Reference Chemical Potency list (RCLP): SARA DA

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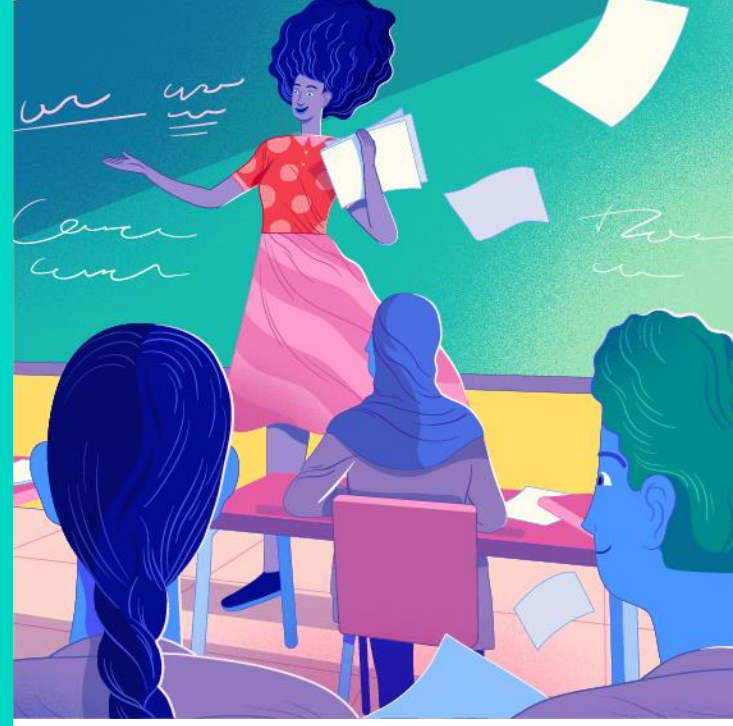
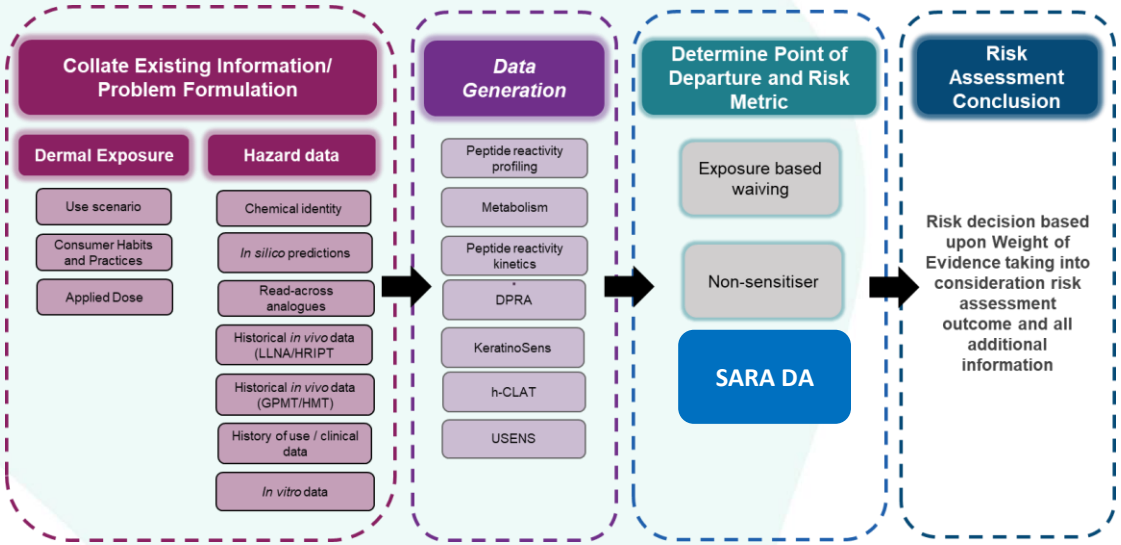
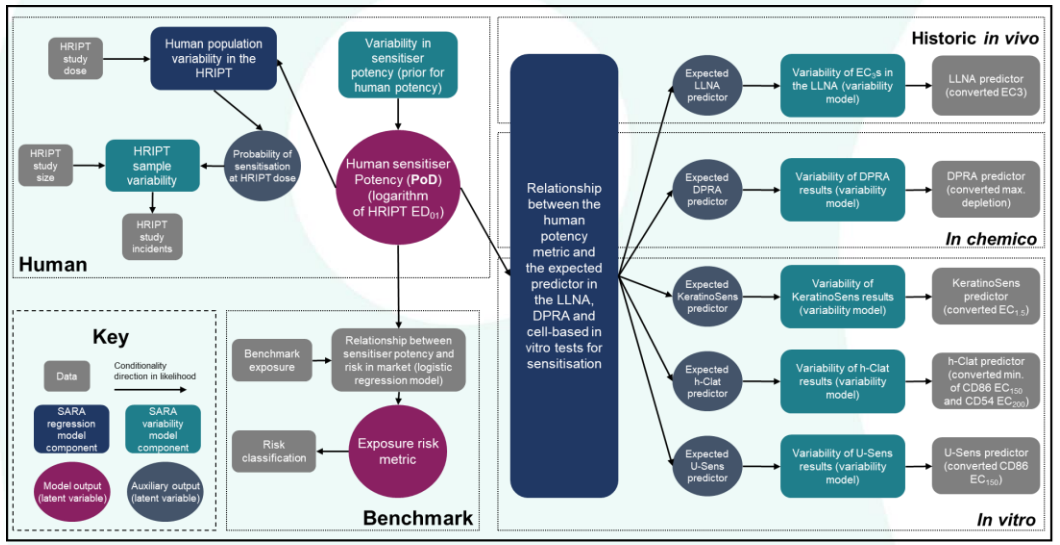
IDEA workshop 22nd September 2023

