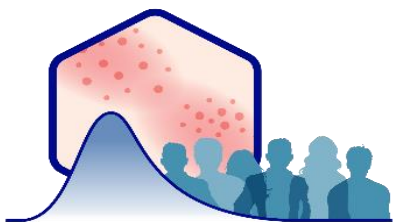


A Deep-Dive into the Application of Defined Approaches for Skin Sensitization in OECD GL 497 – SARA-ICE

Skin Sensitization: Safety Assessment Using NAMs for Substances in Cosmetics and Personal Care Products Webinar

Georgia Reynolds, MSc.
Safety Science Leader
Unilever
April 9, 2026



Section 1 – SARA-ICE Basics

Intro to SARA-ICE DA
Input data options
Data output



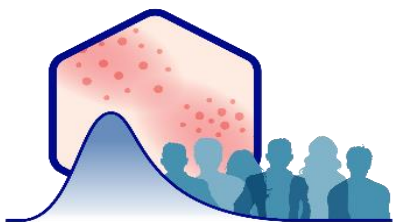
Section 2 – SARA-ICE Walkthrough

Web Platform Walkthrough



Section 3 – Application of SARA-ICE in Risk Assessment

Geraniol Case Study
PoD NAM Acceptable MoE



Section 1 – SARA-ICE Basics

Intro to SARA-ICE DA
Input data options
Data output



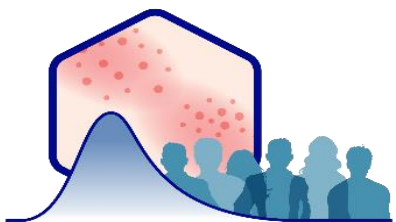
Section 2 – SARA-ICE Walkthrough

Web Platform Walkthrough



Section 3 – Application of SARA-ICE in Risk Assessment

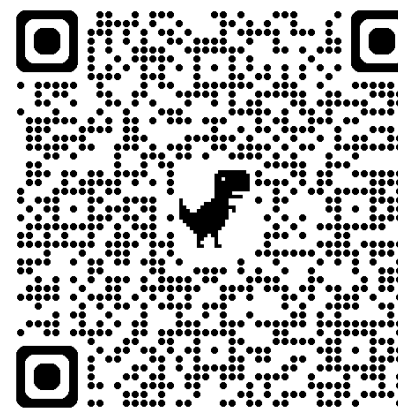
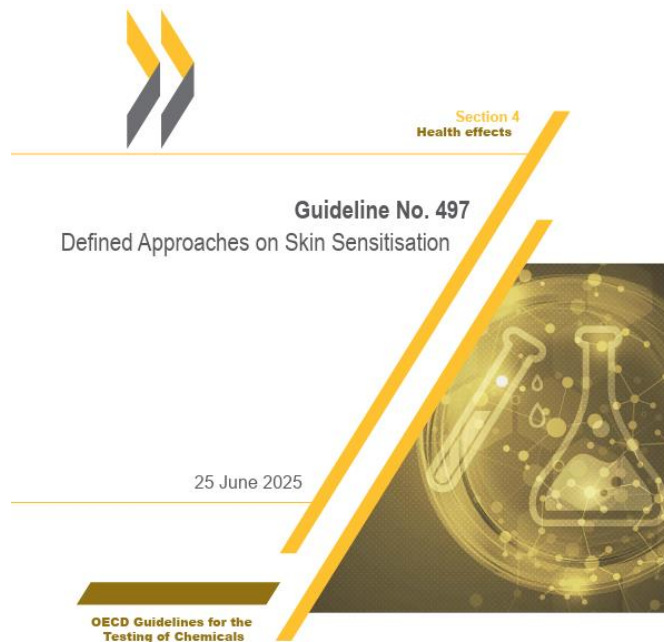
Geraniol Case Study
PoD NAM Acceptable MoE



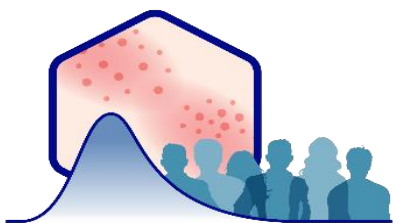
Defined Approaches for Skin Sensitisation

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 GL 497 to incorporate DAs for PoD determination (i.e. SARA-ICE), the updated GL, including SARA-ICE was released in June 2025.



