SARA-ICE
A Model for Predicting a Human Relevant Point-of-Departure for Skin Sensitisation Risk Assessment

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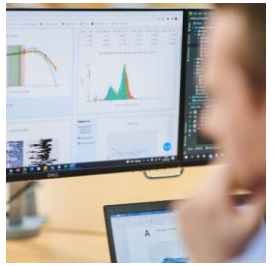
SERS
Safety, Environmental & Regulatory Science

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A new tool for skin allergy risk assessment

Skin Allergy Risk Assessment – Integrated Chemical Environment (SARA-ICE) is a probabilistic model which has been developed into;

- a defined approach (DA) for point of departure (PoD) determination
- an extended model tool for flexible application in risk assessment and/or hazard classification

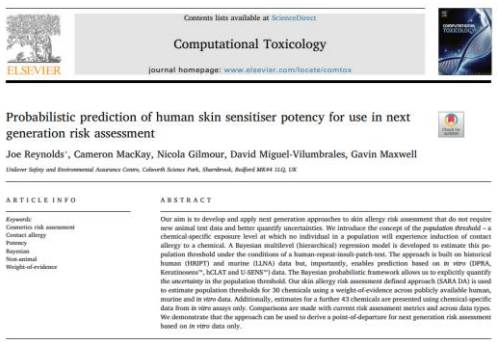
A quick tour:

- ➢ Development history
- ➢ Features and model structure of the SARA-ICE tools
- ➢ Evaluation of SARA-ICE at OECD
- ➢ Application using the publicly available user interface

Development Timeline of Skin Allergy Risk Assessment Models

2017-2019

A prototype Bayesian statistical model was developed at Unilever to estimate a no-effect-dose from HPPT data. This model was published in 2019.


Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.elsevier.com/locate/comtox

Probabilistic prediction of human skin sensitiser potency for use in next generation risk assessment

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ARTICLE INFO

Keywords:
Cosmetics risk assessment
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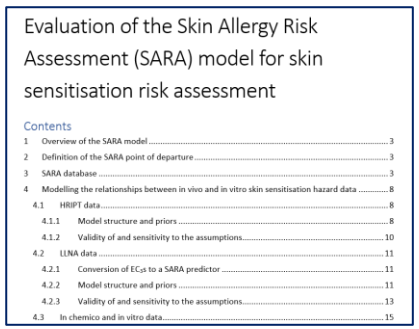
Bayesian
Non-animal
Weight-of-evidence

ABSTRACT

Our aim is to develop and apply next generation approaches to skin allergy risk assessment that do not require new animal test data and better quantify uncertainties. We introduce the concept of the *population threshold* – a chemical-specific exposure level at which no individual in a population will experience induction of contact allergy to a chemical. A Bayesian multilevel (hierarchical) regression model is developed to estimate this population threshold under the conditions of a human-repeat-insult-patch-test. The approach is built on historical human (HRIPT) and murine (LLNA) data but, importantly, enables prediction based on in vitro (DPRA, Keratinosens™, hCLAT and U-SENS™) data. The Bayesian probabilistic framework allows us to explicitly quantify the uncertainty in the population threshold. Our skin allergy risk assessment defined approach (SARA DA) is used to estimate population thresholds for 30 chemicals using a weight-of-evidence across publicly available human, murine and in vitro data. Additionally, estimates for a further 43 chemicals are presented using chemical-specific data from in vitro assays only. Comparisons are made with current risk assessment metrics and across data types. We demonstrate that the approach can be used to derive a point-of-departure for next generation risk assessment based on in vitro data only.

2019-2021

The model and underlying database are revised and expanded. Unilever performs an internal evaluation and applies the model for risk assessment.


Evaluation of the Skin Allergy Risk Assessment (SARA) model for skin sensitisation risk assessment

Contents

2021-2022

SARA is published within a set of 3 papers describing the model and exploring its use in case study risk assessment scenarios.


Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Decision making in next generation risk assessment for skin allergy: Using historical clinical experience to benchmark risk

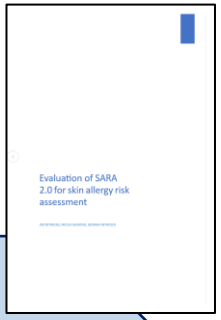
J. Reynolds , N. Gilmour , M.T. Baltazar , G. Reynolds , S. Windebank , G. Maxwell

ARTICLE INFO

ABSTRACT

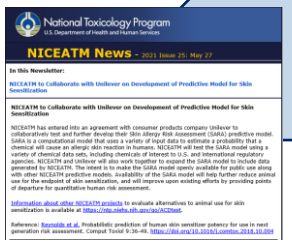
2023 - present

Unilever begin to develop SARA 2.0, starting from the SARA-ICE database and evaluate the model.


Evaluation of SARA 2.0 for skin allergy risk assessment

2021 - present

Unilever begin 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 and evaluated at the OECD.


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 streams to predict the probability that a chemical will cause an allergic skin response 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/ACCtest.

Reference: Reynolds et al. Probabilistic prediction of human skin sensitiser potency for use in next generation risk assessment. Comput Toxicol 9:36-49. https://doi.org/10.1016/j.comtox.2018.10.004


Current Research in Toxicology

Volume 8, 2025, 100205

Research Paper

The skin allergy risk assessment-integrated chemical environment (SARA-ICE) defined approach to derive points of departure for skin sensitization

Emily N. Reinke a, Joe Reynolds b, Nicola Gilmour b, Georgia Reynolds b, Judy Strickland a, Dori Germolec c, David G. Allen a, Gavin Maxwell b, Nicole C. Kleinstreuer a

OECD Defined Approaches (DAs) for Skin Sensitisation (TG 497)

- In 2021, OECD Test Guideline 497 was adopted.
- TG 497 meets regulatory requirements for:
  - DAs that discriminate between sensitizers and non-sensitizers
  - DAs that discriminate strong from weak/moderate sensitizers (i.e., GHS potency categories)

- In 2021, the US and UK began a joint led feasibility study project under OECD for **evaluating a defined approach** that can provide a **point of departure** for quantitative risk assessment
- In 2024, the project began drafting an update to OECD TG 497 to incorporate DAs for PoD determination (i.e. SARA-ICE), expected to be released mid-2025.

- *In parallel, a self-contained version of the model and user interface have been developed, accessed via NICEATMs website.*

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SARA-ICE

The aim of the Unilever and NICEATM collaboration was to create a version of the SARA Model, SARA-ICE, which would be useful to wider industry, a model that could define points of departure (PoD) for use in risk assessment and have functionality for regulatory classification.

Database

The core dataset underpinning the model uses data in the ICE database.

434 chemicals
1,407 in vivo studies
2,575 in vitro studies

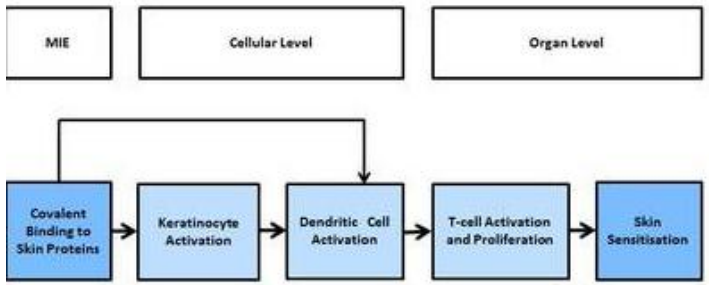
Integrated Chemical Environment

Input Assay Types

OECD TG NAM Assays aligned to key events in the skin allergy AOP.

- DPRA, kDPRA (KE1)
- KeratinoSens (KE2)
- U-Sens, hCLAT (KE3)

- Human (HMT/HRIPT) & LLNA studies may also be used.



