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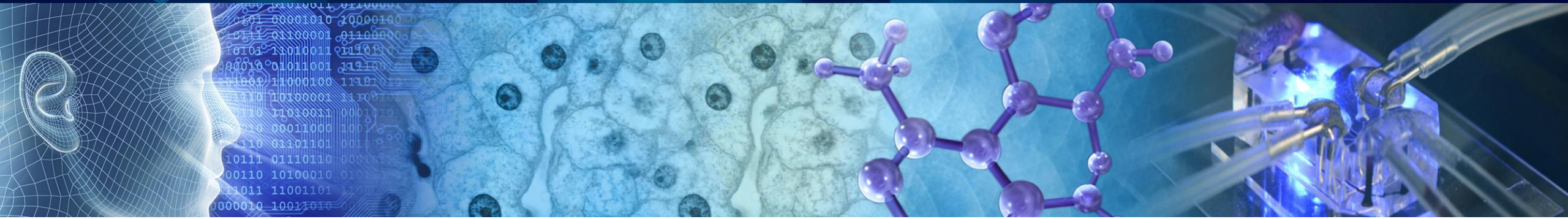

The SARA-ICE Model for Predicting Skin Sensitizer Potency

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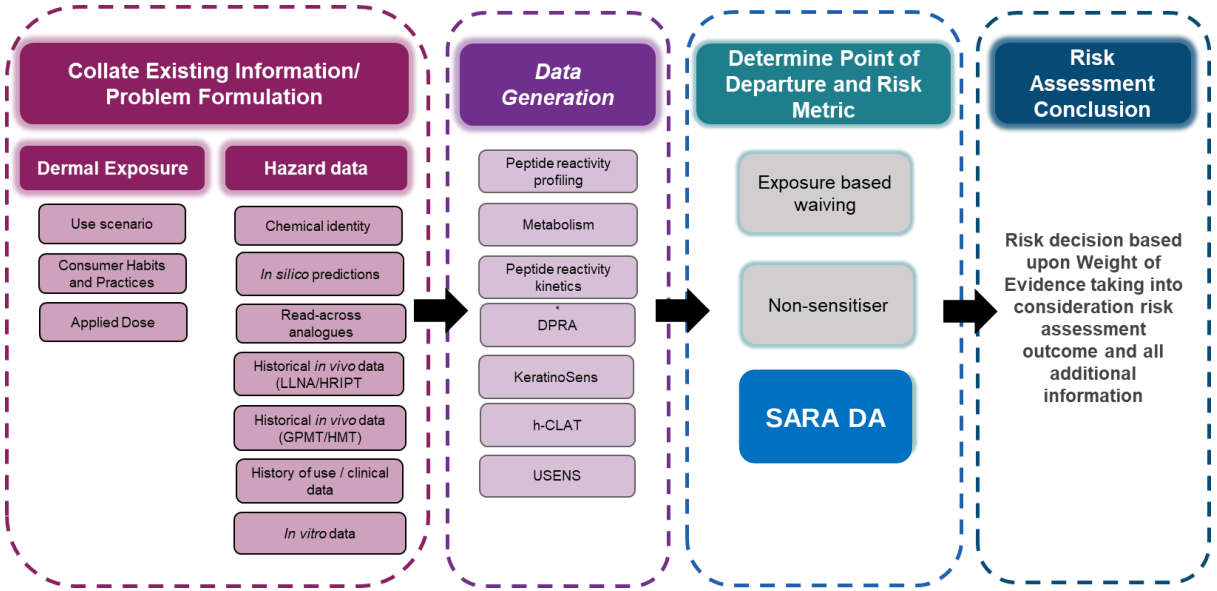
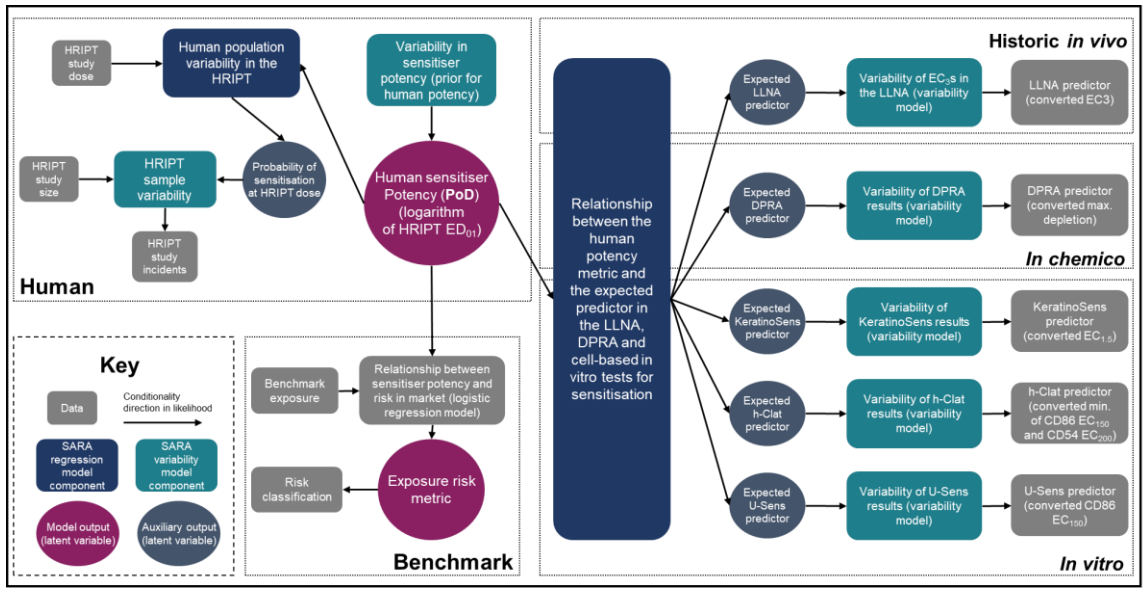
31st August 2023, WC12, Niagara Falls, Canada