OECD GL 497



SARA-ICE Model Overview

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

Database

The core SARA-ICE dataset uses 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 (HPPT: 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)

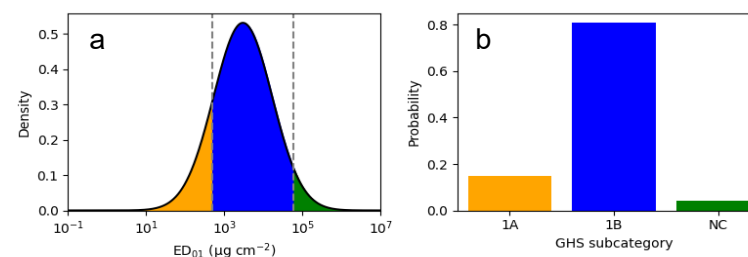
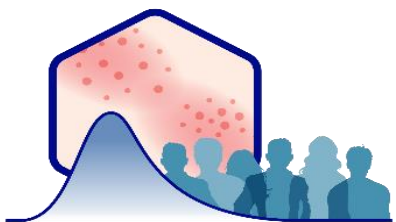


Figure (a) Example estimate of ED_{01} distribution with overlay of GHS subcategories 1A, 1B and NC defined thresholds, (b) probability of each GHS subcategory from ED_{01} distribution



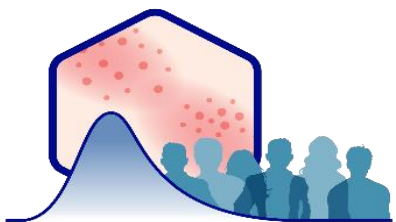
SARA-ICE Model Overview

- SARA-ICE estimates a **human-relevant metric** of sensitiser potency, the HPPT 1% sensitising dose (ED_{01} , in $\mu\text{g}/\text{cm}^2$).
- Data Inputs:

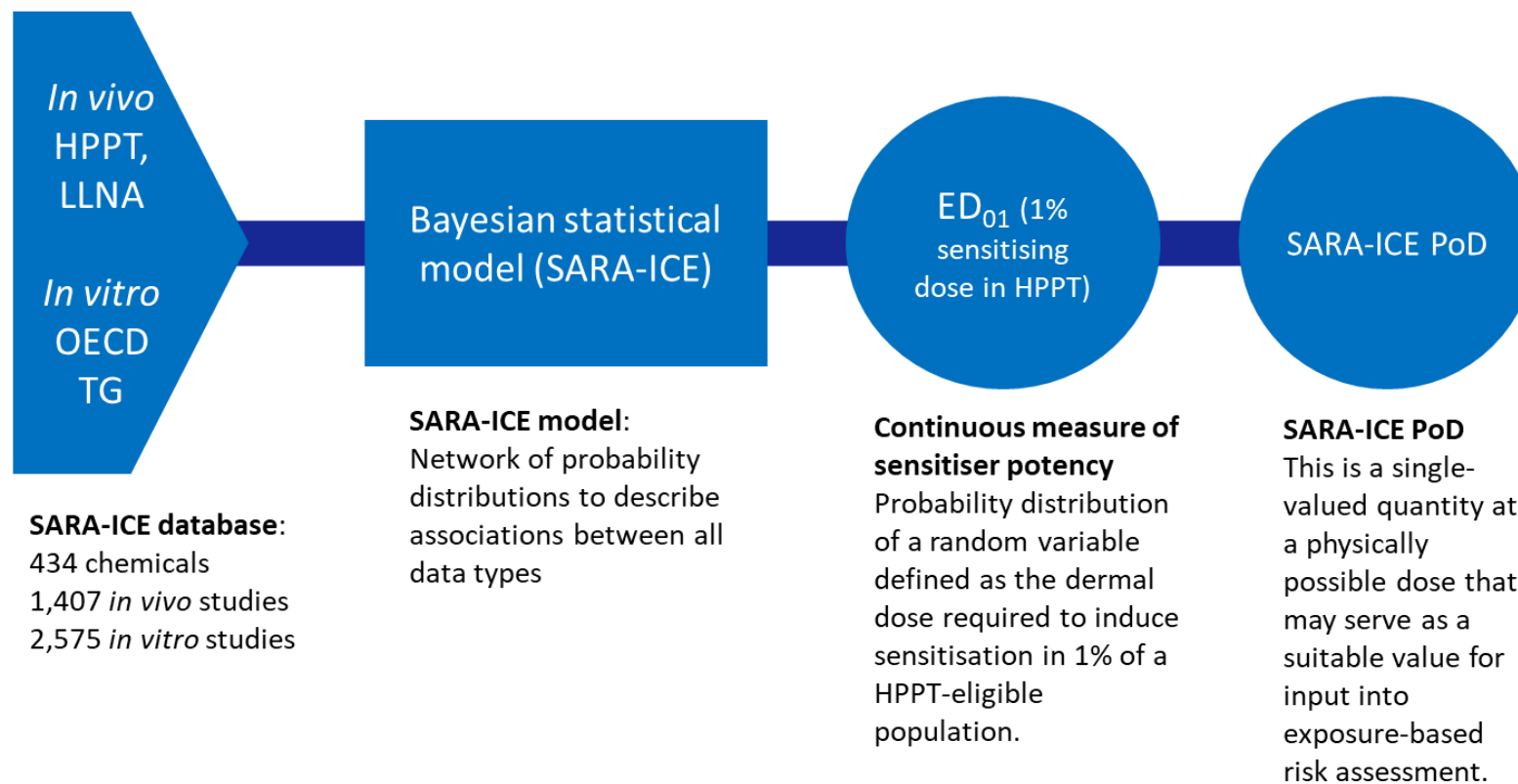
Study type	HPPT	LLNA	DPRA	kDPRA	KeratinoSens	h-CLAT	U-Sens
Inputs into SARA-ICE	Dermal dose, number tested, number sensitised	EC_3 or maximum concentration tested if no response observed	% depletion of cysteine and lysine peptides	Log Kmax	$EC_{1.5}$ or maximum concentration tested IC50 or maximum concentration tested	CD86 EC_{150} , CD50 EC_{200} or maximum concentration tested CV_{75} or maximum concentration tested	CD86 EC_{150} or maximum concentration tested CV_{75} or maximum concentration tested
Number of studies in database	871	536	650	361	972	428	164
Number of unique CASRN with this study type (434 distinct CASRN)	276	195	251	185	258	211	90

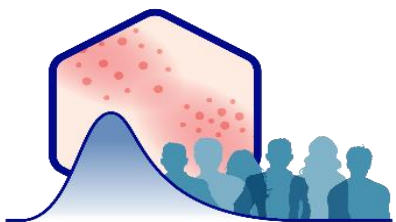
*All metrics are required for an individual data type, or the model will not run

Predictions can be made on partial data sets, but a minimum of two different KE data types required for acceptance under MAD



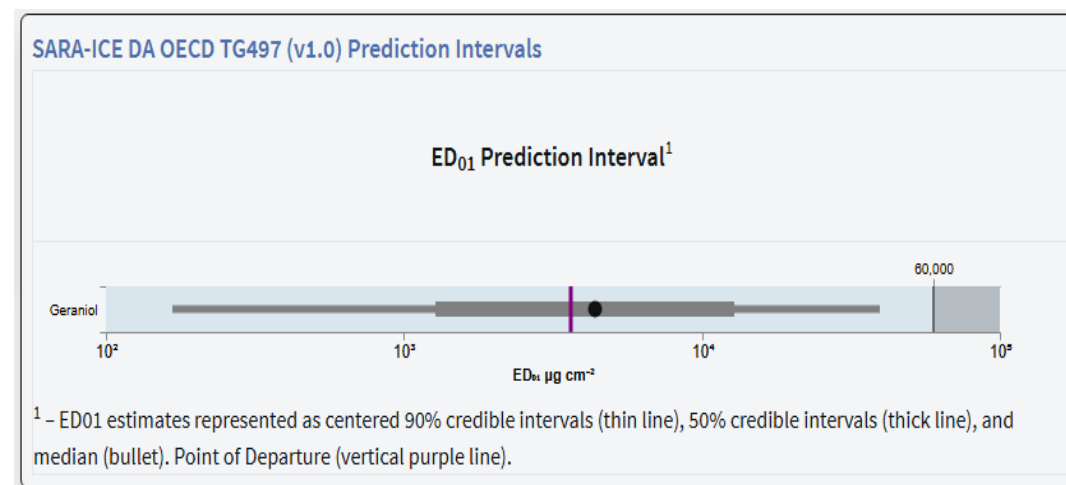
SARA-ICE DA (OECD GL 497)