Model Outputs

SARA-ICE, a Bayesian probabilistic model, gives a continuous measure of sensitiser potency: *ED_{01} (1% sensitising dose in human patch test)*.

- A PoD (SARA-ICE DA)

Or

- GHS Classification (SARA-ICE Extended)

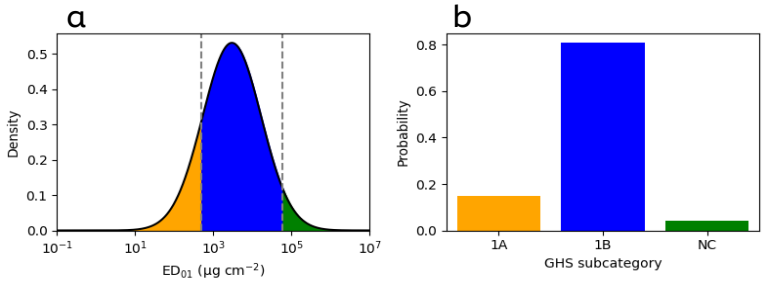


Figure (a) Example estimate of ED_{01} distribution with overlay of GHS subcategories 1A, 1B and NC defined thresholds, (b) probability of each GHS subcategory from ED_{01} distribution

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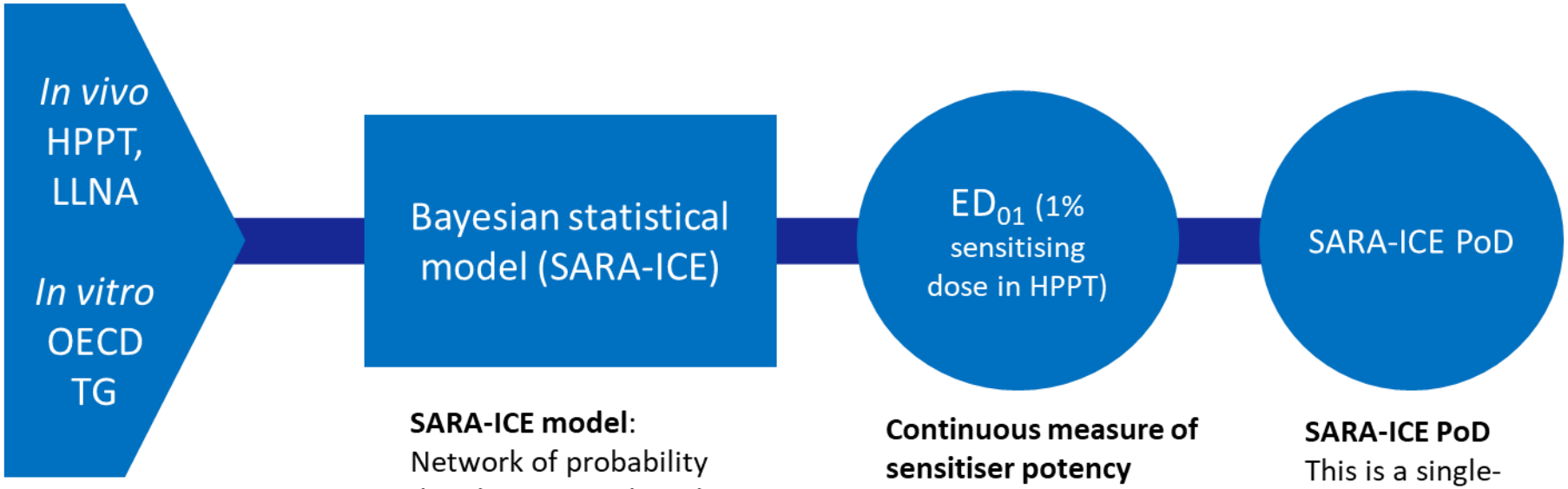
SARA-ICE DA (Proposed OECD TG 497 Version)

Input



SARA-ICE database:
434 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.