01/02/2024



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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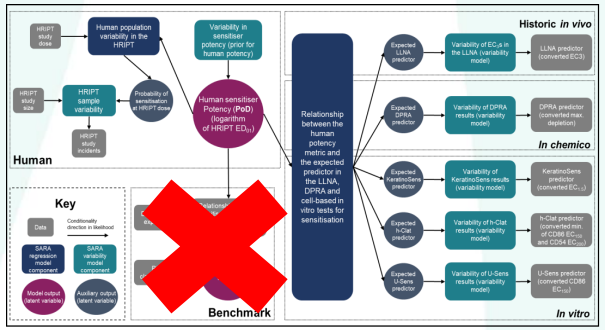
SARA DA is NOT the same as SARA-ICE

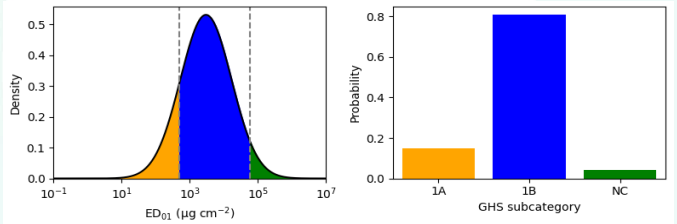
Database and input data

Integrated Chemical Environment

Risk benchmarking



GHS classification



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

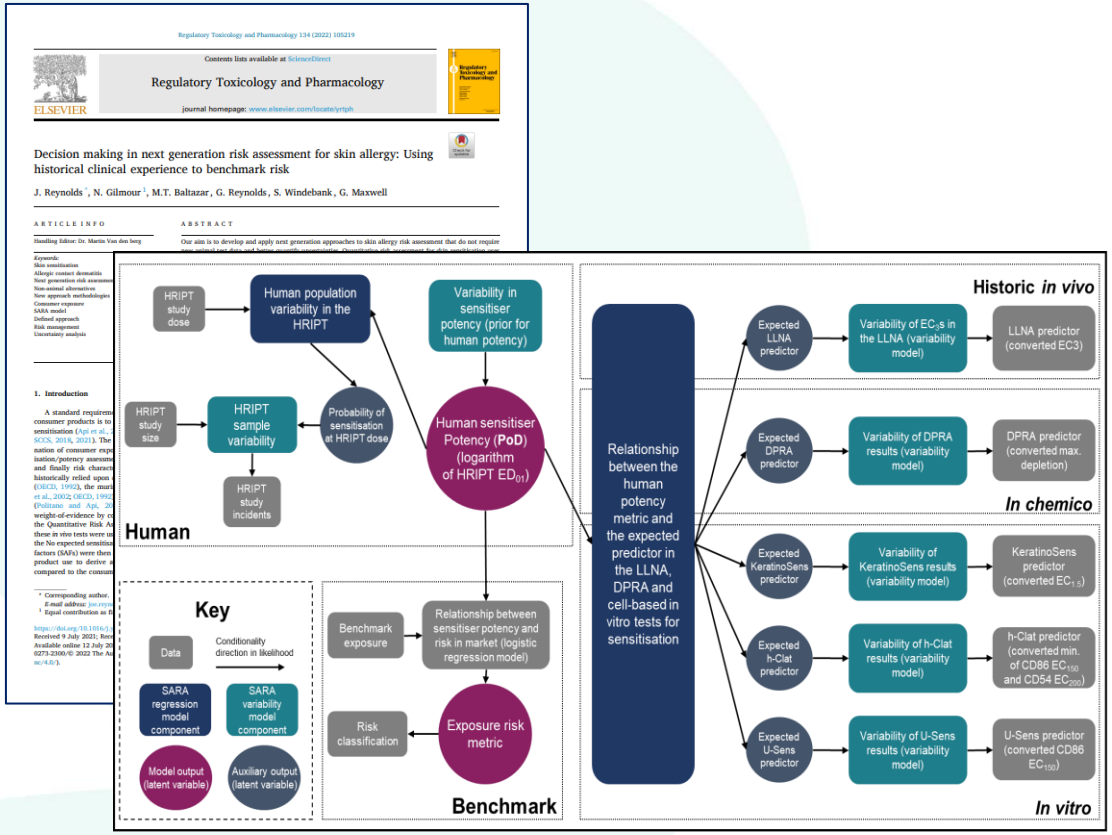
NICEATM has entered into an agreement with consumer products company Unilever to collaboratively test and further develop their Skin Allergy Risk Assessment (SARA) predictive model. SARA is a computational model that uses a variety of input data to estimate a probability that a chemical will cause an 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

Unilever

SARA DA: updates



- DATABASE EXPANSION
- RELAXED ASSUMPTION CONDITION OF USE IS FOR SENSITISER
- NEW INPUTS
  - HMT
  - Reactivity information (R/NR/HPC)
  - kDPRA