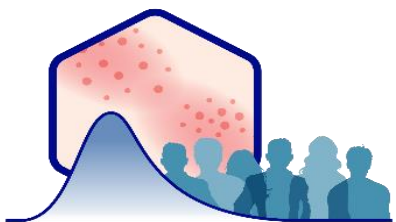




SARA-ICE DA (OECD GL 497)

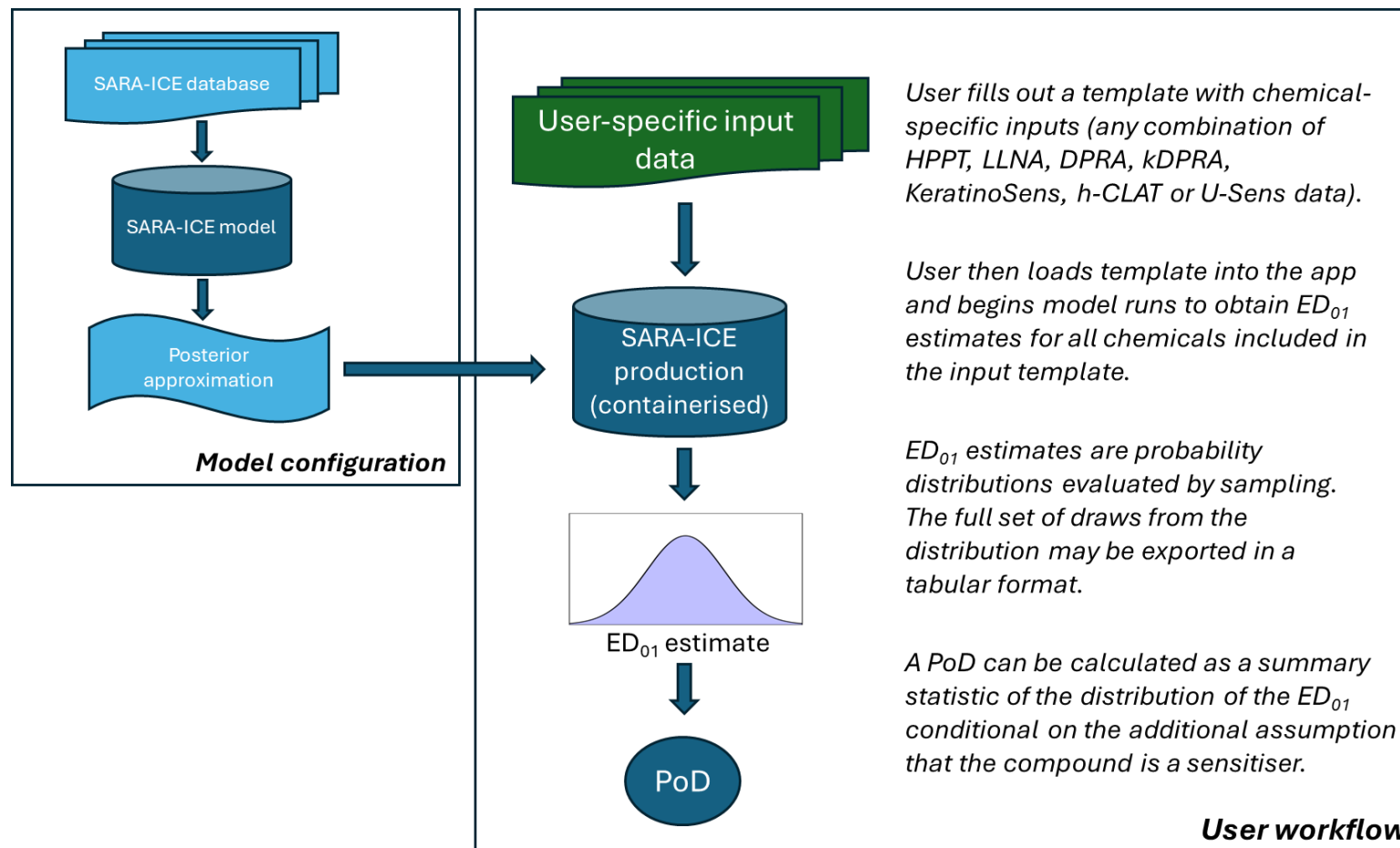
- Derives the PoD from the ED₀₁ distribution for use in risk assessment.
- Presumes that the substance under evaluation by the model is a skin sensitiser.
- The ED₀₁ distribution has an upper limit of 60,000 µg/cm² (highest dose used in an HPPT).
- Distribution is centered on the 90% credible interval (interval between the 5th and 95th percentiles of the distribution)
- ***The PoD is defined as the mean of the distribution.***
- **Acceptable for use under MAD**