SARA-ICE PoD
This is a single-valued quantity at a physically possible dose that may serve as a suitable value for input into exposure-based risk assessment.

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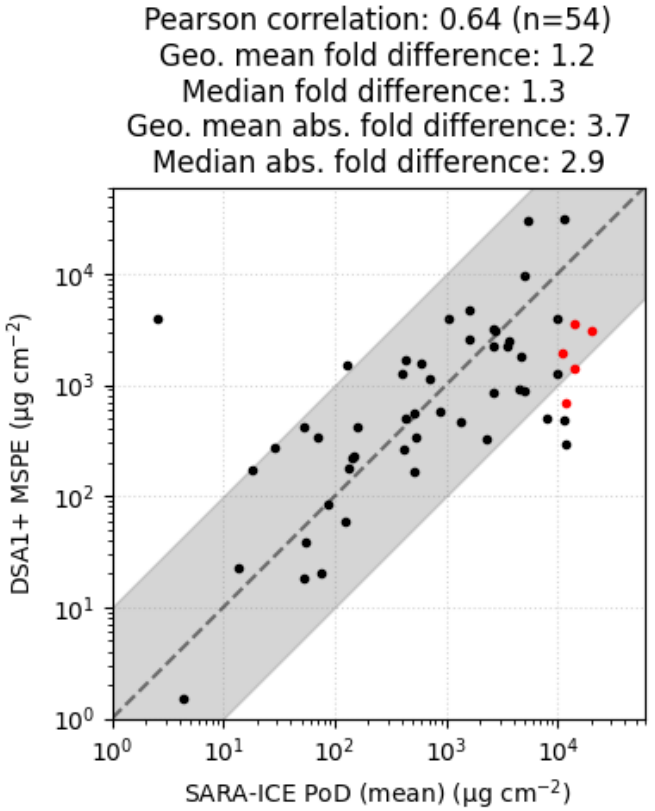
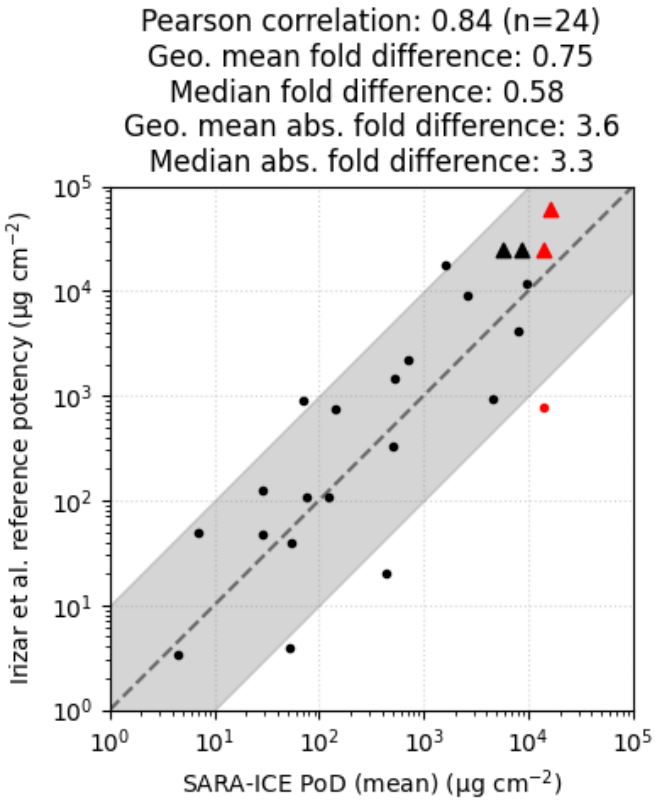
Evaluation of the SARA-ICE PoD

SARA-ICE vs reference DSA1+



SARA-ICE mean PoDs (from NAM data) relatively unbiased relative to reference DSA1+.
PoDs on average around 3-fold away.