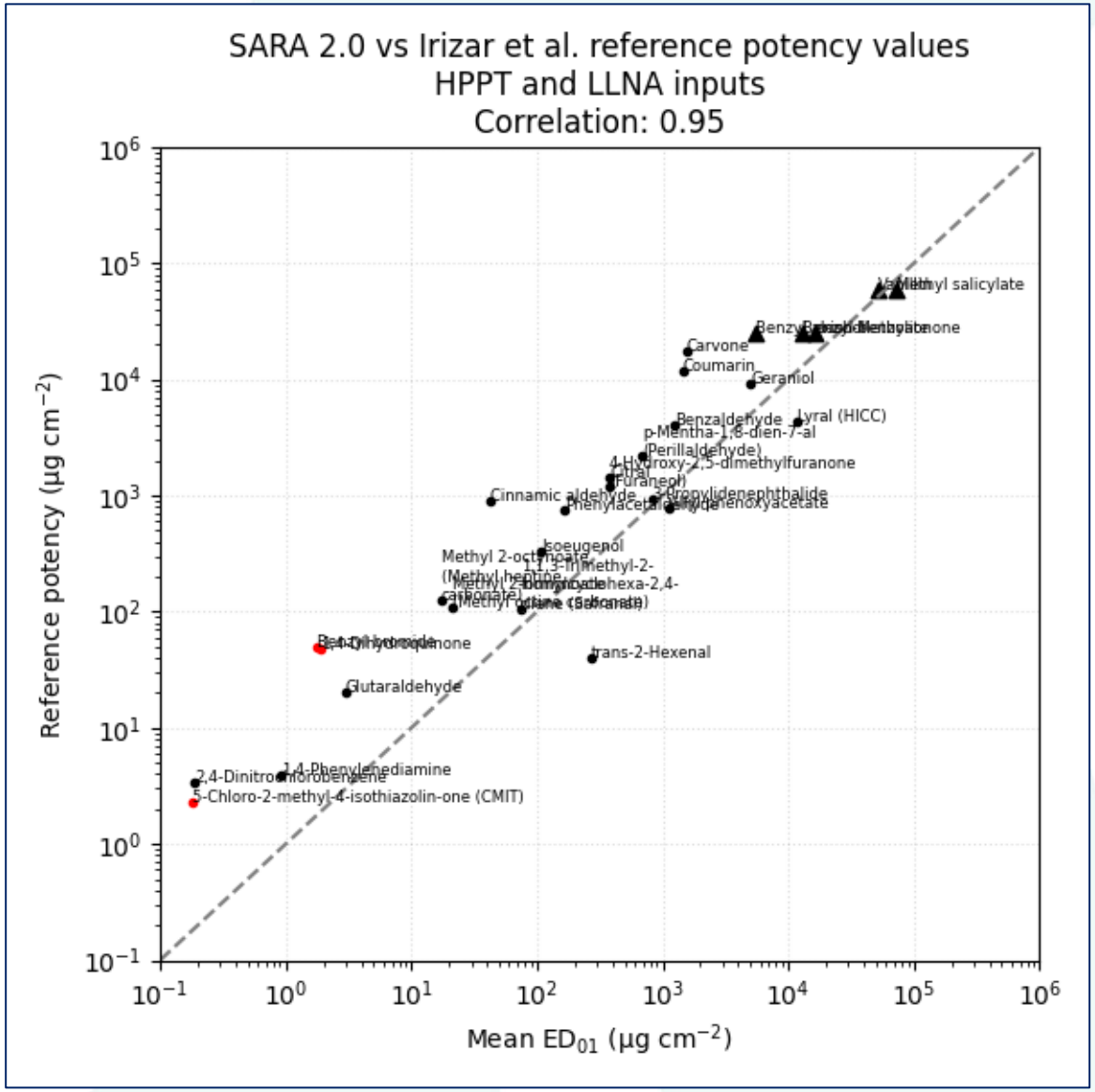
Reynolds J *et al* 2022 https://pubmed.ncbi.nlm.nih.gov/35835397/

SARA ED_{01} estimated from *in vivo* data correlated against RCLP PV

INPUTS (where available)

