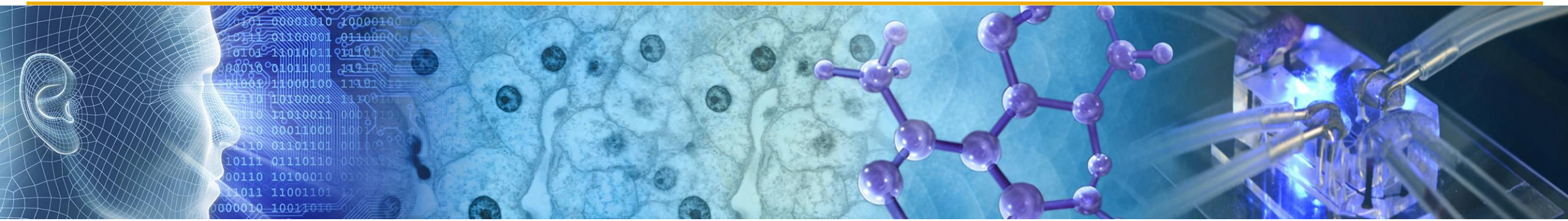


Modification of the Skin Allergy Risk Assessment (SARA) Model for GHS classification

Judy Strickland, PhD, DABT
Inotiv, Inc., in support of NICEATM

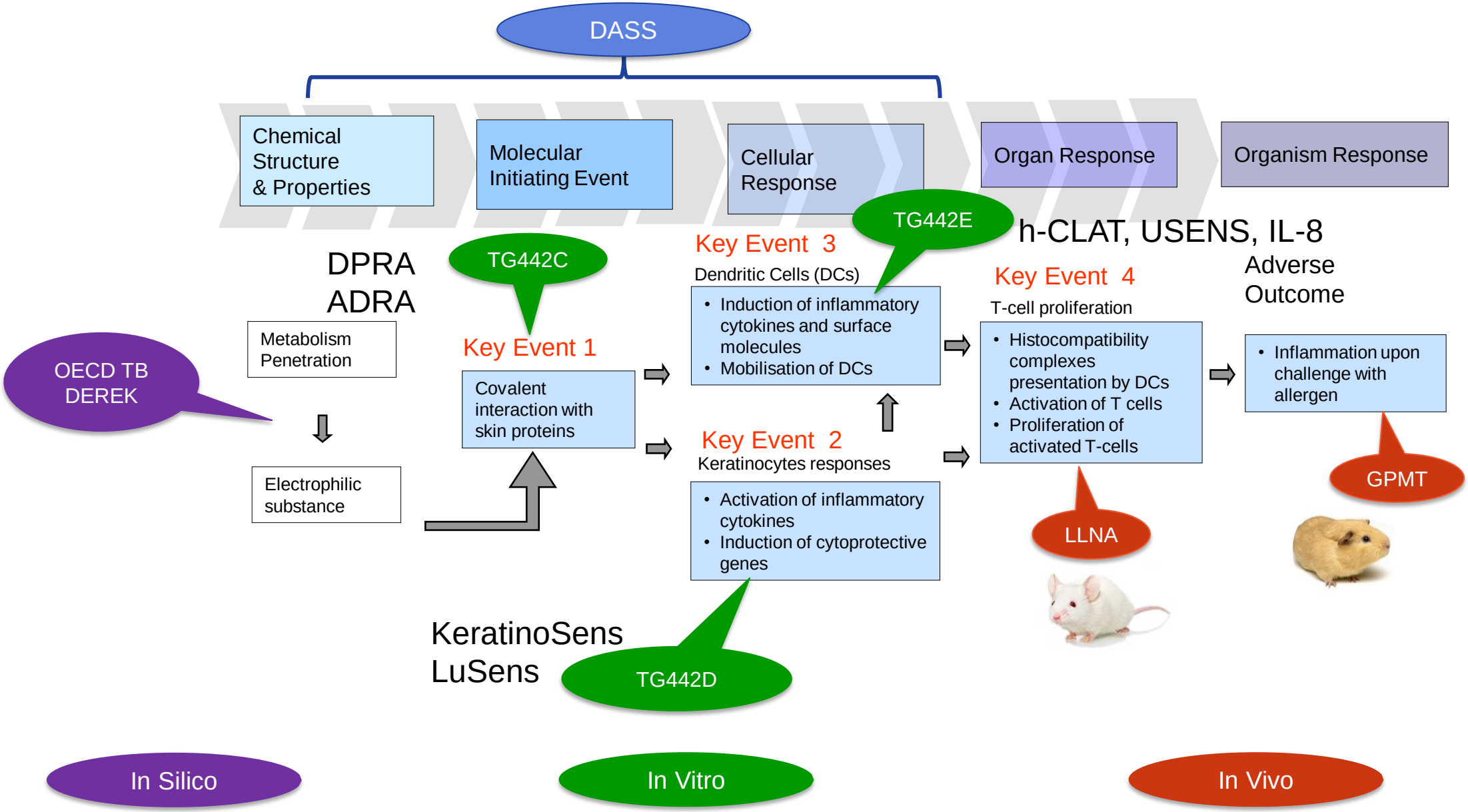
SOT 61st Annual Meeting
March 28th, 2022

