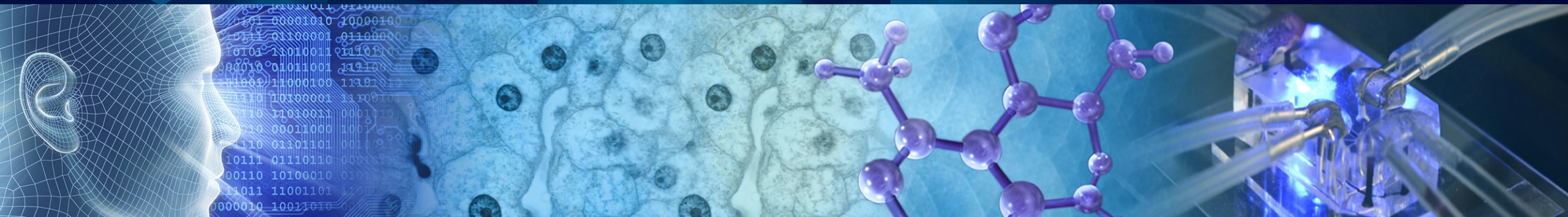




National Institute of
Environmental Health Sciences
Division of Translational Toxicology



New Apps for Skin Sensitization

Emily N. Reinke, PhD, DABT

Inotiv, Inc., in support of National Toxicology Program Interagency Center for the Evaluation of
Alternative Test Methods (NICEATM)

September 12, 2025

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

National Institutes of Health • U.S. Department of Health and Human Services



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Impetus for Development of Skin Sensitization Applications and Tools

- NICEATM goals include the development of user-friendly applications and tools for multiple endpoints
 - Examples include the IVIVE and PBPK models available in ICE
- Development and acceptance of Defined Approaches for Skin Sensitization Test Guideline 497 at OECD means integrating data from multiple sources into one decision
 - Guideline 497 includes approaches for determining hazard, UN GHS sub-categorization, and derivation of a point-of-departure
- Multiple options for risk assessment – Human predictive patch test (HPPT) data or Skin Allergy Risk Assessment – Integrated Chemical Environment (SARA-ICE) model

Latest updates on Guideline 497

- Guideline 497 updated to include three sections and additional test methods:
 - Hazard identification – 2 out of 3 (2o3) DA
 - Added six additional test methods for use within the DA (24 potential combinations)
 - KE1: Amino acid-derived reactivity assay (ADRA), Direct Peptide Reactivity Assay (DPRA)
 - KE2: EpiSensA, LuSens, KeratinoSens
 - KE3: U-SENS, IL-8, GARDskin, Human Cell Line Activation Test (h-CLAT)
 - GHS sub-categorization – Integrated Testing Strategy (ITS) DA (12 potential combinations)
 - Added 3 new assays for use
 - KE1: ADRA, DPRA
 - KE3: U-SENS, GARDskin, h-CLAT
 - **New:** Potency estimate – (SARA-ICE)

DASS app developed for use with Guideline 497

- Initially launched in 2023 to aid in prediction of 2o3 and ITS for the original Guideline 497
 - Required that borderline predictions in the 2o3 be accounted for
 - Calculated ITS scoring based on data input
- Updated in 2024 and 2025 to include the addition of the new methods and their scoring criteria
 - Calculates borderline calls from individual runs for all included test methods
 - Added ability to evaluate performance (user provided reference data) or against chemical reference lists in ICE. Presented as confusion matrices



<https://ntp.niehs.nih.gov/whatwestudy/niceatm/test-method-evaluations/skin-sens/da/dass-app>

DASS app



Home » NICEATM: Alternative Methods » Test Method Evaluations » Identification of Skin Sensitizers » Defined Approaches to Identify Potential Skin Sensitizers » **DASS App**

DASS App

<https://ntp.niehs.nih.gov/go/952311>

Web App for Using Defined Approaches to Predict Skin Sensitization Hazard and Potency

REPORT A PROBLEM

The DASS App

The DASS App applies defined approaches on skin sensitization (DASS) to predict skin sensitization hazard (sensitizer or non-sensitizer) and potency (based on UN GHS categories). The defined approaches (DA) generate predictions by integrating data from in vitro assays that represent key events in the Adverse Outcome Pathway for Skin Sensitization and in silico hazard predictions.

For more information about DASS and their regulatory applications, visit the [NICEATM Defined Approaches to Identify Potential Skin Sensitizers](#) webpage.

[User Guide](#)

[Contact Us](#)

[Manuscript](#)

[Launch App in New Window](#)

Select Defined Approach

Upload Data

Select Data Columns

Review Selection

Results

Compare

To begin, select the DA to be implemented from the choices below. Click on the information buttons next to the DA names to view a description of the DA and the test methods required to implement the DA.

