Incorporating expert knowledge in the Skin Allergy Risk Assessment (SARA) Model:

an integrated approach to testing and assessment (IATA) demonstrated in case studies

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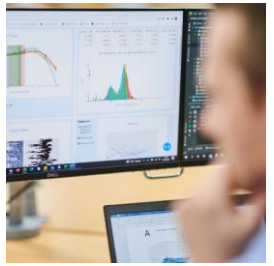

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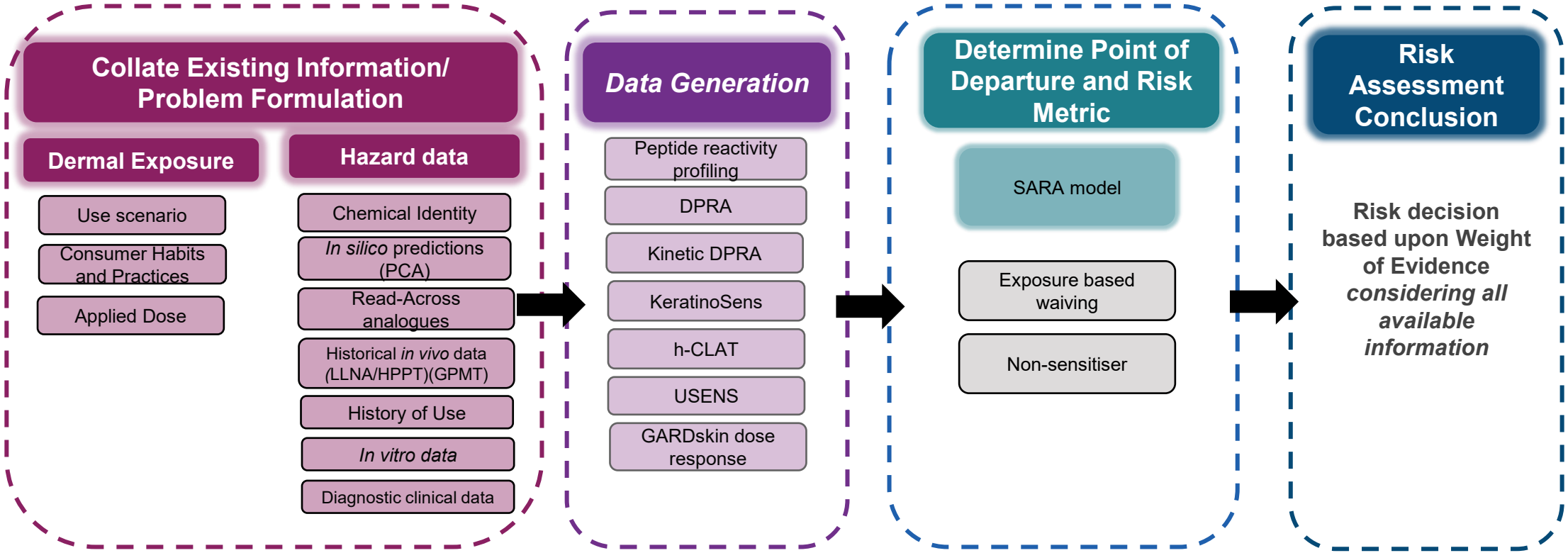
Next Generation Risk Assessment (NGRA) framework for Skin Allergy

- Unilever NGRA framework designed to use a **weight of evidence (WoE)** based upon all available information, accommodate range of consumer product exposure scenarios and provide a **quantitative point of departure (PoD)** and **risk metric**
- Development of the **Unilever Skin Allergy Risk Assessment (SARA) model**



SARA Model – The Timeline

2017-2019

A prototype Bayesian statistical model was developed to estimate a no-effect-dose from human repeat insult patch test (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