- HRIPT
- HMT
- LLNA

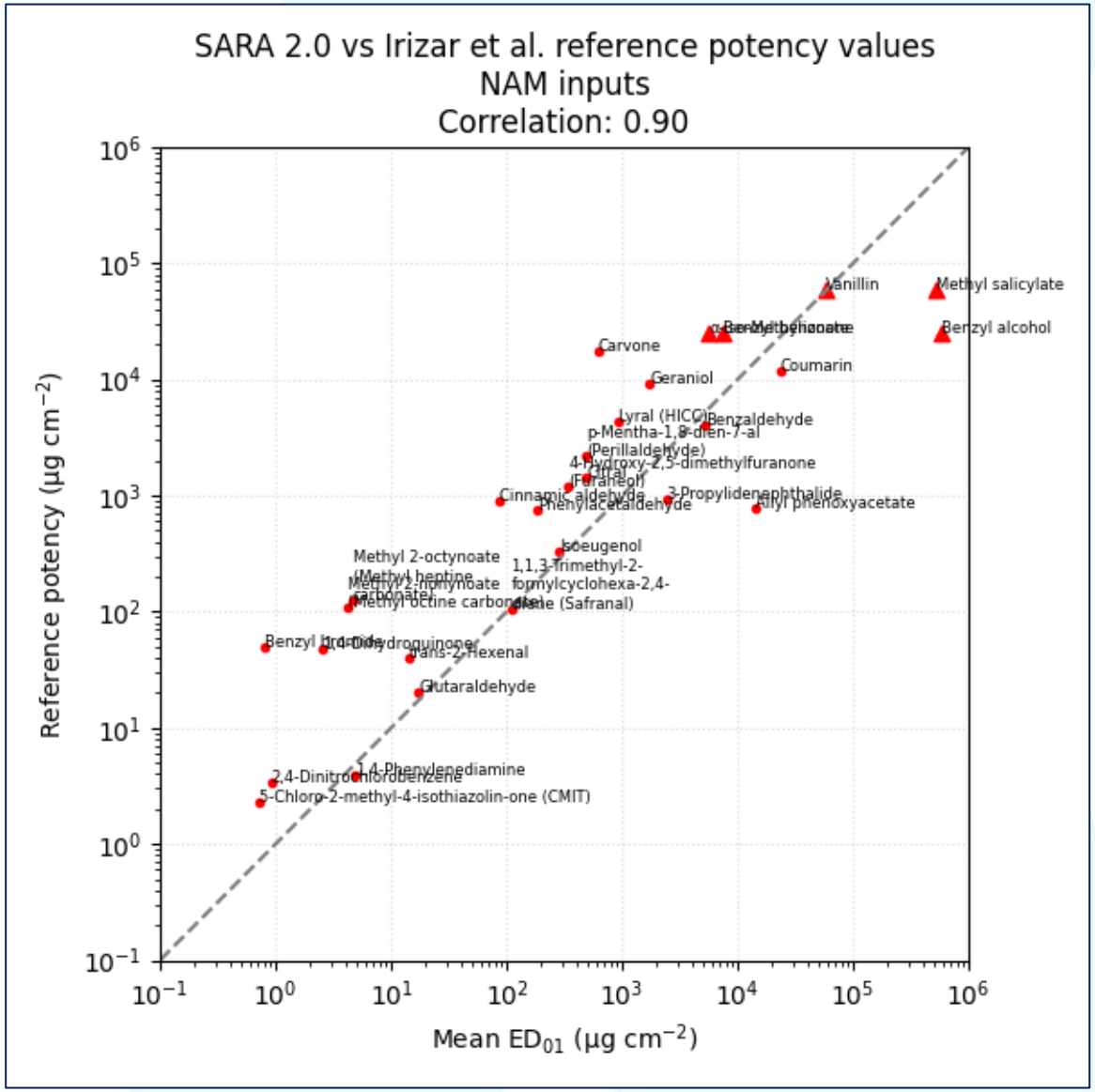
Black – human data available
Red – only LLNA data informing ED_{01} estimate
Triangle – reference value reported as "greater than"