Skin Allergy Risk Assessment Defined Approach (SARA DA) was developed for application as part of a tiered, WoE NGRA framework





- **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 → **SARA DA**

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

1. ED_{01}, for all chemicals in the SARA database (which may include data for some chemical of interest)
2. probability that a consumer exposure to some chemical is 'low risk', conditional on the available data and the model

Reynolds et al 2022 https://pubmed.ncbi.nlm.nih.gov/35835397/

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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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Modification of SARA DA to create SARA-ICE

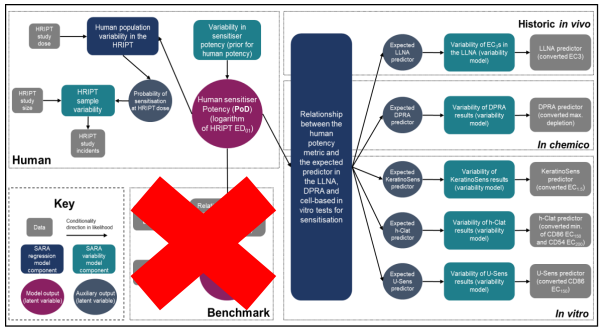
Database
Aim to expand the core dataset underpinning the model using data in the ICE database (relaxing the constraint that chemicals be limited to cosmetic ingredients).

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.

Integrated Chemical Environment

ICE: Integrated Chemical Environment (nih.gov)



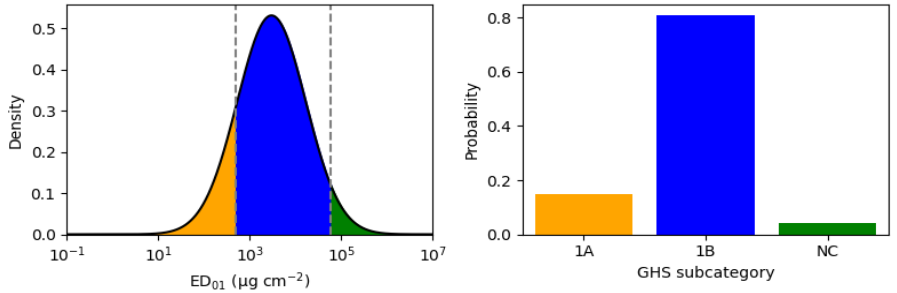


Figure (a) Example estimate of ED_{01} distribution with overlay of GHS subcategories 1A, 1B and NC defined thresholds, (b) probability of each GHS subcategory from ED_{01} distribution