Defined Approaches

- ☒ 2 out of 3 (2o3) ⓘ
- ☐ Integrated Testing Strategy (ITS) ⓘ
- ☐ Key Event 3/1 Sequential Testing Strategy (KE 3/1 STS) ⓘ

2o3 Borderline Evaluation

- ☐ Flag borderline assay results prior to applying DA 2o3 (Requires data from individual runs) ⓘ

Confirm DA Selection



<https://ntp.niehs.nih.gov/whatwestudy/niceatm/test-method-evaluations/skin-sens/da/dass-app>

DASS app

Before uploading your file, ensure that the data meet the data and formatting requirements. More details are available in the user guide.

A table template is provided in tab-delimited or Excel format. The template contains columns for every possible assay endpoint. If an assay endpoint will not be used, the corresponding column can be deleted but that is not required. Using the template is not required.

[Download Data Template \(.xlsx\)](#)
[Download Data Template \(.txt\)](#)

☒ Use demo data

Show 10 entries

Sort	CASRN	Curated_name	ADRA_call	ADRA_mean_dep	ADRA_NAC_dep	ADRA_NAL_dep	DPRA_call	DPRA_mean_dep	DPRA_Cys_dep	DPRA_Lys_dep	KeratinoSens_call	LuSens
A	All	All	All	All	All	All	All	All	All	All	All	All
1	514-10-3	Abietic acid	1	65.35	97.6	33.1	1	58.1	99.9	16.3	1	
2	100-06-1	Acetanisole	0	0.286475	0.572950749	0	0	2.411942781	4.7238855620000004	0.1	1	
3	874-23-7	2-Acetylcyclohexanone	NA	NA	NA	NA	0	2.5	5	0	1	
4	140-67-0	4-Allylanisole	1	26.26794	41.38529284	11.15058522	1	10.31				
5	7493-74-5	Allyl phenoxyacetate	1	9.15	13.6	4.7	0					

Select Columns

Below, there are sections corresponding to the information sources required for your selected DA. Within each section, use the dropdown lists to select the columns containing the data for the endpoint shown. Columns are automatically selected for an endpoint if the column name matches the corresponding column name in the data template. A column must be selected for each endpoint shown. When you are finished, click "Done".

Click on the information buttons next to the dropdown list label to view information about the required data and formatting. Values that are incorrectly formatted or invalid will be treated as missing data and may affect the results. More details are given in the User Guide.

Key Event 1

KE1 Call

☐ Derive call from quantitative data.

Call Column

ADRA_call

Key Event 2

KE2 Call

Call Column

KeratinoSens_call

Key Event 3

KE3 Call

Call Column

GARDskin_call

Done

DASS app

Results of the DASS App analysis are appended to your data in the table below. By default, the table shows the first three columns of data, your selected input columns, and the DA results. The "Column Visibility" dropdown list above the table can be used to hide or show columns. Use the "Download Results" button to export your results to an Excel spreadsheet or text file, which may allow for easier viewing.

Table Key Column Visibility ▾ Download Results ▾ Show 10 ▾ entries : must

Sort ▴ ▾	CASRN ▴ ▾	Curated_name ▴ ▾	ADRA_call* ▴ ▾	KeratinoSens_call* ▴ ▾	GARDskin_call* ▴ ▾	2o3.hazard ▴ ▾
All	All	All	All	All	All	All
1	514-10-3	Abietic acid	1	1	1	Positive
2	100-06-1	Acetanisole	0	1	NA	Inconclusive

Select One or More Reference Columns

HDSG_call ▾

ICE Reference Data ⓘ

☒ Use reference data from ICE.

Choose the reference chemical lists you want to use. The data will be matched by a chemical identifier that you specify. Use the dropdown list to select the column in your data containing the appropriate chemical identifiers.

Select ICE Chemical Quick List

- ☒ OECD Defined Approach to Skin Sensitization: Human (R)
☐ OECD Defined Approach to Skin Sensitization: LLNA (R)

Select Identifier Type

- ☒ CASRN
☐ DTSXID
☐ QSAR-Ready SMILES

DASS app

Select Reference

HDSG_call

Comparison Tables
Reference Column: HDSG_call
Prediction Column: 2o3 Hazard

Confusion Matrix

		Reference	
		Positive	Negative
Predicted	Positive	38	1
	Negative	7	9
	Inconclusive	4	1

Performance Metrics

Metric	Value
N	55
True Positive	38
False Positive	1
False Negative	7
True Negative	9
Inconclusive	29
Sensitivity	84%
Specificity	90%
Balanced Accuracy	87%
Accuracy	85%
F1 Score	90%