SARA ED_{01} estimated from *NAM* data correlated against RCLP PV

INPUTS

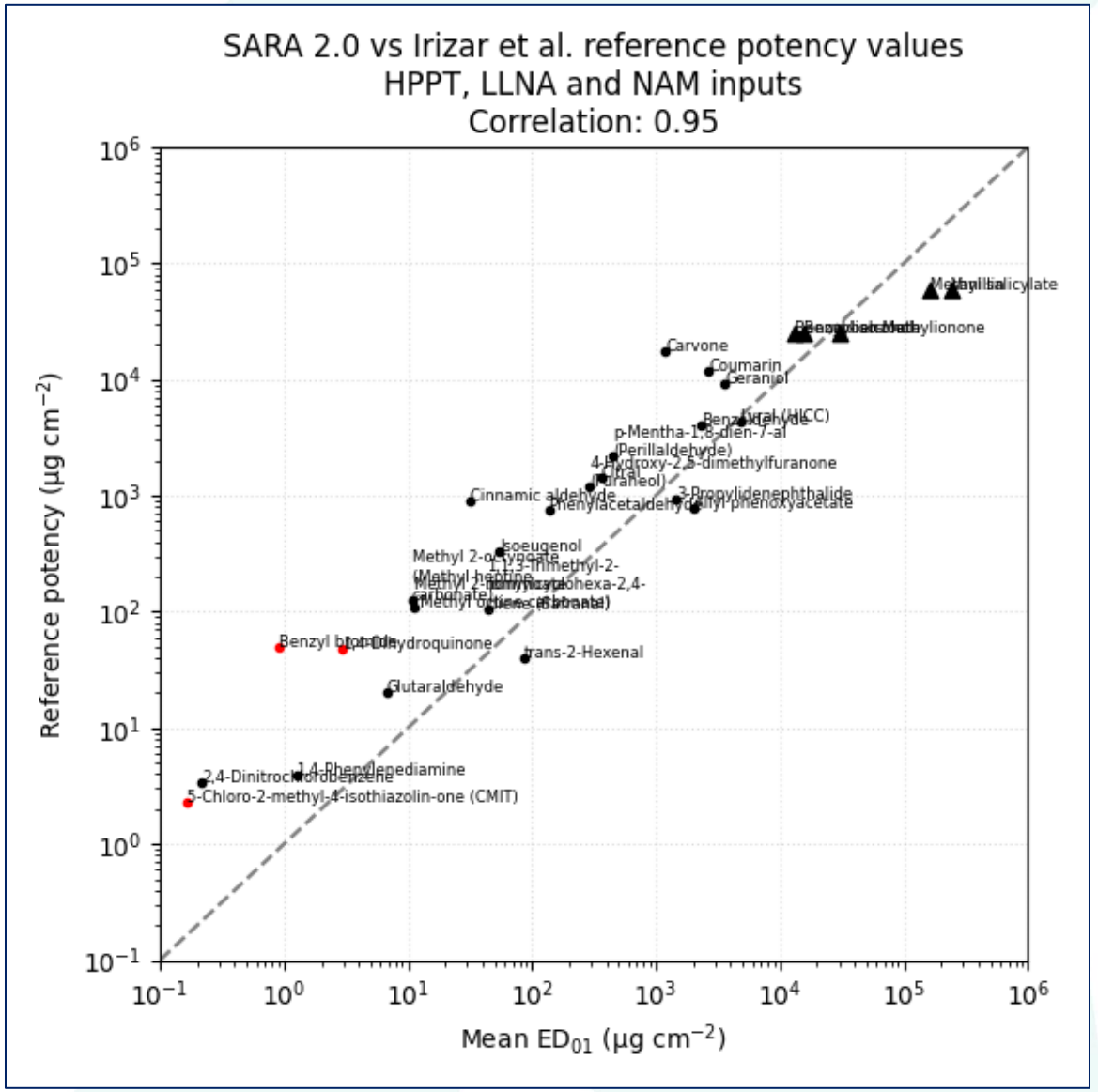
- Reactivity –Yes /No/HPC
- DPRA
- KeratinoSensTM
- H-CLAT
- KDPRA