SARA-ICE PoDs vs Irizar et al. benchmarks



SARA-ICE mean PoDs (from NAM data) relatively unbiased relative to Irizar et al. reference potency.
PoDs on average around 3.5-fold away.

Red points: compounds predicted to be non-sensitising at a hazard probability threshold of 0.77

SARA-ICE DA (Extended Version)

Input

In vivo
HPPT,
LLNA

In vitro
OECD
TG

SARA-ICE database:
434 chemicals
1,407 *in vivo* studies
2,575 *in vitro* studies

Bayesian statistical model (SARA-ICE)

SARA-ICE model:
Network of probability distributions to describe associations between all data types

ED_{01} (1% sensitising dose in HPPT)

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.

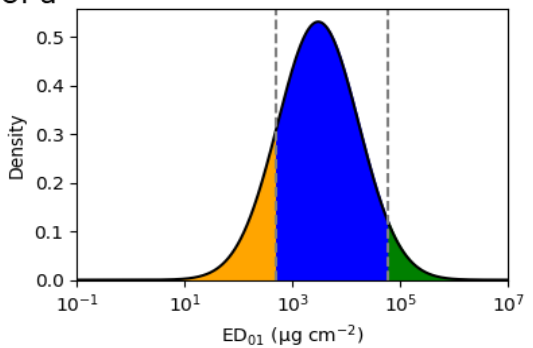
GHS classification thresholds:
Threshold 1A/1B: 500 µg cm^{-2}
Thresholds 1B/NC: 60,000 µg cm^{-2}

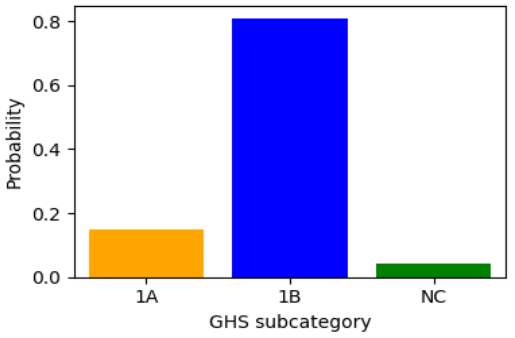
GHS classification probabilities

Categorical measure of sensitiser potency
Probability that chemical potency should be categorised as GHS 1A, 1B or NC.

GHS classification decision model

GHS classification
GHS call if probability passes thresholds chosen within the decision model





θ_{bin} = selected probability threshold for making a binary classification (1/NC)

θ_{sub} = selected threshold for making a sub-classification of 1A of 1B, contingent on class 1 being true