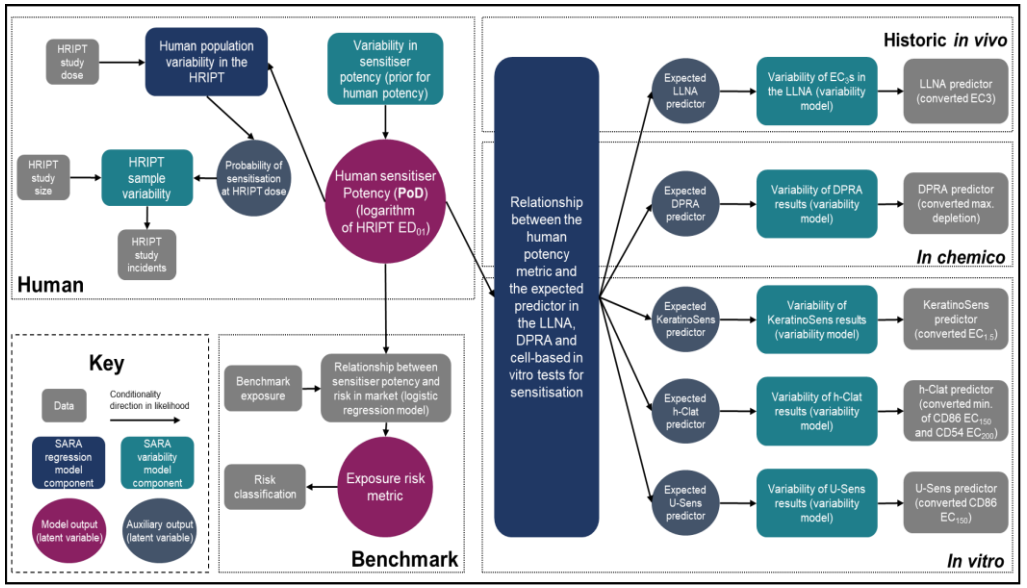
SARA model published within a set of 3 papers#, exploring the model and its use in case study risk assessments.

*https://doi.org/10.1016/j.comtox.2018.10.004

The use-case of the **SARA model** is to estimate:

1. **PoD**: an ED_{01}, defined as the dermal dose (µg/cm^{-2}) required to sensitise 1% of 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

Schematic of the relationships between variables in the SARA model



#Applying the Model: Practical Insights from Risk Case Studies

1. Reynolds et al. (2021). **A hypothetical skin sensitisation next generation risk assessment for coumarin in cosmetic products**. Regul Toxicol Pharmacol, 2022. DOI: https://doi.org/10.1016/j.yrtph.2021.105075

2. Reynolds et al. (2022). **Decision making in next generation risk assessment for skin allergy: Using historical clinical experience to benchmark risk**. Regul Toxicol Pharmacol. DOI: https://doi.org/10.1016/j.yrtph.2022.105219

3. Gilmour et al. (2022). **Next generation risk assessment for skin allergy: Decision making using new approach methodologies**. Regul Toxicol Pharmacol. DOI: https://doi.org/10.1016/j.yrtph.2022.105159

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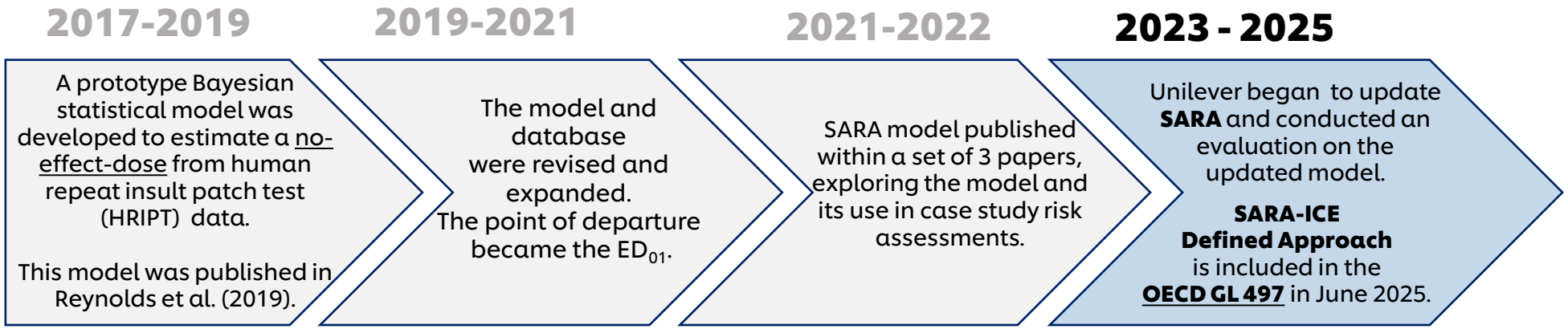
SARA Model – Development Overview