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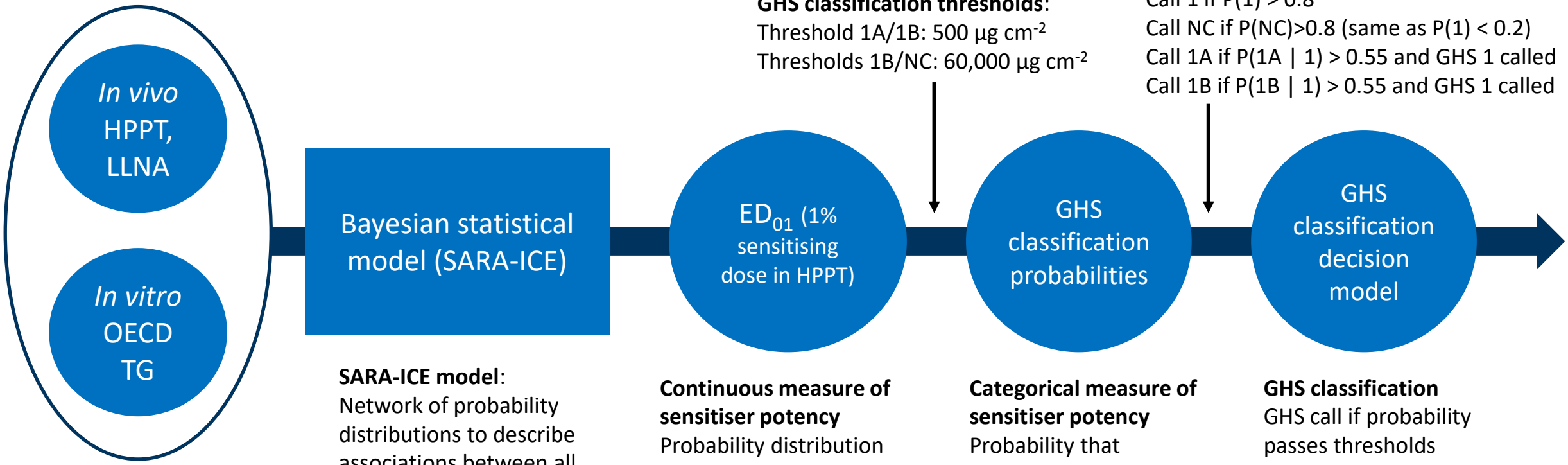
SARA-ICE DA: Skin Allergy Risk Assessment - Integrated Chemical Environment Defined Approach



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-ICE NAM vs OECD DASS benchmarks

Binary classifications

Human, θ_{bin} = 0.80	**SARA 1**	**SARA NC**	**Inconclusive**	**Total**
OECD 1	37	4	14	55
OECD NC	0	4	7	11
Total	37	8	21	66
Sensitivity: 90% Specificity: 100% **Balanced accuracy: 95%**				
LLNA, θ_{bin} = 0.80	**SARA 1**	**SARA NC**	**Inconclusive**	**Total**
OECD 1	87	6	42	135
OECD NC	2	19	12	33
Total	89	25	54	168
Sensitivity: 94% Specificity: 90% **Balanced accuracy: 92%**				

SARA-ICE NAM vs OECD DASS benchmarks

Subcategory classifications

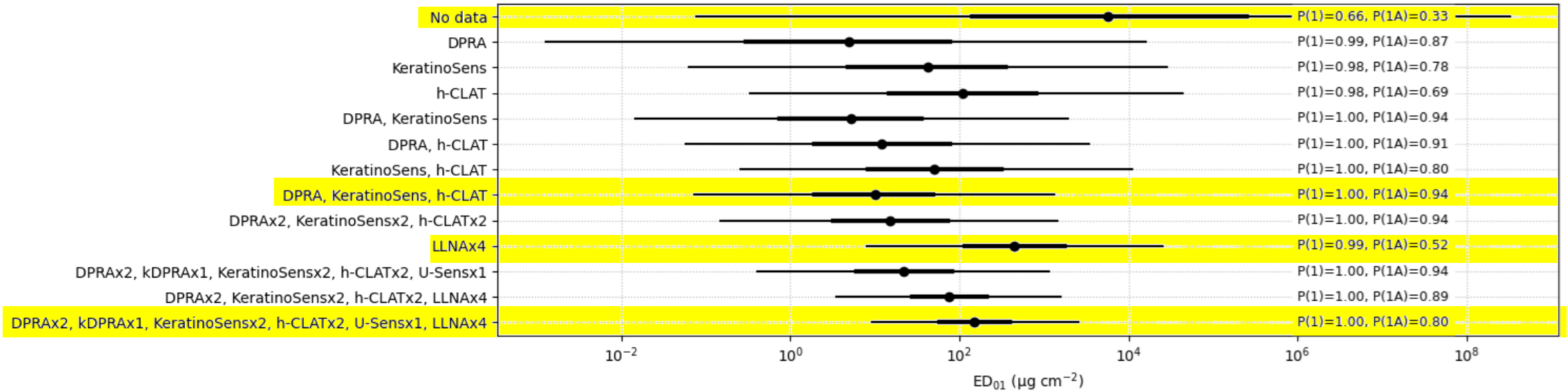
Human, θ_{bin} = 0.80, θ_{sub}=0.55	**SARA 1A**	**SARA 1B**	**SARA NC**	**Inconclusive**	**Total**
OECD 1A	14	2	0	5	21
OECD 1B	4	9	4	14	31
OECD NC	0	0	4	7	11
Total	18	11	8	26	63
Sensitivity 1A: 88%, Specificity 1A: 81%, Balanced accuracy 1A: 84% Sensitivity 1B: 53%, Specificity 1B: 90%, Balanced accuracy 1B: 71% Sensitivity NC: 100%, Specificity NC: 88%, Balanced accuracy NC: 94% **Average balanced accuracy: 83%**					