Disclaimer: Inotiv staff provide technical support for NICEATM, but do not represent NIEHS, NTP, or the official positions of any federal agency.

Skin Sensitization or “Allergic Contact Dermatitis”

- Accounts for 10-15% of all occupational disease (Anderson et al. 2011)
- Major safety issue for cosmetics, pesticides, industrial chemicals, etc.

Test Methods Mapped to AOP

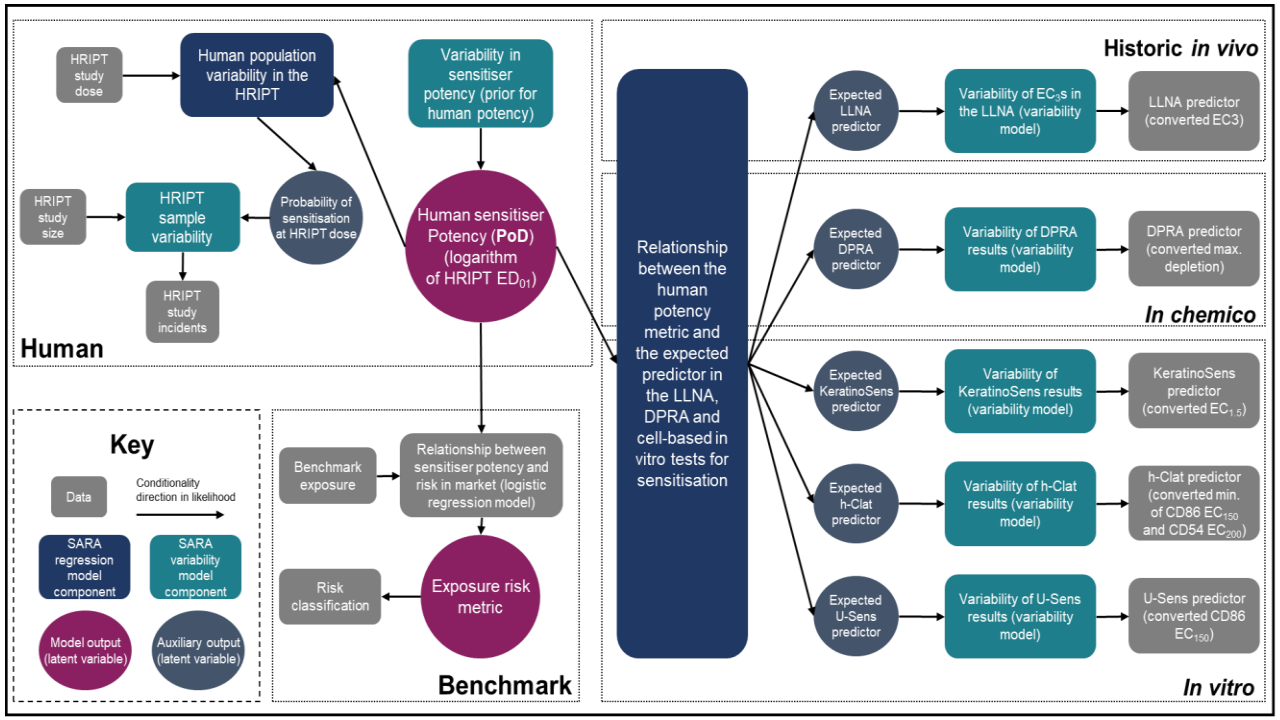


OECD Defined Approaches for Skin Sensitization Guideline Project

- Extensive curation efforts undertaken to build LLNA (168 substances) and human (66 substances) reference databases
- Applicability domain and DA confidence were defined
- The resulting Guideline 497 was adopted in 2021
- It meets regulatory requirements of:
  - DAs that discriminate between sensitizers and non-sensitizers
  - DAs that discriminate strong from weak/moderate sensitizers (i.e., GHS potency categories)
- Future work will cover DAs that address regulatory needs of quantitative risk assessment
  - US and UK have submitted a proposal to OECD for evaluating a defined approach that can provide a point of departure for quantitative risk assessment