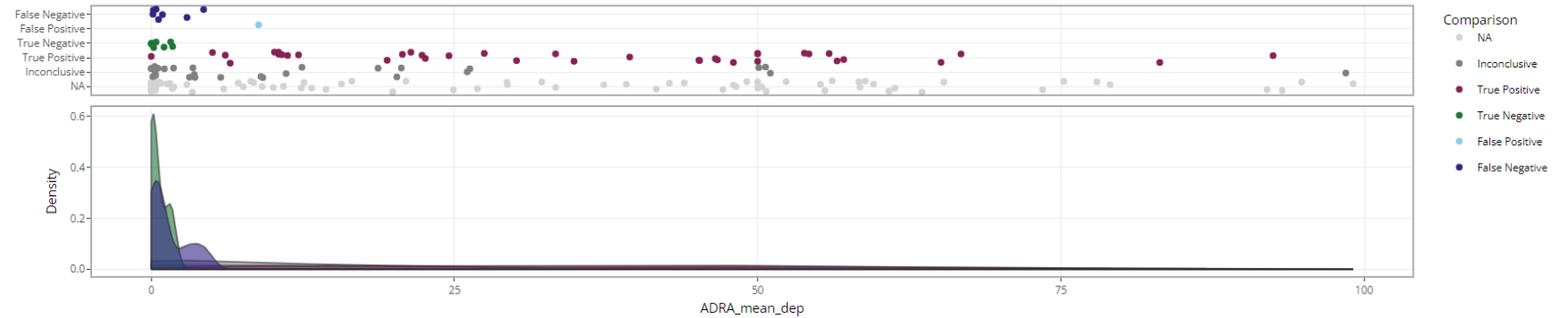
Select Reference to Visualize

HDSG_call

Select Quantitative Data to Visualize

ADRA_mean_dep

DA 2o3 Hazard Prediction vs. HDSG_call



Quantitative Data Summary

	N	Min	Mean	Median	Max
True Positive	38	0	35.42	34.1	92.5
True Negative	9	0	0.58	0.2	1.76
False Positive	1	8.85	8.85	8.85	8.85
False Negative	7	0.14	1.36	0.6	4.32
Inconclusive	27	0	15.85	5.73	98.49
NA	84	0	28.91	18.23	99.1

SARA-ICE for a point-of-departure development timeline

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.

2019-2021

The model and underlying database were revised and expanded. Unilever performed an internal evaluation and applied the model for risk assessment.

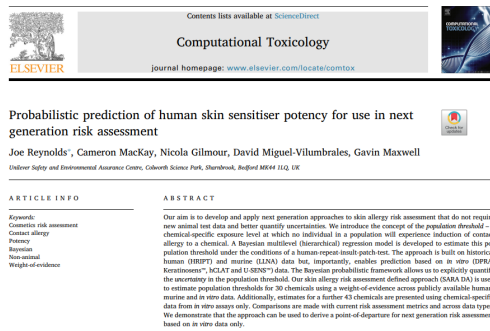
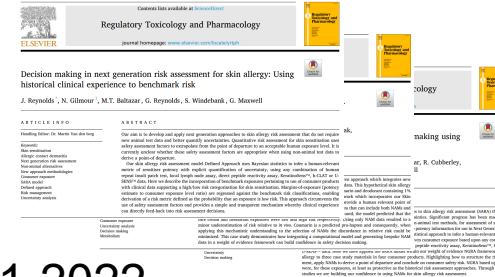
2021-2022

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

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

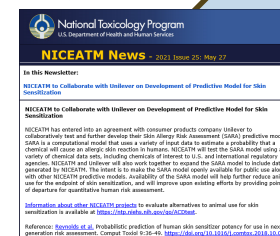


Evaluation of the Skin Allergy Risk Assessment (SARA) model for skin sensitisation risk assessment

Contents	
1	Overview of the SARA model.....3
2	Definition of the SARA point of departure.....3
3	SARA database.....3
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4.2	LLNA data.....11
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4.2.2	Model structure and priors.....11
4.2.3	Validity of and sensitivity to the assumptions.....13
4.3	In chemico and in vitro data.....15

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.



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

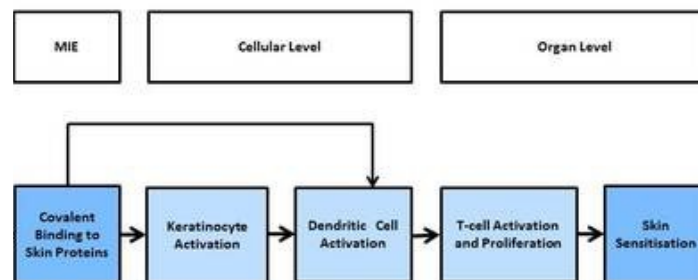


Integrated
Chemical
Environment

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)