*https://doi.org/10.1016/j.comtox.2018.10.004

- **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 (OECD 442c)** 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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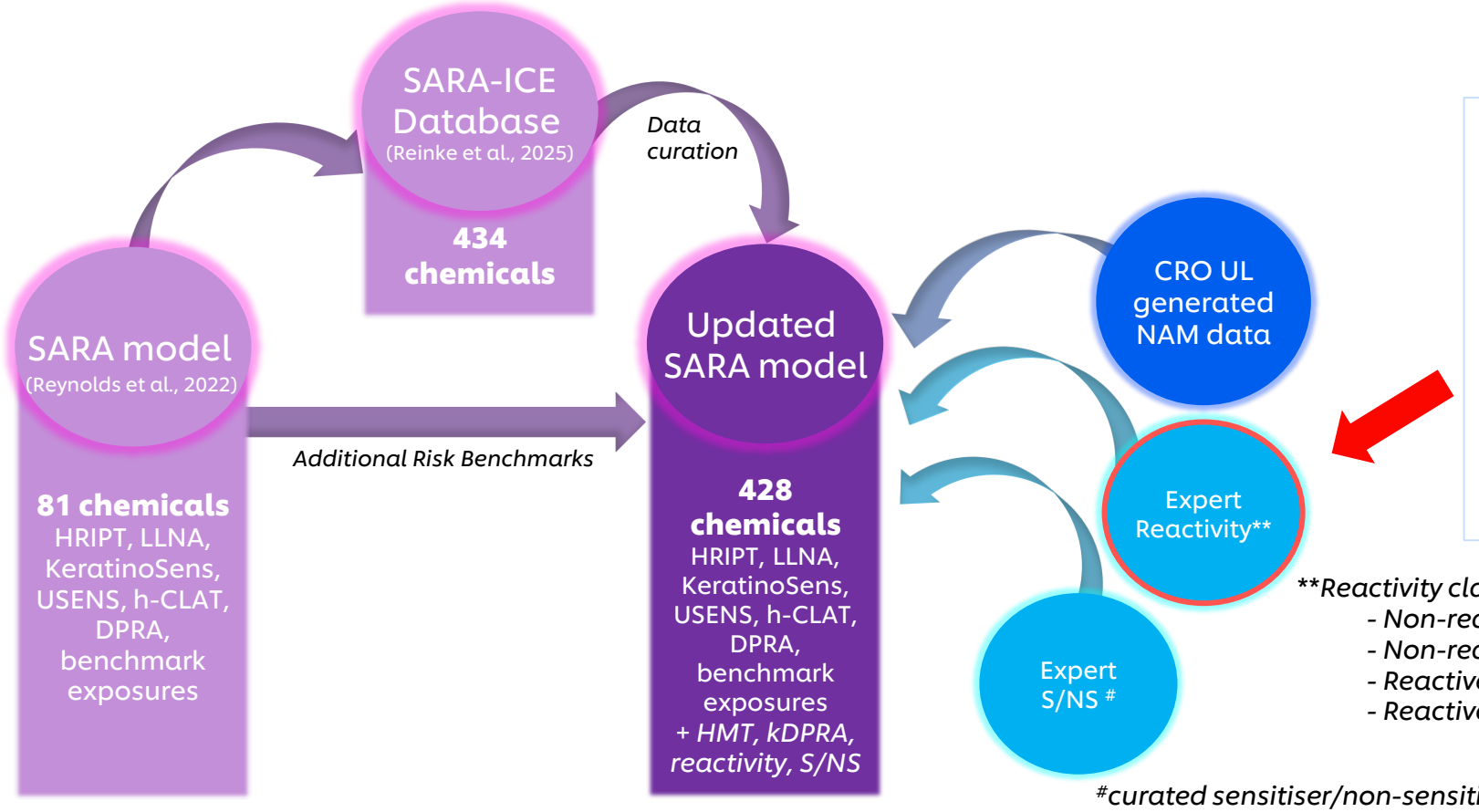
Database expansion & Mechanistic Classification of Skin Sensitisers