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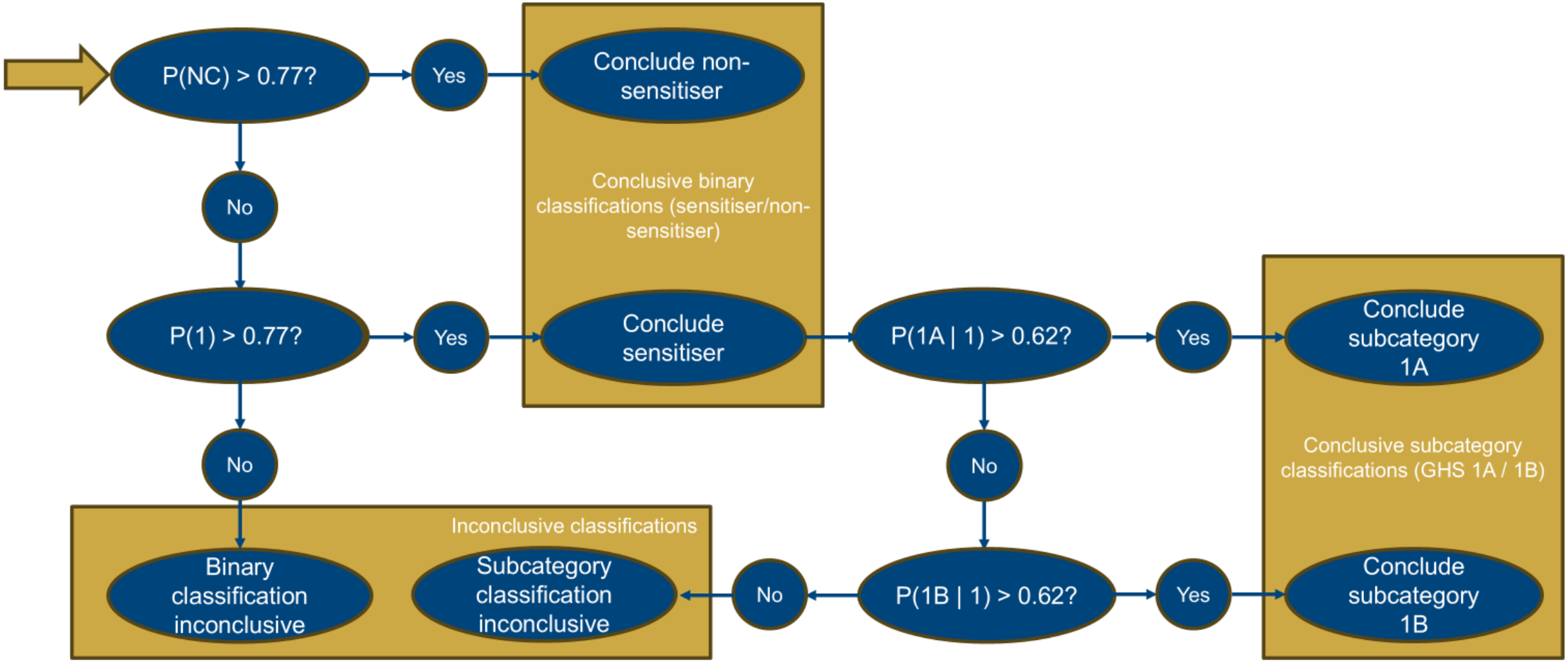
GHS Classification Decision Model (SARA-ICE Extended)



SARA-ICE NAM vs OECD DASS benchmarks

The SARA-ICE decision model has been evaluated against OECD benchmark classifications.

Binary classifications

Human, Θ_{bin} = 0.77	SARA-ICE 1	SARA-ICE NC	Inconclusive	Total
Reference 1	37	5	13	55
Reference NC	0	5	6	11
Total	37	10	19	66

Sensitivity: 88%
Specificity: 100%
Balanced accuracy: 94%
Inconclusive rate on reference class 1: 24%
Inconclusive rate on reference class NC: 55%

LLNA, Θ_{bin} = 0.77	SARA-ICE 1	SARA-ICE NC	Inconclusive	Total
Reference 1	89	9	37	135
Reference NC	2	19	12	33
Total	91	28	49	168

Sensitivity: 91%
Specificity: 90%
Balanced accuracy: 91%
Inconclusive rate on reference class 1: 27%
Inconclusive rate on reference class NC: 36%

Subcategory classifications

Human, Θ_{bin} = 0.77, Θ_{sub}=0.62	SARA 1A	SARA 1B	SARA NC	Inconclusive	Total
Reference 1A	14	2	0	5	21
Reference 1B	3	7	5	16	31
Reference NC	0	0	5	6	11
Total	17	9	10	27	63

Sensitivity 1A: 88%, Specificity 1A: 85%, Balanced accuracy 1A: 86%
Sensitivity 1B: 47%, Specificity 1B: 90%, Balanced accuracy 1B: 69%
Sensitivity NC: 100%, Specificity NC: 84%, Balanced accuracy NC: 92%
Average balanced accuracy: 82%
Inconclusive rate on reference class 1A: 24%
Inconclusive rate on reference class 1B: 52%
Inconclusive rate on reference class NC: 55%