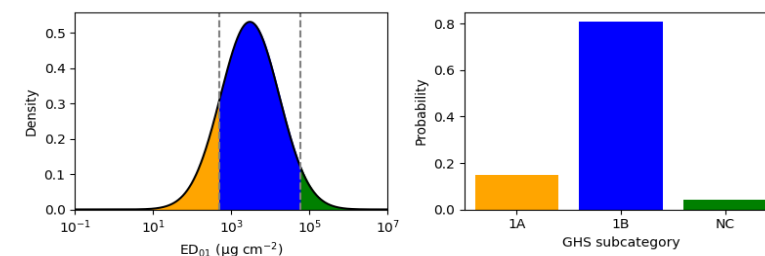
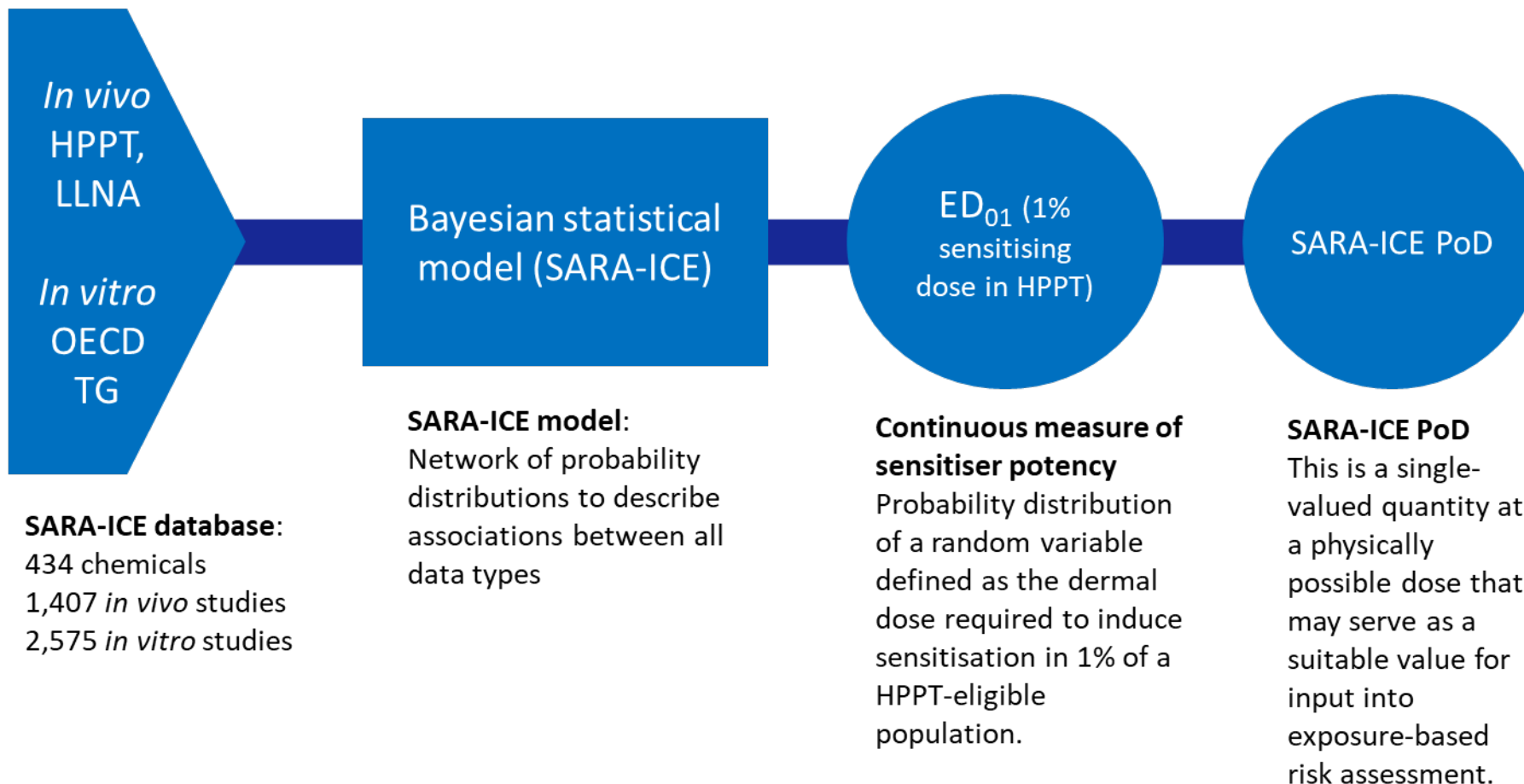


