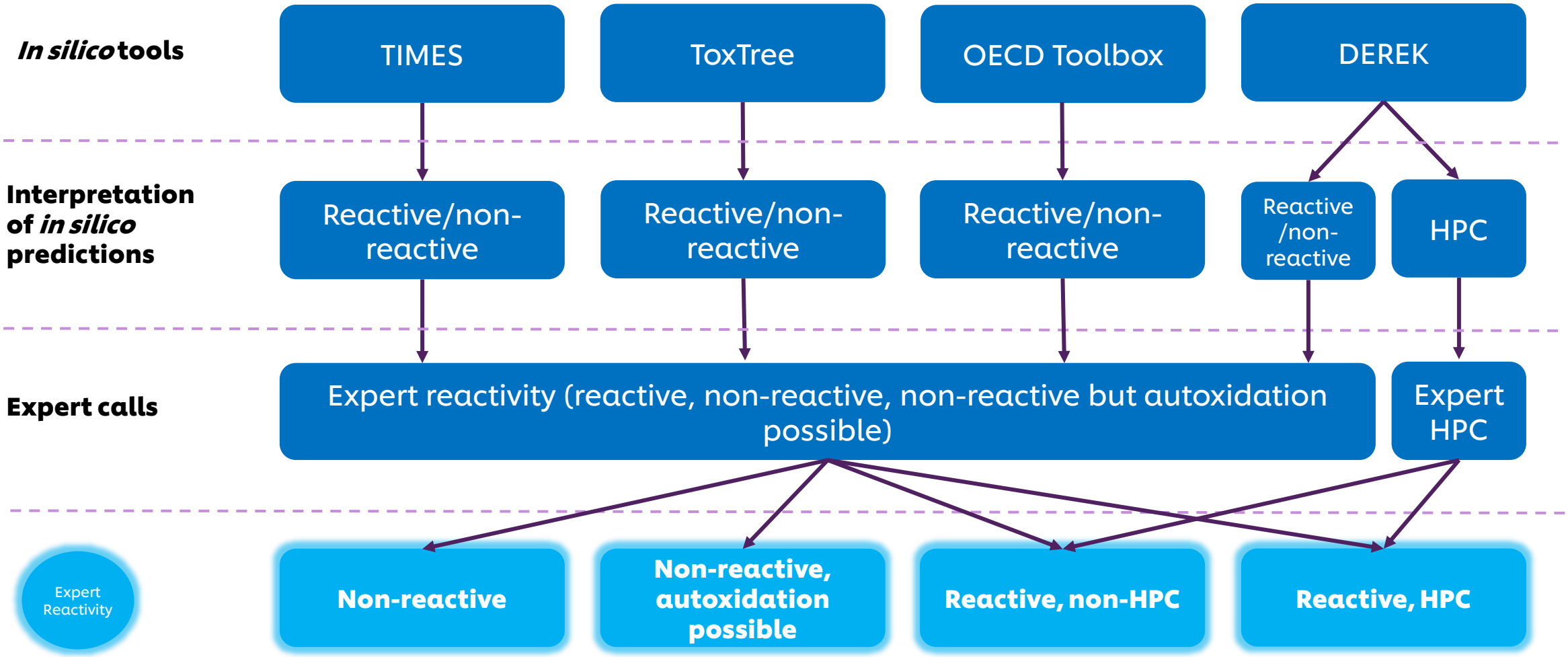
Rules from this paper have been implemented in ToxTree and OECD Toolbox

Principles (structure-based) for identification of high potency chemicals (HPC) were published by *Roberts et al, 2015* and were encoded in several *in silico* tools (e.g. TIMES, DEREK)