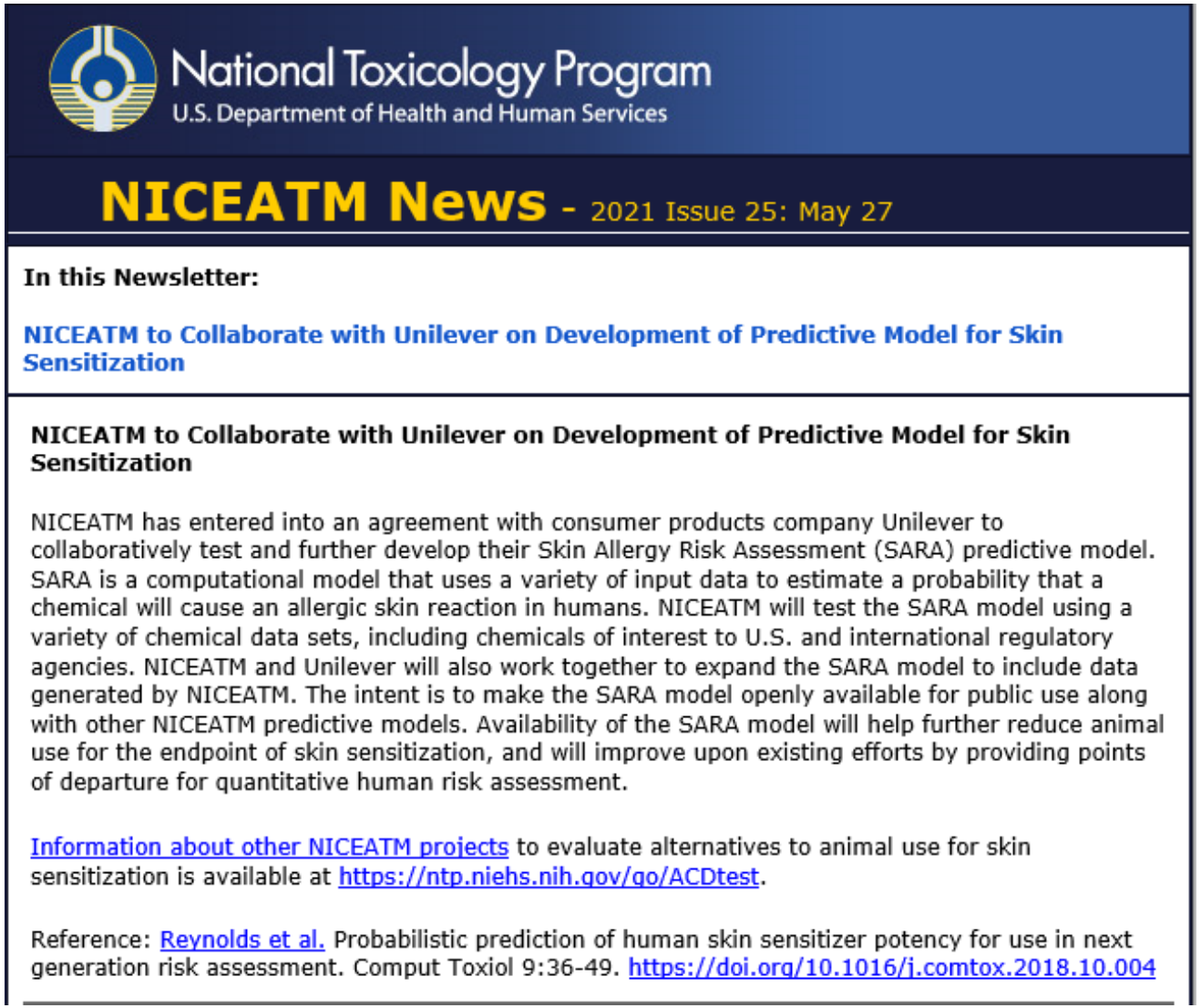
The Skin Allergy Risk Assessment (SARA) Model

- Developed by Unilever as a defined approach for skin allergy risk assessment
- A Bayesian statistical model which infers a human-relevant metric of sensitiser potency (termed ED_{01}), the dose with a 1% chance of human skin sensitisation
- Accounts for variability of the input data and explicitly quantifies uncertainty
- Utilises any combination of human repeat insult patch test (HRIPT), LLNA, direct peptide reactivity assay (DPRA), KeratinoSens™, h-CLAT, U-SENS™ data
- The SARA Model was designed to be used within an NGRA Framework for decision making.