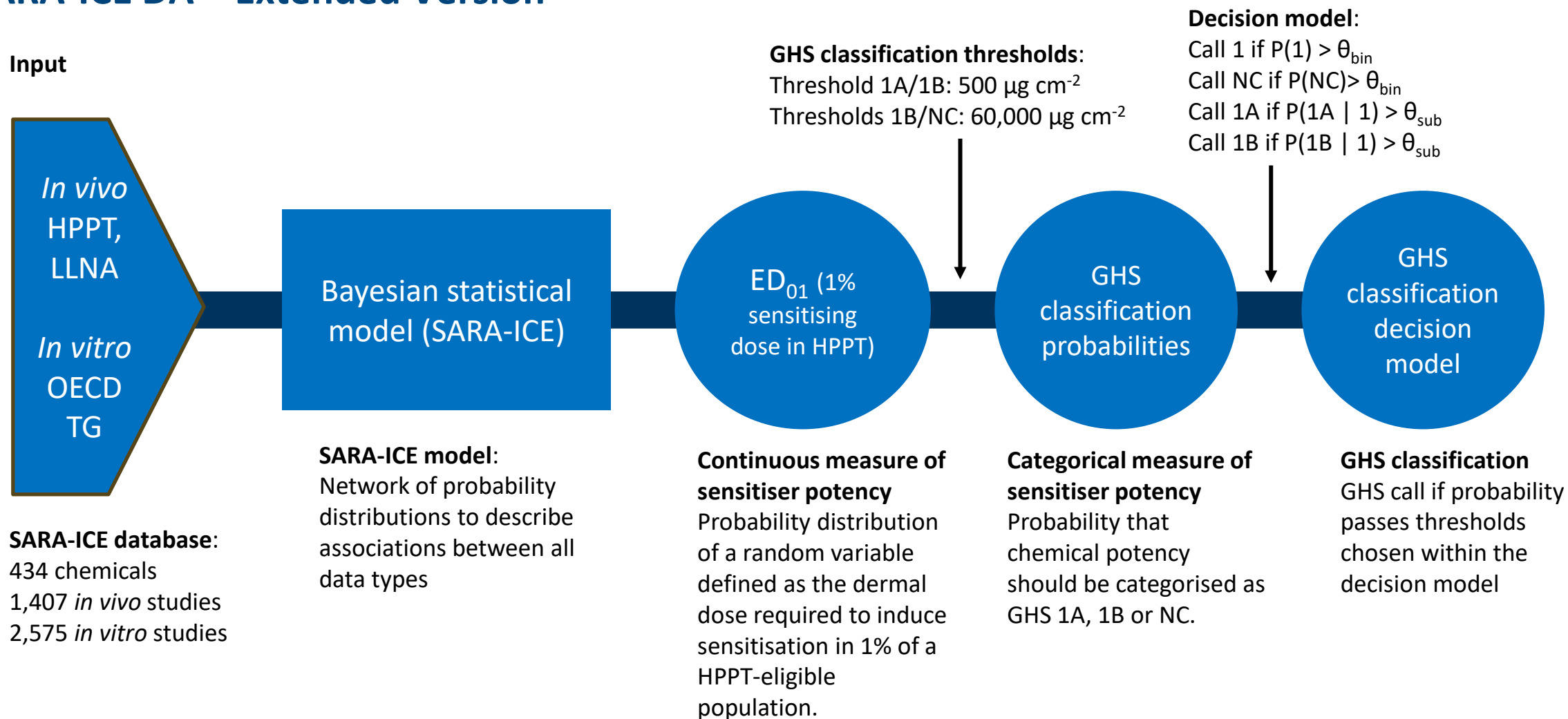
Figure (a) Example estimate of ED_{01} distribution with overlay of GHS subcategories 1A, 1B and NC defined thresholds, (b) probability of each GHS subcategory from ED_{01} distribution

SARA-ICE DA (OECD TG 497 Version)

Input



SARA-ICE DA – Extended Version

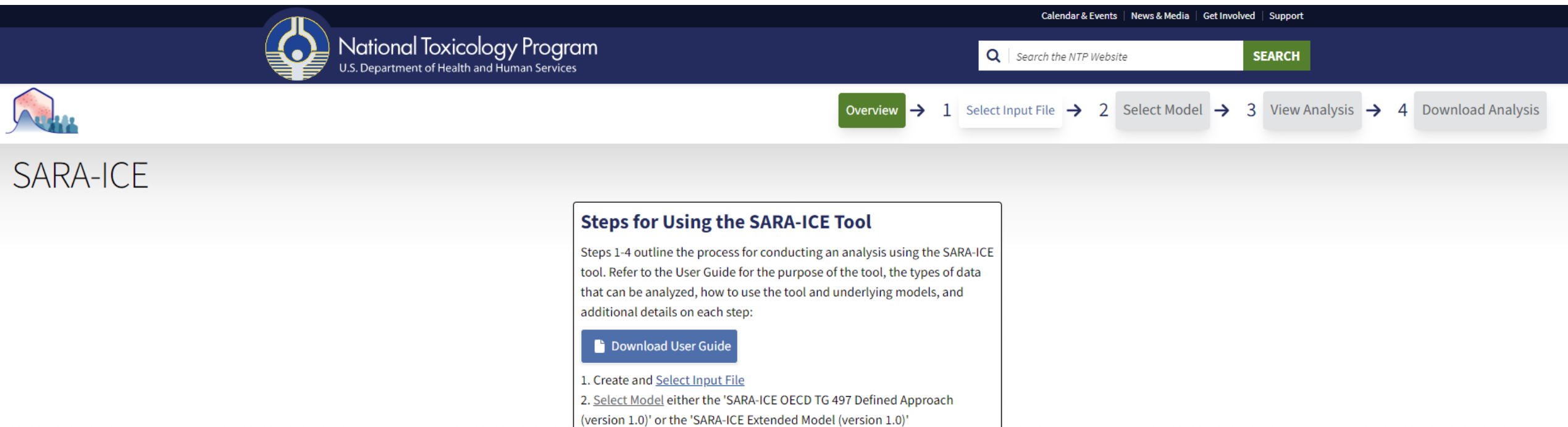


θ_{bin} = selected probability threshold for making a binary classification (1/NC)

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

SARA-ICE Webapp

- User-friendly tool to run the model(s)
 - Two outputs
 - OECD Guideline 497 ED₀₁ point-of-departure (static model)
 - Extended version (modifiable in future)