LLNA, θ_{bin} = 0.80, θ_{sub}=0.55	**SARA 1A**	**SARA 1B**	**SARA NC**	**Inconclusive**	**Total**
OECD 1A	28	4	0	6	38
OECD 1B	16	22	5	42	85
OECD NC	0	1	19	13	33
Total	44	27	24	61	156
Sensitivity 1A: 88%, Specificity 1A: 75%, Balanced accuracy 1A: 81% Sensitivity 1B: 51%, Specificity 1B: 90%, Balanced accuracy 1B: 71% Sensitivity NC: 95%, Specificity NC: 93%, Balanced accuracy NC: 94% **Average balanced accuracy: 82%**					

SARA-ICE - MIT (2-Methyl-4-isothiazolin-3-one) example – input data

Chemical	DPRA	kDPRA	KeratinoSens™	h-Clat	U-Sens™	Local Lymph Node Assay (LLNA)
MIT	Cysteine depletion: 97.9% Lysine depletion: 0% *Source*: Natsch et al., 2013	Log Kmax: -0.25 $M^{-1}s^{-1}$ *Source*: Natsch & Gerberick, 2022	$EC_{1.5}$: 11.78 µM IC_{50}: 139 µM *After unit conversion* $EC_{1.5}$: 1.4 µg ml^{-1} IC_{50}: 16 µg ml^{-1} *Source*: Natsch et al., 2013 & Urbisch et al., 2015 (lmax)	CD54 EC_{200}: 7.89 µg ml^{-1} CD86 EC_{150}: 9.23 µg ml^{-1} CV75: 24.7 µg ml^{-1} *Source*: Urbisch et al. 2015	CD86 EC_{150}: 9 µg ml^{-1} CV75: 44.3 µg ml^{-1} *Source*: Piroird et al., 2015	
	Cysteine depletion: 100% Lysine depletion: 0% *Source*: Kleinstreuer et al., 2018		$EC_{1.5}$: 9.54 µM IC_{50}: 108.25 µM After unit conversion $EC_{1.5}$: 1.1 µg ml^{-1} IC_{50}: 12 µg ml^{-1} *Source*: Kleinstreuer et al., 2018	CD54 EC_{200}: 11.6 µg ml^{-1} CD86 EC_{150}: 11.8 µg ml^{-1} CV75: 24.6 µg ml^{-1} *Source*: Kleinstreuer et al., 2018		EC_3: 2.2% EC_3: 0.4% EC_3: 0.863% EC_3: >4.5% *Source:* Kleinstreuer et al., 2018

SARA-ICE - MIT example – ED_{01} PoD estimates



Summaries of ED_{01} estimates for MIT conditional on different combinations of input data. Distributions are represented as centred 95% credible intervals (thin lines), centred 50% credible intervals (thick lines) and median (bullet). Predictions are ordered, from largest (top) to smallest (bottom), with respect to the uncertainty in the estimate.