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

*# curated sensitiser/non-sensitiser classification*

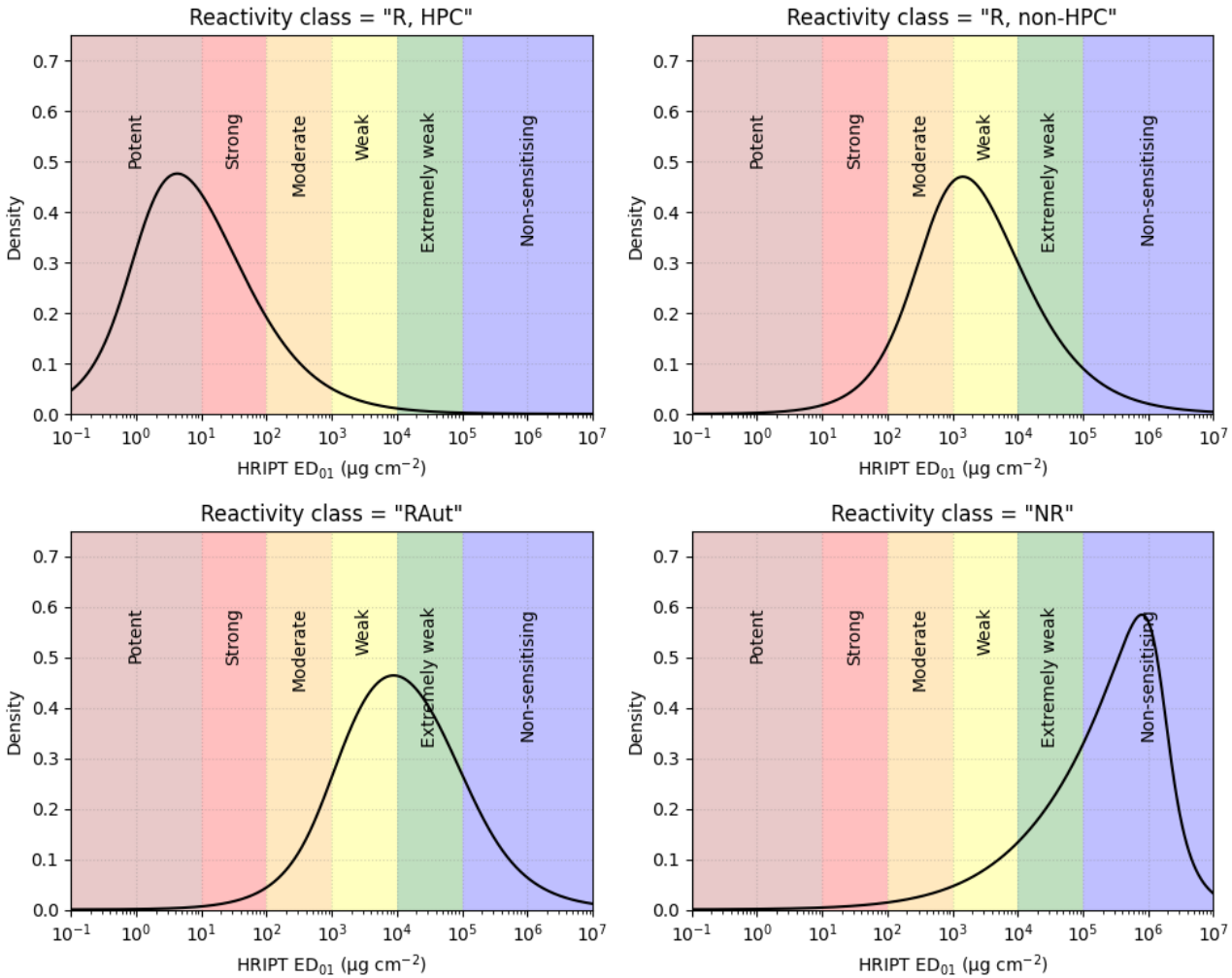
# Determining expert reactivity classifications for SARA v2