The screenshot shows the SARA-ICE Webapp interface. At the top, there is a dark blue header with the NIH logo and text: "National Institute of Environmental Health Sciences, Division of Translational Toxicology". Below this is a white section with the "SARA-ICE Webapp" title. A bulleted list describes the tool: "User-friendly tool to run the model(s)", "Two outputs", "OECD Guideline 497 ED₀₁ point-of-departure (static model)", and "Extended version (modifiable in future)". The bottom part of the image shows a screenshot of the webapp's navigation bar and main content area. The navigation bar includes the National Toxicology Program logo, a search bar, and a progress indicator with steps: Overview, 1 Select Input File, 2 Select Model, 3 View Analysis, and 4 Download Analysis. The main content area is titled "SARA-ICE" and contains a section titled "Steps for Using the SARA-ICE Tool" with instructions and a "Download User Guide" button.

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Q Search the NTP Website SEARCH

Overview → 1 Select Input File → 2 Select Model → 3 View Analysis → 4 Download Analysis

SARA-ICE

Steps for Using the SARA-ICE Tool

Steps 1-4 outline the process for conducting an analysis using the SARA-ICE tool. Refer to the User Guide for the purpose of the tool, the types of data that can be analyzed, how to use the tool and underlying models, and additional details on each step:

 Download User Guide

1. Create and [Select Input File](#)
2. [Select Model](#) either the 'SARA-ICE OECD TG 497 Defined Approach (version 1.0)' or the 'SARA-ICE Extended Model (version 1.0)'

SARA-ICE DA – Test Guideline 497 Version



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SEARCH



Overview → 1 Select Input File → 2 Select Model → 3 **View Analysis** → 4 Download Analysis

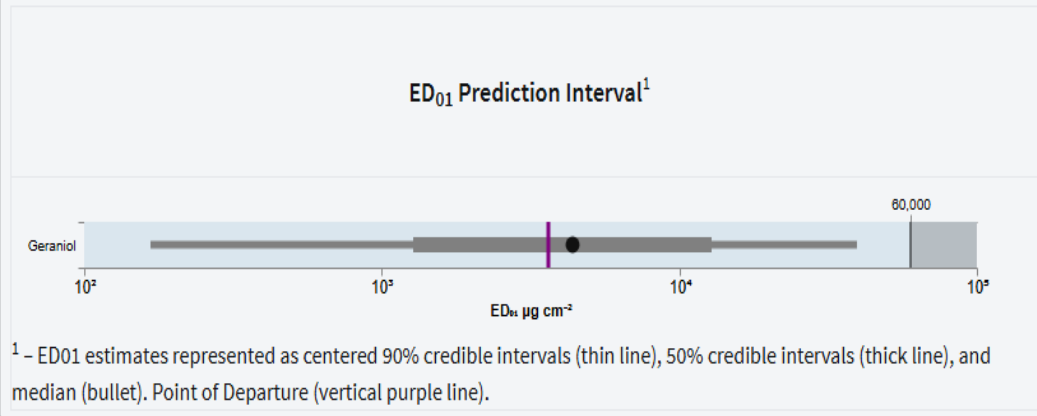
SARA-ICE

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

Substance	CASRN	POD*	ED ₀₁ Percentiles ($\mu\text{g cm}^{-2}$)		
			5th	50th	95th
Geraniol	8007-13-4	3,600	170	4,400	39,000

POD* - Point of departure - geometric mean of the ED₀₁, predicated on being a sensitizer

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



[Download Analysis >](#)

SARA-ICE DA – Extended Version



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SEARCH



Overview → 1 Select Input File → 2 Select Model → 3 View Analysis → 4 Download Analysis

SARA-ICE

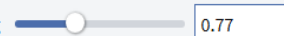
GHS Thresholds

Users can select Probability Thresholds for GHS Call for their own individual use requirements. Sliders are restricted to minimum allowable thresholds for predicting hazard or sub-category as defined in the evaluation found in [Reinke et al., 2025](#). Evaluation of categorization performance was carried out using thresholds of 0.77 (hazard) and 0.62 (sub-category), as described in Supplementary Data 2: Performance of SARA-ICE against OECD benchmark GHS dataset.

GHS Hazard Probability Threshold

Category 1 vs Not Categorized (NC)

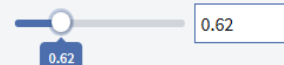
Minimum: 0.67



GHS Sub-Cat Probability Threshold

1A vs 1B (assuming Category 1)