SARA Model overview: Reynolds et al (submitted)

Unilever-NICEATM Collaboration



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

The goal of the project is to develop a version of the SARA model for different skin sensitisation hazard and risk assessment regulatory use-cases.

The project has a capability build phase and an evaluation phase.

Project proposal led by the US and UK submitted to OECD to be considered in April 2022.

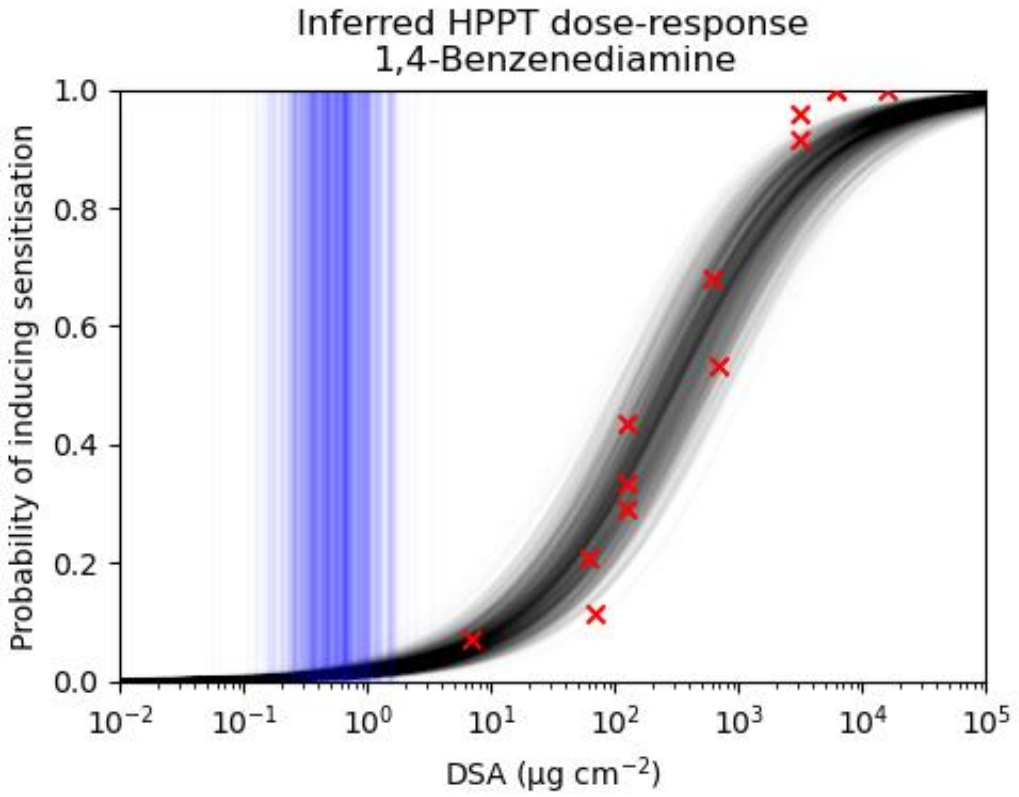
SARA-ICE Model

Notable changes made for the SARA-ICE model are:

- **Significant increase in database size (81 to 1460 chemicals!)**
- **Introduction of HMT data** in addition to HRIPT data (combined HPPT)
- New model output for **probabilistic GHS Classification**
- Updated modelling assumptions for variability of HPPT outcomes

	Number of Studies	
Study Type	**SARA Database**	**SARA-ICE Database**
HPPT	143	1940
LLNA	266	790
DPRA	281	614
KeratinoSens	210	1009
h-CLAT	148	501
USENS	152	307

Example HPPT interpretation



Red x – proportion of subjects in separate HPPT studies

Black lines – dose-response (probability of inducing sensitisation in a HPPT) consistent with data and modelling assumptions

Blue lines – possible values for the ED_{01} consistent with data and modelling assumptions