SARA ED_{01} estimated from *all available* data correlated against RCLP PV

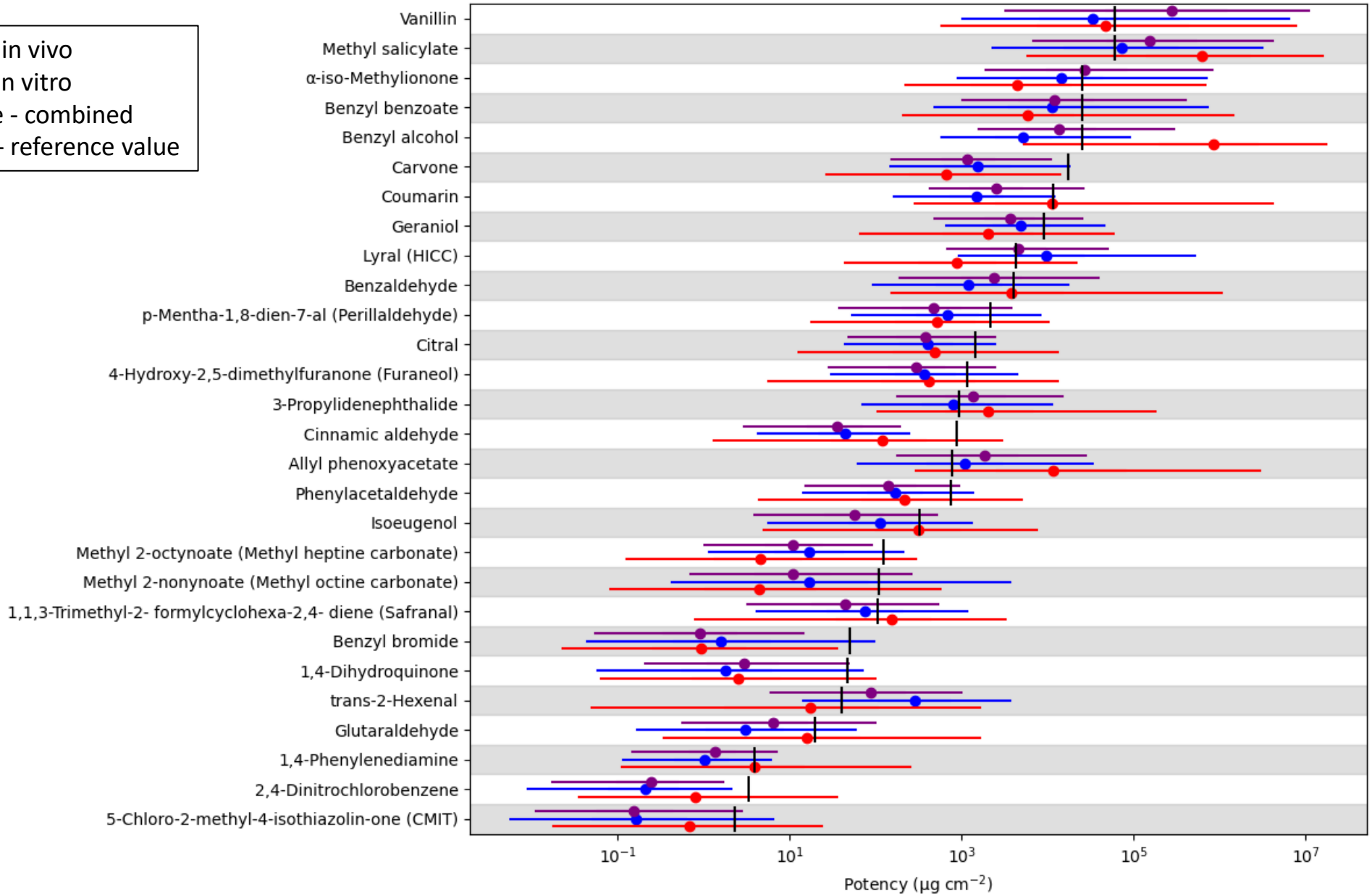
INPUTS

- Reactivity –Yes /No/HPC
- DPRA
- KeratinoSensTM
- H-CLAT
- KDPRA
- HMT
- HRIPT
- LLNA