LLNA, Θ_{bin} = 0.77, Θ_{sub}=0.62	SARA 1A	SARA 1B	SARA NC	Inconclusive	Total
Reference 1A	27	3	0	8	38
Reference 1B	12	22	8	43	85
Reference NC	0	1	19	13	33
Total	39	26	27	64	156

Sensitivity 1A: 90%, Specificity 1A: 81%, Balanced accuracy 1A: 85%
Sensitivity 1B: 52%, Specificity 1B: 92%, Balanced accuracy 1B: 72%
Sensitivity NC: 95%, Specificity NC: 89%, Balanced accuracy NC: 92%
Average balanced accuracy: 83%
Inconclusive rate on reference class 1A: 21%
Inconclusive rate on reference class 1B: 51%
Inconclusive rate on reference class NC: 39%

Estimates of the ED_{01} use NAM data only (1xDPRA, 1xKeratinoSens, 1xh-CLAT, 1xkDPRA).
Sensitivity, specificity and accuracy is computed for **conclusive** classifications only.

Application of the SARA-ICE Models

Example Case Study: Geraniol

- Using NAM data only, generate a PoD (SARA-ICE DA) and GHS Classification (SARA-ICE Extended)

SARA-ICE Input Data:

Substance Name	CASRN	MW (g/mol)
Geraniol	8007-13-4	154.25

DPRA	
Depletion Cys (%)	Depletion Lys (%)
12.3	2.6

kDPRA
log Kmax (M-1 s-1)
-3.4

KeratinoSens
EC1.5 (uM)
209.8

hCLAT	
CD54, EC200 (ug/ml)	CD86, EC150 (ug/ml)
>168	123

USENS
CD86, EC150 (ug/ml)
53.6

SARA-ICE DA (Proposed OECD TG 497 Version)

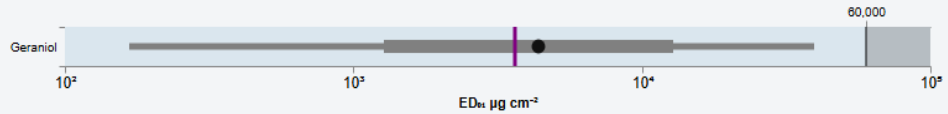
SARA-ICE DA OECD TG497 (v1.0) Results

Substance	CASRN	POD*	ED_{01} Percentiles (µg cm^{-2})		
			5th	50th	95th
Geraniol	8007-13-4	3,600	170	4,400	39,000

POD* - Point of departure - geometric mean of the ED_{01}, predicated on being a sensitizer