Can be done by an expert – following the chemistry rules in Aptula & 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*
- *Non-reactive, but autooxidation possible*
- *Reactive, non-HPC*
- *Reactive, HPC*

#curated sensitiser/non-sensitiser classification

Reinke et al. (2025). **The skin allergy risk assessment-integrated chemical environment (SARA-ICE) defined approach to derive points of departure for skin sensitization**. Curr Res Toxicol. . DOI: https://doi.org/10.1016/j.crtox.2024.100205

Aptula & Roberts (2006). **Mechanistic applicability domains for nonanimal-based prediction of toxicological end points: general principles and application to reactive toxicity**. Chem Res Toxicol. DOI: https://doi.org/10.1021/tx0601004

Roberts et al. (2015). **Principles for identification of High Potency Category Chemicals for which the Dermal Sensitisation Threshold (DST) approach should not be applied**. Regul Toxicol Pharmacol. DOI: https://doi.org/10.1016/j.yrtph.2015.03.001

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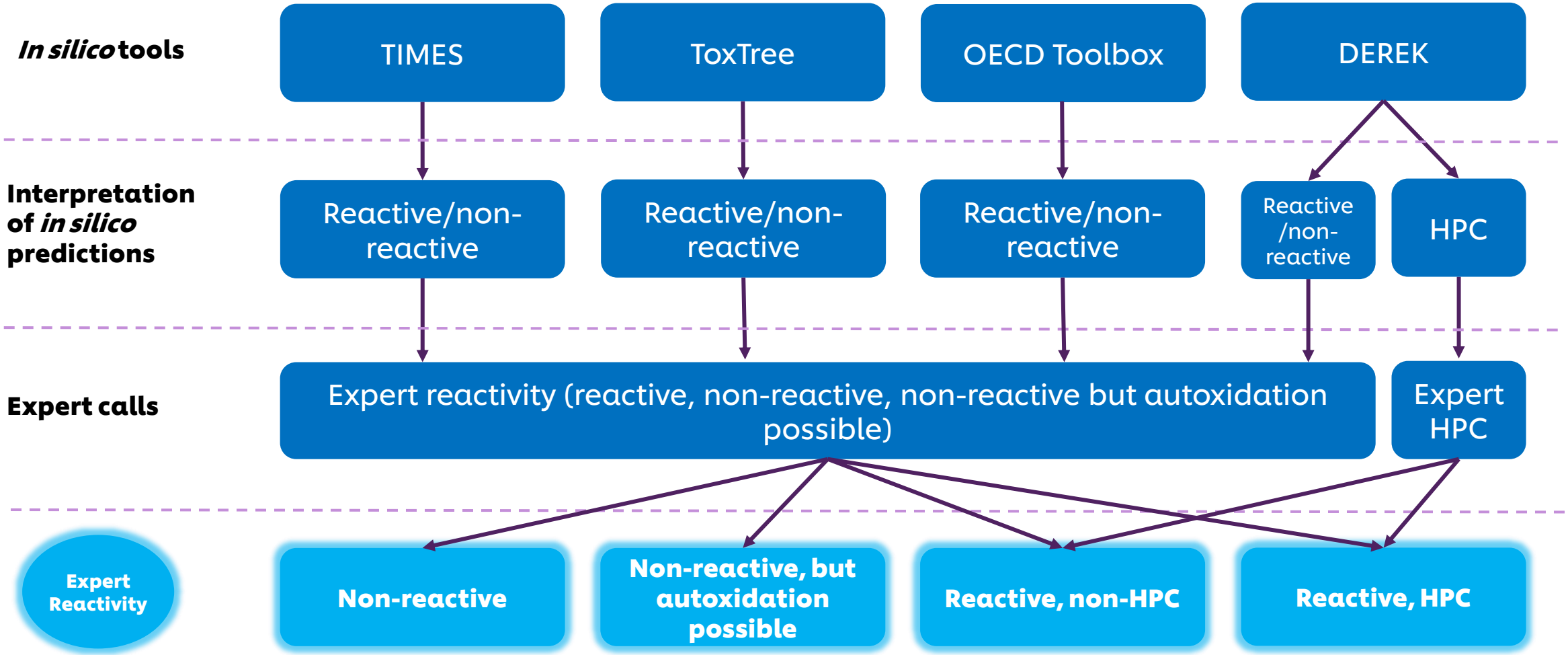
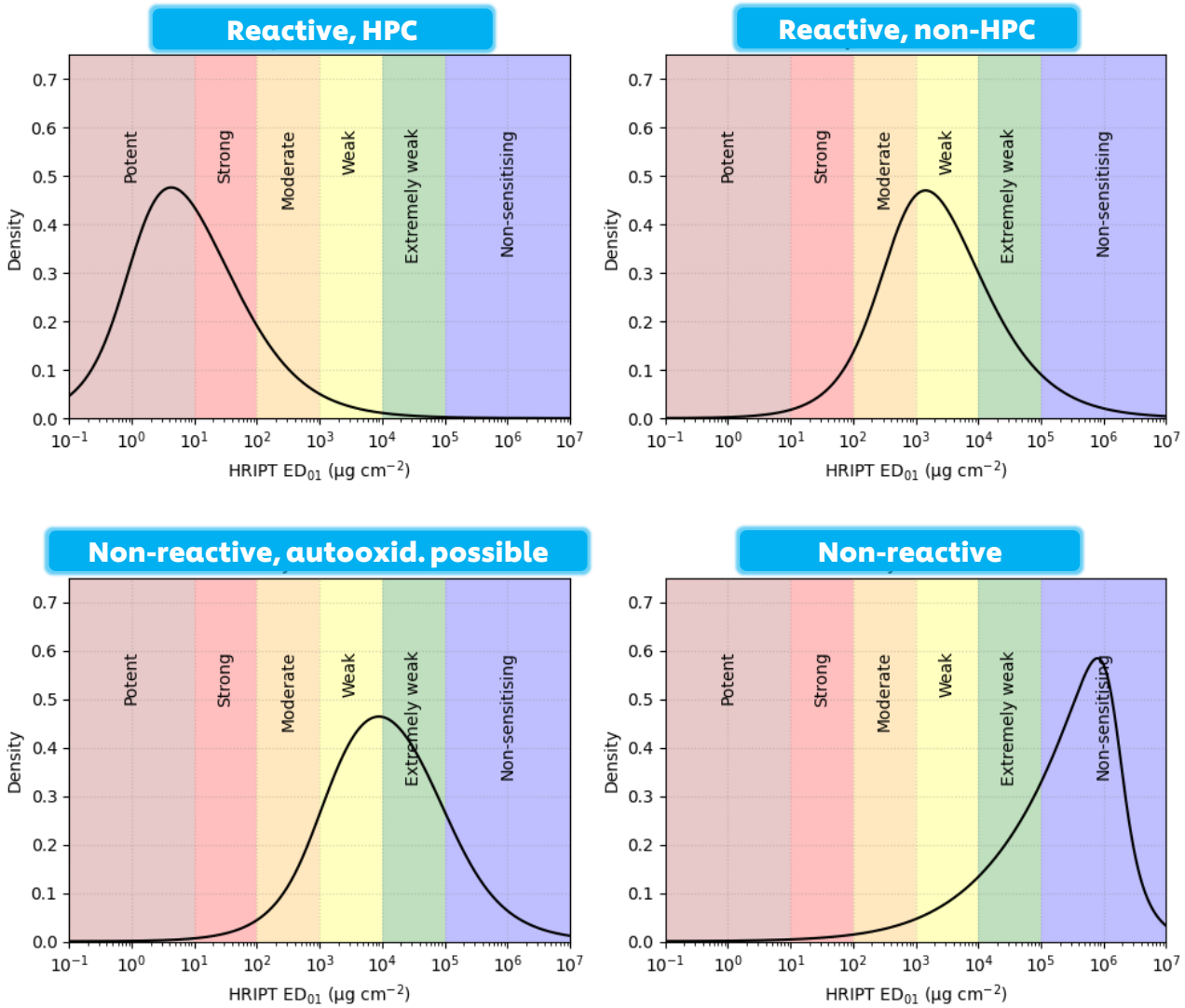
Determining expert reactivity classifications for SARA model