All combinations vs s RCLP with uncertainty

Blue - in vivo
Red - in vitro
Purple - combined
Black - reference value



SARA DA probability exposure is low risk, NAM inputs only

Chemical	Exposure (µg/cm2)													
	0.01	0.03	0.1	0.3	1	3	10	30	100	300	1000	3000	10000	30000
5-Chloro-2-methyl-4-isothiazolin-one (CMIT)	0.51	0.4	0.29	0.2	0.13	0.09	0.06	0.04	0.03	0.02	0.01	0.01	0.01	0.01
2,4-Dinitrochlorobenzene	0.54	0.43	0.31	0.22	0.14	0.1	0.06	0.04	0.03	0.02	0.01	0.01	0.01	0.01
1,4-Phenylenediamine	0.7	0.6	0.48	0.37	0.26	0.19	0.13	0.09	0.06	0.04	0.03	0.02	0.02	0.01
Glutaraldehyde	0.8	0.72	0.61	0.5	0.38	0.29	0.2	0.14	0.1	0.07	0.04	0.03	0.02	0.02
trans-2-Hexenal	0.76	0.68	0.58	0.48	0.37	0.28	0.19	0.13	0.09	0.06	0.04	0.03	0.02	0.01
1,4-Dihydroquinone	0.65	0.54	0.41	0.3	0.21	0.14	0.09	0.06	0.04	0.03	0.02	0.01	0.01	0.01
Benzyl bromide	0.53	0.41	0.3	0.21	0.14	0.09	0.06	0.04	0.03	0.02	0.01	0.01	0.01	0.01
1,1,3-Trimethyl-2-formylcyclohexa-2,4-diene (Safranal)	0.9	0.85	0.77	0.69	0.57	0.46	0.34	0.24	0.16	0.11	0.07	0.05	0.03	0.02
Methyl 2-nonynoate(Methyl octine carbonate)	0.7	0.59	0.47	0.36	0.25	0.17	0.11	0.08	0.05	0.03	0.02	0.02	0.01	0.01
Methyl 2-octynoate(Methyl heptinecarbonate)	0.7	0.6	0.47	0.36	0.25	0.18	0.12	0.08	0.05	0.04	0.02	0.02	0.01	0.01
Isoeugenol	0.93	0.9	0.84	0.77	0.66	0.55	0.43	0.32	0.22	0.15	0.1	0.07	0.04	0.03
Phenylacetaldehyde	0.92	0.88	0.81	0.73	0.62	0.51	0.38	0.28	0.19	0.13	0.08	0.06	0.04	0.03
Allyl phenoxyacetate	0.99	0.98	0.97	0.95	0.93	0.89	0.83	0.77	0.68	0.6	0.52	0.46	0.4	0.36
Cinnamic aldehyde	0.88	0.83	0.75	0.66	0.55	0.43	0.31	0.22	0.15	0.1	0.06	0.04	0.03	0.02
3-Propylidenephthalide	0.97	0.96	0.93	0.9	0.84	0.77	0.67	0.56	0.44	0.34	0.26	0.2	0.15	0.12
4-Hydroxy-2,5-dimethylfuranone(Furaneol)	0.93	0.89	0.84	0.77	0.68	0.58	0.45	0.35	0.25	0.18	0.12	0.09	0.06	0.05
Citral	0.94	0.91	0.87	0.81	0.71	0.61	0.48	0.37	0.26	0.18	0.12	0.08	0.06	0.04