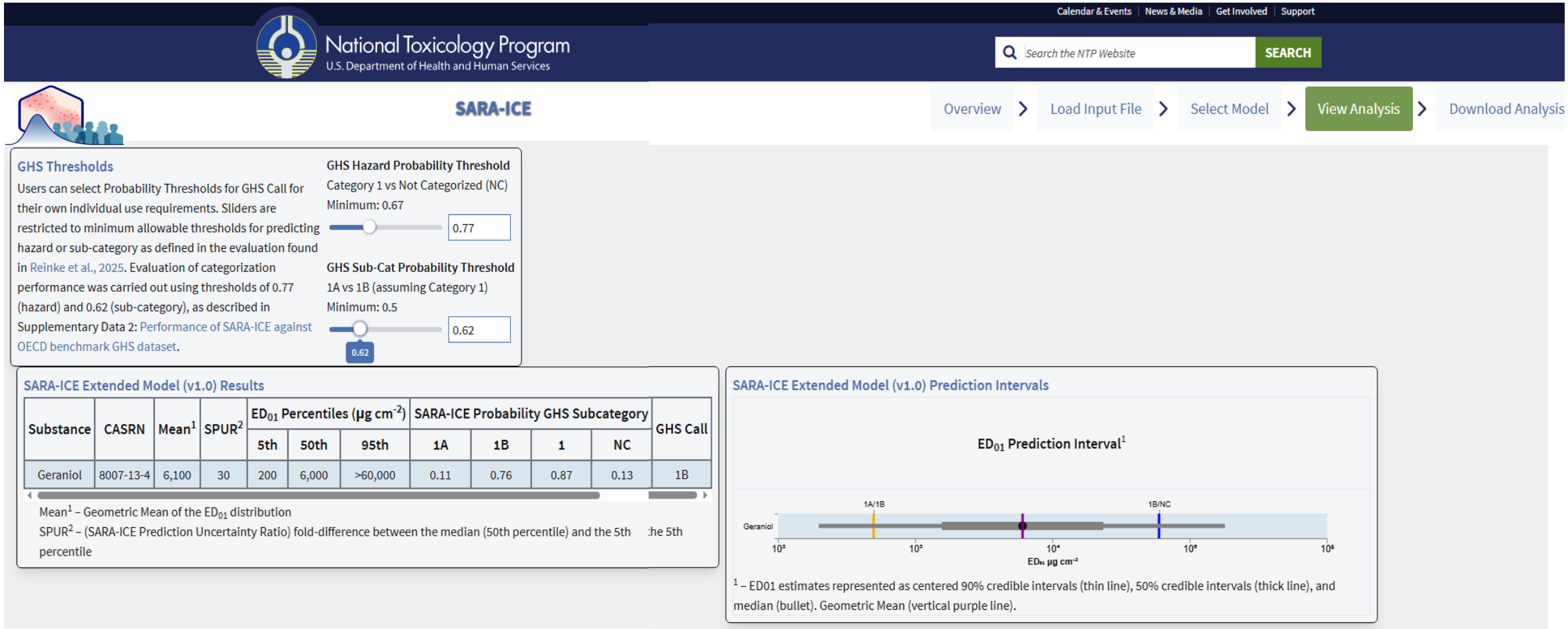
SARA-ICE DA OECD TG497 (v1.0) Prediction Intervals

ED_{01} Prediction Interval[1]



[1] – ED01 estimates represented as centered 90% credible intervals (thin line), 50% credible intervals (thick line), and median (bullet). Point of Departure (vertical purple line).

SARA-ICE DA (Extended Version)



NAM PoD Margin of Safety (MoS) in Risk Assessment

Acceptable MoS = a value above which a risk assessor may usually conclude low risk for their safety assessment

Traditionally, values of 100 or above have been used as acceptable MoS.

To convert **acceptable MoS for a human derived NESIL → acceptable MoS for NAM PoDs**, statistically analyse

a) differences between NESILs vs benchmark exposures
b) differences between NESILs and NAM PoD.

$$\log_{10}(\text{Acceptable NAM MoE}) = \beta + \beta_{\text{NAM}} + (\log_{10}(\text{Acceptable NESIL MoE}) - \beta)\sqrt{1 + \frac{\sigma^2_{\text{NAM}}}{\sigma^2}}$$

Acceptable MoE NESIL	Acceptable MoE SARA-ICE PoD | NAM inputs (geometric mean)
100	100
300	360
1000	1,500

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Summary

- SARA-ICE DA fulfils a gap in the current OECD TG 497 on defining a PoD for risk assessment
- SARA-ICE Extended enables a more flexible use of the model, and allows for GHS classifications to be made
- SARA-ICE allows flexible use of a range of OECD TG NAMs (as well as historical LLNA/Human data)
- SARA-ICE WebApp is nearly ready for public release and will be available on the NICEATM website (https://ntp.niehs.nih.gov/whatwestudy/niceatm)
- A margin of safety can be calculated and applied for NAM PoDs to provide equivalent protectiveness against human benchmarks as a traditional NESIL for skin sensitisation risk assessment (Reynolds et al., manuscript in preparation)

Thank You

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The NICEATM Group