*HPC – high potency chemical*

# Addition of reactivity classifications to inform SARA model 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*.

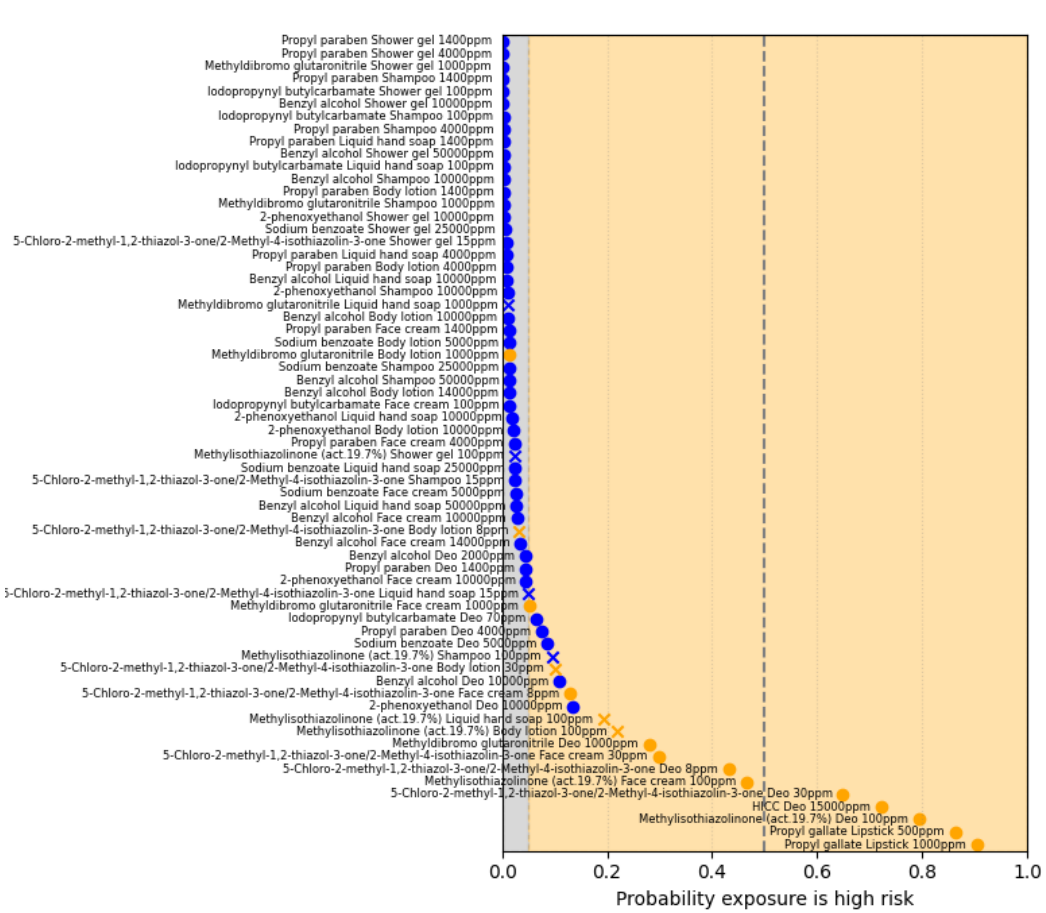


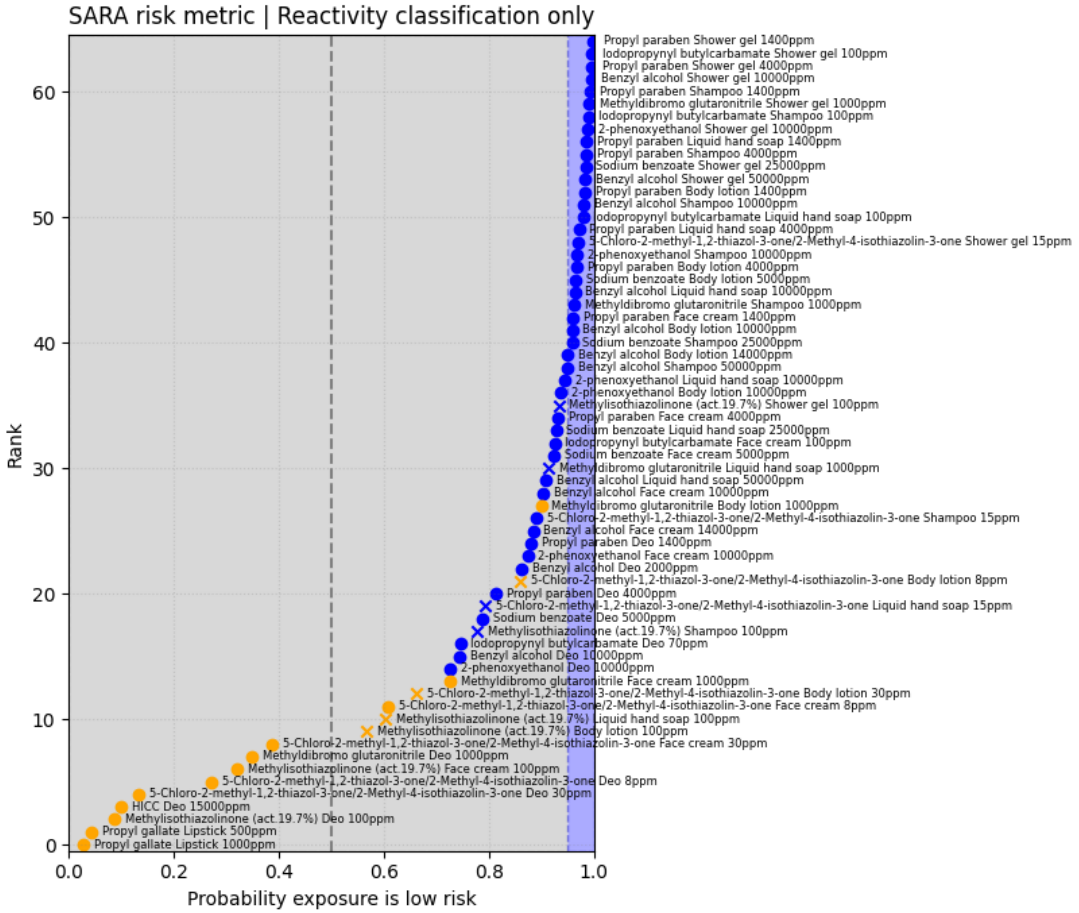
# Cross-validation

Cross-validation exercises were performed conditional on different sets of inputs. A decision model is proposed to translate the risk metric into classifications of “low risk”, “high risk” or “inconclusive”:

1. The model outperforms a traditional approach of QRA using dermal sensitisation thresholds when compared to SARA v2 with reactivity-only inputs
2. Inclusion of *in vitro* inputs in addition to reactivity boosts performance further