Minimum: 0.5



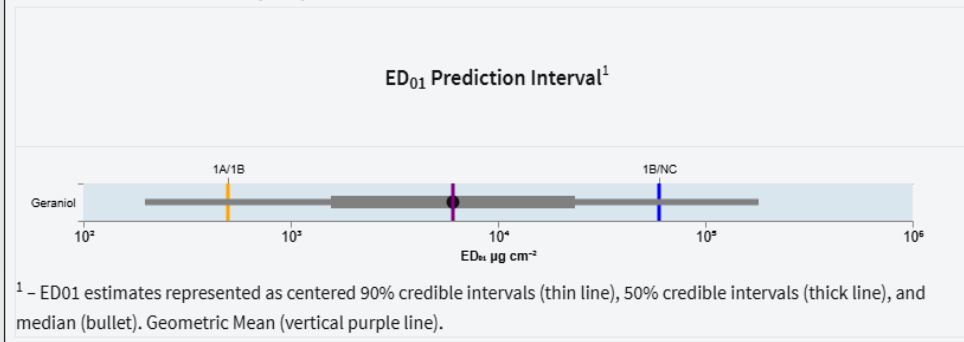
SARA-ICE Extended Model (v1.0) Results

Substance	CASRN	Mean ¹	SPUR ²	ED ₀₁ Percentiles (μg cm ⁻²)			SARA-ICE Probability GHS Subcategory				GHS Call
				5th	50th	95th	1A	1B	1	NC	
Geraniol	8007-13-4	6,100	30	200	6,000	>60,000	0.11	0.76	0.87	0.13	1B

Mean¹ – Geometric Mean of the ED₀₁ distribution

SPUR² – (SARA-ICE Prediction Uncertainty Ratio) fold-difference between the median (50th percentile) and the 5th percentile

SARA-ICE Extended Model (v1.0) Prediction Intervals



Future development of SARA-ICE

- Guideline 497 model must remain static unless reviewed by OECD DASS EG
- Extended model can be updated/modified
 - Future plans:
 - Add new methods to database/input options
 - GARDskin/GARD Dose Response, EpiSensA, SENS-IS
 - In silico reactivity structural alert (OECD QSAR Toolbox)
 - Add new features
 - Addition of “ED_x” – extrapolate the dose at which X% of the population will be sensitized
 - User input feature
 - Local version
 - Additional suggestions are always welcome

HPPT App to Classify Human Data

2023

HPPT Database was created to support the development and evaluation of non-animal approaches for skin sensitization assessment.

Contains information for 1366 unique substances.

2024

Developed new GHS classification approach for hazard and potency classification.

Addresses borderline results.

Incorporates the number of sensitized subjects to better inform on potency.

2025

user-friendly, open-source R Shiny-based HPPT App was developed to facilitate public use of the modified classification approach.

Allows users to easily classify their HPPT data in a way that reflects human potency.

<https://ntp.niehs.nih.gov/go/hppt>



Home > Archives of Toxicology > Article

A database of human predictive patch test data for skin sensitization

Review Article | Open access | Published: 24 August 2023

Volume 97, pages 2825–2837, (2023) [Cite this article](#)

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Judy Strickland, Jaleh Abedini, David G. Allen, John Gordon, Victoria Hull, Nicole C. Kleinstreuer, Hon-Sum Ko, Joanna Matheson, Hermann-Josef Thierse, James Truax, Jens T. Vanselow & Matthias Herzler

<https://doi.org/10.1007/s00204-023-03530-3>

Archives of Toxicology (2024) 98:1253–1269
<https://doi.org/10.1007/s00204-023-03656-4>

REVIEW ARTICLE

Use of human predictive patch test (HPPT) data for the classification of skin sensitization hazard and potency

Matthias Herzler¹ · Jaleh Abedini² · David G. Allen² · Dori Germolec² · John Gordon⁴ · Hon-Sum Ko⁵ · Joanna Matheson⁴ · Emily Reinke² · Judy Strickland² · Hermann-Josef Thierse¹ · Kim To² · James Truax² · Jens T. Vanselow¹ · Nicole Kleinstreuer²

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Abstract

Since the 1940s, patch tests in healthy volunteers (Human Predictive Patch Tests, HPPTs) have been used to identify chemicals that cause skin sensitization in humans. Recently, we reported the results of a major curation effort to support the development of OECD Guideline 497 on Defined Approaches (DAs) for skin sensitization (OECD in Guideline No. 497: Defined Approaches on Skin Sensitization, 2021a, <https://doi.org/10.1787/h92879a4-en>). In the course of this work, we compiled and published a database of 2277 HPPT results for 1366 unique test substances (Strickland et al. in Arch Toxicol 97:2825–2837, 2023, <https://doi.org/10.1007/s00204-023-03530-3>). Here we report a detailed analysis of the value of HPPT data for classification of chemicals as skin sensitizers under the United Nations' Globally Harmonized System of Classification and Labelling of Chemicals (GHS). As a result, we propose the dose per skin area (DSA) used for classification by the GHS to be replaced by or complemented with a dose descriptor that may better reflect sensitization incidence [e.g., the DSA causing induction of sensitization in one individual (DSA1+) or the DSA leading to an incidence of induction in 5% of the tested individuals (DSA05)]. We also propose standardized concepts and workflows for assessing individual HPPT results, for integrating multiple HPPT results and for using them in concert with Local Lymph Node Assay (LLNA) data in a weight of evidence (WoE) assessment. Overall, our findings show that HPPT results are often not sufficient for deriving unambiguous classifications on their own. However, where they are, the resulting classifications are reliable and reproducible and can be integrated well with those from other skin sensitization data, such as the LLNA.