p-Mentha-1,8-dien-7-al(Perillaldehyde)	0.95	0.92	0.87	0.81	0.72	0.61	0.48	0.36	0.25	0.17	0.11	0.08	0.05	0.04
Benzaldehyde	0.98	0.97	0.95	0.93	0.89	0.83	0.75	0.66	0.55	0.46	0.37	0.3	0.24	0.21
Lyral (HICC)	0.96	0.94	0.9	0.85	0.77	0.68	0.56	0.44	0.32	0.23	0.15	0.11	0.08	0.06
Geraniol	0.97	0.95	0.92	0.88	0.82	0.74	0.62	0.51	0.38	0.28	0.2	0.14	0.1	0.07
Coumarin	0.99	0.98	0.98	0.96	0.94	0.91	0.86	0.81	0.74	0.68	0.61	0.54	0.49	0.44
Carvone	0.95	0.93	0.89	0.83	0.74	0.64	0.51	0.39	0.27	0.19	0.12	0.08	0.06	0.04
Benzyl alcohol	1	1	1	1	1	1	0.99	0.99	0.98	0.97	0.96	0.95	0.93	0.92
Benzyl benzoate	0.98	0.97	0.96	0.94	0.91	0.86	0.79	0.72	0.63	0.54	0.46	0.39	0.33	0.29
α-iso-Methylionone	0.98	0.97	0.95	0.93	0.88	0.83	0.75	0.66	0.55	0.46	0.37	0.3	0.25	0.21
Methyl salicylate	1	1	1	1	1	0.99	0.99	0.99	0.98	0.97	0.96	0.95	0.93	0.91
Vanillin	0.99	0.99	0.98	0.98	0.97	0.95	0.92	0.88	0.83	0.78	0.72	0.67	0.61	0.57

SARA DA risk metric can be compared to a threshold (0.85 for low risk, 0.15 for high risk) to decide whether an exposure is acceptable or not. Choice of thresholds dependent on risk assessors desired level of confidence.

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Conclusions

1. There is a high degree of correlation between the RCLP PV and SARA DA derived ED_{01}
   - In vivo data (comparable inputs)
   - NAM
   - All data

2. Would expect (and observe) some divergence between SARA DA and RCLP
   - Vastly different data interpretation approaches
   - Different definitions of potency metric (1% sensitising dose versus 4% sensitising dose)

3. SARA DA provides a continuous measure of confidence pertaining to whether an exposure can be considered low risk for induction of skin sensitisation
   - Confidence measure can be used to inform a risk assessment decision.
   - Characterising exposure risk can be achieved responsibly using NAM inputs only.

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