3. Using in vivo inputs only, comparable performance with QRA - but better protectiveness.
4. SARA v2 exhibits far greater discriminatory power of the benchmark risk classifications than the previous versions of SARA

# SARA 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% |

# Conclusions

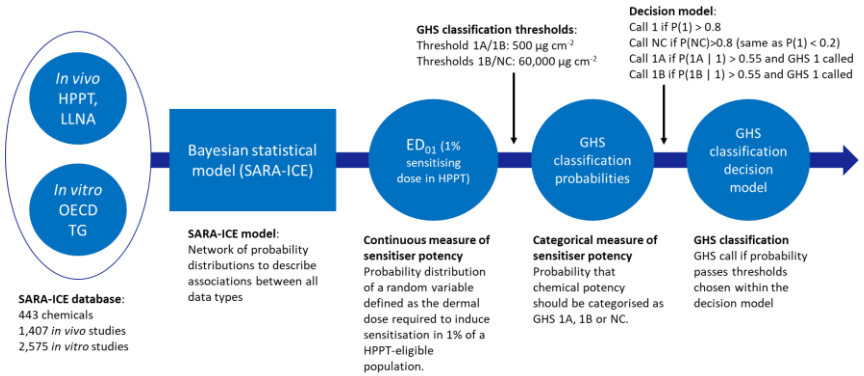
- SARA now incorporates additional input information, including reactivity classifications.
    - Improved decision making for consumer goods; allowing consistent integration of information across a range of data inputs (*in silico, in chemico, in vitro, in vivo*) with quantified uncertainty.
- The reactivity 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 share updates to the model to follow.