Access the HPPT App

<https://rstudio.niehs.nih.gov/hppt-app/>



NICEATM and ICCVAM Presentations at WC13

<https://ntp.niehs.nih.gov/go/niceatm-wc13>

13th World Congress on Alternatives and Animal Use in the Life Sciences
August 31–September 4, 2025 – Rio de Janeiro, Brazil

Abstract 288: [Web Application to Classify and Subcategorize Skin Sensitizers Using Human Data](#)

Authors: Unnikrishnan A, To K, Herzler M, Germolec D, Reinke E, Kleinstreuer N

HPPT App

chemical_identifier	concentration_percent	dsa_ug_cm2	n_testsubjects	n_positive
10032-02-7	6	3888	25	0
DTXSID8039241	4	2700	25	1
Ammoniated mercur	2	1296	100	14
5870-93-9	12	8100	24	5
626-82-4	4	2700	30	2

HPPT User Input File

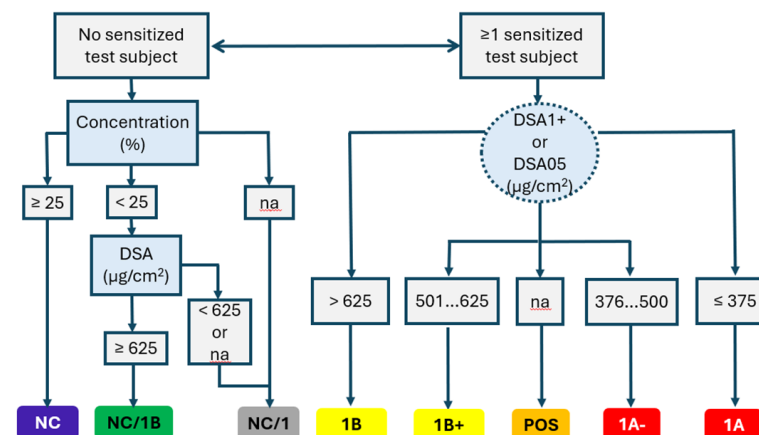
DSA1+

- Dose per skin area that sensitizes one test subject

DSA05

- Dose per skin area that sensitizes 5% of test subjects

Choose Potency Measure



* Figure adapted from Herzler et al. 2024

Modified Classification Approach

HPPT App

CSV

Excel

Chemical Identifier ?	WoE_bin ?	WoE_sub ?	WoE_border ?	Total Tests ?
All	All	All	All	All
DTXSID8039241	1	1B	1B	1
Ammoniated mercury	1	1A	1A	1
626-82-4	1	1B	1B	1
5870-93-9	1	1B	1B	1
10032-02-7	NA	NA	NC/1B	1

Overall WoE GHS Classification

Chemical Identifier ?	WES ?	WES_GHS_bin ?	WES_GHS_sub ?	WES_GHS_border ?	MLLP_bin ?	MLLP_sub ?	MLLP_GHS_bin ?
All	All	All	All	All	All	All	All
DTXSID8039241	1	1	1B				
Ammoniated mercury	2	1	1A				
626-82-4	1	1	1B				

Classification Based on Individual WoE Methods

MLLP_GHS_sub ?	MLLP_GHS_border ?	MSPE ?	MSPE_GHS_bin ?	MSPE_GHS_sub ?	MSPE_GHS_border ?
All	All	All	All	All	All
1B	1B	2700	1		
1A	1A	93	1		
1B	1B	1350	1		

Chemical Identifier ?	Conc (%) ?	DSA (ug/cm2) ?	No. Test Subjects ?	No. Positive ?	Call ?	DSA1+ ?	DSA5% ?	Ex.C ?	WES_indiv ?
All	All	All	All	All	All	All	All	All	All
DTXSID8039241	4	2700	25	1	Active	2700	3375	1B	1
Ammoniated mercury	2	1296	100	14	Active	93	463	1A	2
626-82-4	4	2700	30	2	Active	1350	2025	1B	1
5870-93-9	12	8100	24	5	Active	1620	1944	1B	1
10032-02-7	6	3888	25	0	Inactive	NA	NA	NC/1B	0.5

Individual Classifications by Record

Chemical Identifier ?	WoE_sub ?	WoE_sub Reproducibility ?	Total Tests (Reproducibility) ?
All	All	All	All
10124-43-3	1B	100	3
10124-48-8	1B	77.78	18
103-16-2	1B	62.5	24
104-21-2	1B	100	2

Reproducibility of HPPT-based WoE Classifications

- Potency classifications generated can serve as reference data for the evaluation of non-animal skin sensitization tests.
- Providing individual classifications along with overall weight of evidence results can help users characterize uncertainty in the overall result.
- App also estimates classification reproducibility for chemicals, indicating agreement or disagreement with overall classification outcome.

Conclusion

- NICEATM has developed a suite of user-friendly tools to assess skin sensitization hazard and potency
 - Usable for risk assessment and screening
 - Streamlines decision process
- NICEATM will continue to focus on development of computational or other tools to help make regulatory decisions or complex models more available to stakeholders



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