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): non-sensitising, extremely weak, weak, moderate, strong, potent*.



Reynolds et al. (manuscript in preparation)

Gerberick et al. (2001) **Understanding fragrance allergy using an exposure-based risk assessment approach**. Contact Dermatitis. DOI: https://doi.org/10.1034/j.1600-0536.2001.450603.x

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 Quantitative Risk Assessment (QRA)[a] using dermal sensitisation thresholds (DST)[b,c,d] when compared to SARA 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 now exhibits far greater discriminatory power of the benchmark risk classifications than the previous versions of SARA

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%

Reynolds et al. (manuscript in preparation)

[a]Api et al. (2020). **Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials**. Regul Toxicol Pharmacol 118:104805. https://doi.org/10.1016/j.yrtph.2020.104805.
[b]Safford et al. (2011). **Refinement of the Dermal Sensitisation Threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains**. Regul Toxicol Pharmacol, 60(2), 218-224. doi:10.1016/j.yrtph.2011.03.009
[c]Safford et al. (2015). **Extension of the Dermal Sensitisation Threshold (DST) approach to incorporate chemicals classified as reactive**. Regul Toxicol Pharmacol, 72(3), 694-701. doi:10.1016/j.yrtph.2015.04.020.
[d]Nishijo et al. (2020). **Application of the dermal sensitization threshold concept to chemicals classified as high potency category for skin sensitization assessment of ingredients for consumer products**. Regul Toxicol Pharmacol, 117, 104732. doi:10.1016/j.yrtph.2020.104732

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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)		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**	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**	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**	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**
Updated SARA (Reynolds et al., manuscript in preparation)		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**	Chem prediction: non-reactive NAM Data: negative **SARA prediction: reactivity + 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 / 31,000 / 590,000 / 21,000,000 P(NS) = 0.91 P exposure (low risk) **~1** **Risk outcome low risk**	Chem prediction: reactive (auto) NAM data: mixed **SARA prediction: reactivity + 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**	Chem prediction: reactive NAM data: positive **SARA prediction: reactivity + 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**

Gilmour et al. (2022). **Next generation risk assessment for skin allergy: Decision making using new approach methodologies**. Regul Toxicol Pharmacol. DOI: https://doi.org/10.1016/j.yrtph.2022.105159
Reynolds et al. (2022) **Decision making in next generation risk assessment for skin allergy: Using historical clinical experience to benchmark risk**. Regul Toxicol Pharmacol. DOI: https://doi.org/10.1016/j.yrtph.2022.105219.

Conclusions

- SARA model 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): *non-sensitising, extremely weak, weak, moderate, strong, potent*.
- 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.
- Continue to build SARA model and to include other parameters.

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- **Sue Martin**

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