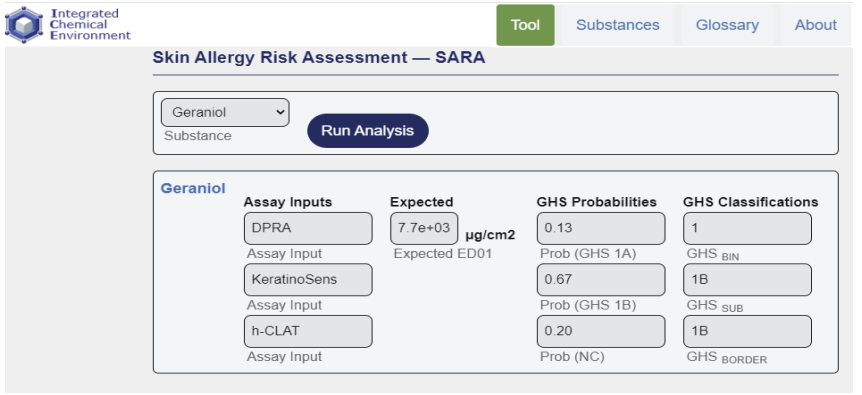
# SARA-ICE Model Development

- 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 v1 and ICE data)**
  - **removal of risk benchmarks**
  - **GHS Classification (binary / potency subcategories)**

- Significant progress made in feasibility study for OECD DASS TG 497
- EPA risk assessment community are early adopters of the approach for fragrance chemical risk assessment
- ***Development of an open access user interface which is currently in beta testing and will be available soon!***

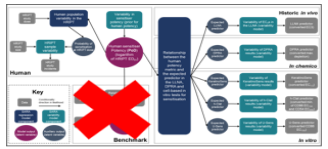



**Database**
Aim to expand the core dataset underpinning the model using data in the ICE database (relaxing the constraint that chemicals be limited to cosmetic ingredients).

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.

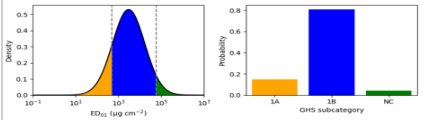


Figure (a) Example estimate of $ED_{01}$ distribution with overlay of GHS subcategories 1A, 1B and NC defined thresholds, (b) probability of each GHS subcategory from $ED_{01}$ distribution

# Thank you

Presentation available at seac.unilever.com

# Back up

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

| | | | | |
|---|---|---|---|---|
| **Exposure** | 0.1% Lactic acid in shampoo | 2% Lactic acid in face cream | 2% geraniol in face cream | 0.2% formaldehyde in face cream |
| **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**

# Expert sensitiser/non-sensitiser classifications

**Step 1: Automated rules using data within SARA database**

Reactivity (R / NR)

LLNA (EC3 / max dose tested)

HPPT (NOEL / LOEL)

→ Sensitiser

Non-sensitiser

**Step 2: Expert review of database and literature data**

Reactivity (*R / NR*)
LLNA (*EC3 / max dose tested*)
HPPT (*NOEL / LOEL*)
GMPT
Clinical evidence

→ Sensitiser

Non-sensitiser

Expert S/NS

→ **Sensitiser**
**268/428 (63%)**

→ **Non-sensitiser**
**67 / 428 (16%)**

→ **Unclassified**
**93 / 428 (22%)**

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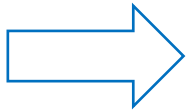
# Benchmark consumer exposure risk classifications expanded and increased in granularity

***SARA v1***

**Binary**

High Risk
Low Risk



***SARA v2***

**Confidence based**

High Risk (High Confidence)
High Risk (Low Confidence)
Low Risk (High Confidence)
Low Risk (Low Confidence)

SARA v2 uses these data as categorical and ordered.

$c_{u,u+1} \sim \text{Normal}(2,1) \quad \text{for } u \in \{1,2,3\}$ ,
$c^* \sim \text{InverseGamma}(1,1)$ ,
$\beta \sim \text{HalfNormal}(0,5)$ .

- These risk classifications better reflect differences in the confidence level at which classifications can be assigned based upon the published clinical evidence.
- Benchmark exposure dataset has been expanded marginally with additional classifications:
  - Methylisothiazolinone (MIT), Shampoo, 100ppm (low risk, low confidence)
  - Methylisothiazolinone (MIT), Shower Gel, 100ppm (low risk, low confidence)

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# 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

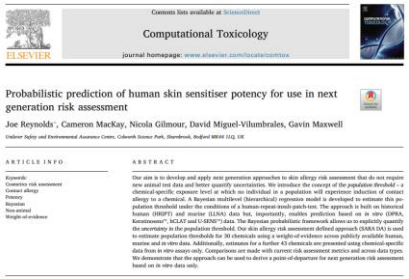
The model and database were revised and expanded. The point of departure became the ED01.

## 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.