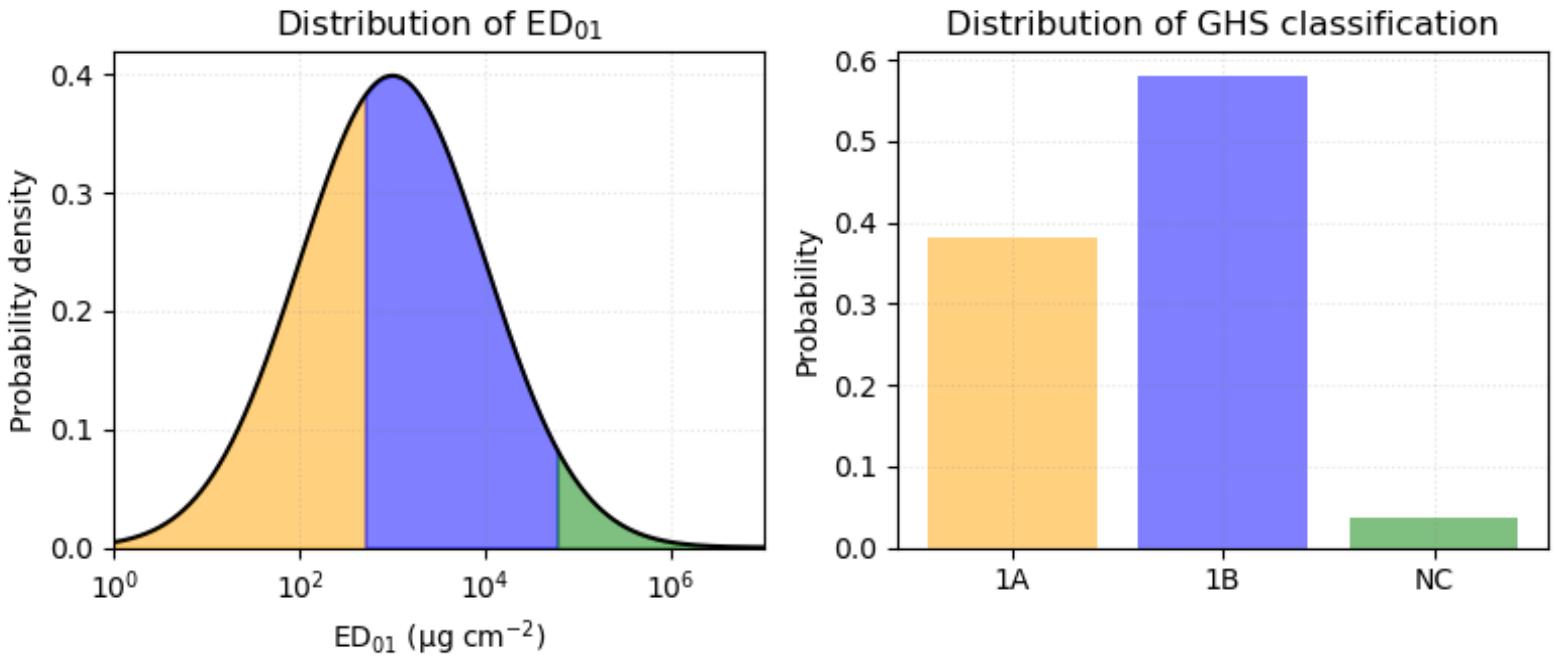
GHS Classification

A GHS classification (1A, 1B, NC) can be derived from the estimate of the ED_{01} obtained from the SARA-ICE model, based on the UN GHS criteria for human response thresholds.

ED_{01} < 500 µg cm^{-2} → GHS 1A

500 µg cm^{-2} < ED_{01} < 60,000* µg cm^{-2} → GHS 1B

60,000* µg cm^{-2} < ED_{01} → NC



hypothetical chemical-specific distribution for the ED_{01}

*60,000 µg cm^{-2} is the maximum possible induction dose for a standard HRIPT

Conclusions

- The SARA-ICE model provides a probabilistic method for integrating multiple skin sensitization data streams and will support
  - GHS classification of skin sensitizers: Category 1A, 1B, and “not classified”
  - Human-relevant point of departure for quantitative risk assessment
- SARA-ICE has been nominated to the OECD for addition to Guideline 497 for defined approaches and will be evaluated using established reference classifications and any additional reference data agreed upon by the OECD expert group
- Regulatory partners have nominated groups of chemicals to be used as case studies for the evaluation of SARA-ICE
- SARA-ICE will be publicly available in the NICEATM Integrated Chemical Environment (https://ice.ntp.niehs.nih.gov/)

With thanks to the SARA-ICE team…

SEAC, Unilever:

Gavin Maxwell

Joe Reynolds

Georgia Reynolds

Nicola Gilmour

NICEATM:

Nicole Kleinstreuer

Dori Germolec

Inotiv:

Jim Truax

Dave Allen