ED_{01} estimates for MIT for different SARA-ICE data inputs

Input Data	ED_{01} ($\mu g\ cm^{-2}$)	ED_{01} percentiles ($\mu g\ cm^{-2}$)					Prob(1A)	Prob(1B)	Prob(NC)
		2.5th	25th	50th	75th	97.5th			
No data	**5,600**	0.077	140	5700	>100,000	>100,000	**0.33**	**0.33**	**0.34**
DPRA	4.7	0.0013	0.29	4.9	78	16,000	0.87	0.12	0.011
KeratinoSens	42	0.063	4.8	42	360	28,000	0.78	0.2	0.015
h-CLAT	110	0.33	15	110	820	44,000	0.69	0.29	0.02
DPRA, KeratinoSens	5.1	0.014	0.73	5.2	36	1,900	0.94	0.061	0.0008
DPRA, h-CLAT	12	0.057	1.9	12	77	3,400	0.91	0.087	0.0021
KeratinoSens, h-CLAT	52	0.26	8.3	51	320	11,000	0.8	0.19	0.0049
DPRA, KeratinoSens™ h-CLAT	**9.8**	0.072	1.9	9.9	49	1,300	**0.94**	**0.058**	**0.0004**
DPRAx2, KeratinoSensx2, h-CLATx2	15	0.15	3.2	15	73	1,500	0.94	0.064	0.0003
LLNA x4	**440**	8.1	110	440	1,800	26,000	**0.52**	**0.47**	**0.011**
DPRAx2, kDPRAx1,KeratinoSensx2, h-CLATx2,U-Sensx1	22	0.41	6	22	81	1,200	0.94	0.058	0.0001
DPRAx2, KeratinoSensx2, h-CLATx2, LLNAx4	76	3.5	28	75	210	1,600	0.89	0.11	0
DPRAx2, kDPRA KeratinoSens™x2, h-CLATx2, U-Sens™ LLNAx4	**150**	9.4	59	150	400	2,600	**0.8**	**0.2**	**0**

SARA-ICE – MIT example – Probability that an exposure is less than the ED_{01}

Input combination	Exposure (μg cm^{-2})											
	0.01	0.03	0.1	0.3	1	3	10	30	100	300	1000	3000
DPRA	0.93	0.89	0.82	0.75	0.65	0.55	0.43	0.32	0.23	0.16	0.096	0.058
KeratinoSens	0.99	0.99	0.97	0.94	0.88	0.79	0.67	0.54	0.39	0.27	0.16	0.092
h-CLAT	1	1	0.99	0.98	0.94	0.89	0.79	0.67	0.51	0.37	0.23	0.14
DPRA, KeratinoSens	0.98	0.96	0.91	0.83	0.71	0.57	0.41	0.27	0.15	0.084	0.038	0.018
DPRA, h-CLAT	0.99	0.99	0.96	0.92	0.82	0.7	0.53	0.37	0.22	0.12	0.057	0.027
KeratinoSens, h-CLAT	1	1	0.99	0.97	0.93	0.86	0.73	0.58	0.4	0.26	0.14	0.067
DPRA, KeratinoSens, h-CLAT	1	0.99	0.97	0.92	0.82	0.69	0.5	0.33	0.17	0.082	0.032	0.012
DPRAx2, KeratinoSensx2, h-CLATx2	1	1	0.98	0.95	0.88	0.76	0.58	0.39	0.21	0.096	0.035	0.012
LLNAx4	1	1	1	1	1	0.99	0.97	0.91	0.77	0.57	0.34	0.17
DPRAx2, kDPRAx1, KeratinoSensx2, h-CLATx2, U-Sensx1	1	1	1	0.98	0.94	0.84	0.66	0.43	0.22	0.091	0.029	0.0091
DPRAx2, KeratinoSensx2, h-CLATx2, LLNAx4	1	1	1	1	1	0.98	0.91	0.73	0.43	0.19	0.047	0.0095
DPRAx2, kDPRAx1, KeratinoSensx2, h-CLATx2, U-Sensx1, LLNAx4	1	1	1	1	1	1	0.97	0.88	0.61	0.32	0.095	0.019

*Comparison of ED01 estimates (based on different combinations of inputs) and probability that exposures are the less than the ED01. Thresholds of 0.2 (**orange - ≥ 80% likelihood that exposure is greater than ED_{01}**) and 0.8 (**blue - ≥80% likelihood that exposure is less than ED_{01}**).*

Conclusions & Next Steps

- SARA DA is being adapted for regulatory use through inclusion of ICE database, removal of risk benchmarks and functionality added to allow GHS classification
- SARA ICE DA shows good concordance with sensitizer binary and GHS sub-category classifications against OECD DASS benchmark data
- MIT case study demonstrated benefits of SARA-ICE DA:
  - estimates human potency (ED_{01}) with uncertainty
  - estimates with in vitro and in vivo data inputs
  - estimates with incomplete and repeat datasets
- Evaluation of the SARA-ICE DA is ongoing within the OECD DASS expert group

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Acknowledgements:

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