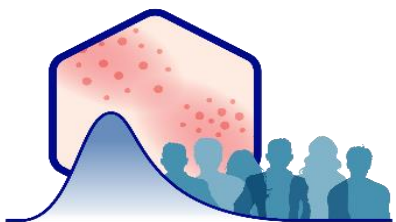




SARA-ICE DA Workflow (OECD GL 497)

The SARA-ICE DA (OECD GL 497) is fixed. The base model is unchanged by user-specific input data and technical updates may only be made after a re-evaluation by the OECD.





Section 1 – SARA-ICE Basics

Intro to the SARA-ICE DA
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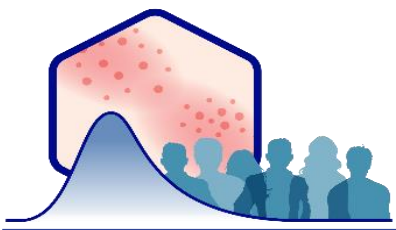
Section 2 –SARA-ICE Walkthrough

Web Platform Walkthrough



Section 3 – Application of SARA-ICE in Risk Assessment

Geraniol Case Study
PoD NAM Acceptable MoE



SARA-ICE Walkthrough

Accessing the Tool

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

An official website of the United States government [Here's how you know](#) ✓

Calendar & Events | News & Media | Get Involved | Support

National Toxicology Program
U.S. Department of Health and Human Services

Search the NTP Website SEARCH

Research | Data & Resources | Publications | Who We Are

Home » NICEATM: Alternative Methods » Test Method Evaluations » Identification of Skin Sensitizers » Defined Approaches to Identify Potential Skin Sensitizers » SARA-ICE Model

https://ntp.niehs.nih.gov/n465041

Defined Approaches

- SARA-ICE Model
- DASS App: Web App to Predict Skin Sensitization

SARA-ICE: Skin Sensitization Risk Assessment - Integrated Chemical Environment Model

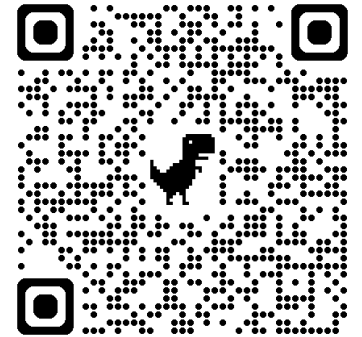
[Access the SARA-ICE Tool](#)

[Download SARA-ICE Template File for use in the tool](#)

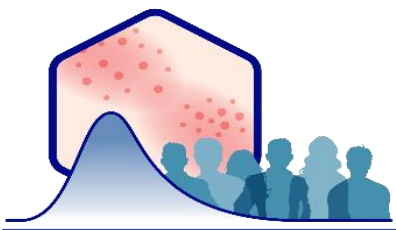
There is an international need for non-animal approaches to identify potential skin sensitizers. While [defined approaches](#) (DAs) are accepted for making a binary prediction of whether or not a substance might be a skin sensitizer (as described in [OECD Guideline 497](#) ¹), there remains a need for non-animal approaches for quantitative prediction of skin sensitizer potency.

The Skin Sensitization Risk Assessment – Integrated Chemical Environment ([SARA-ICE](#)) DA is a Bayesian statistical model developed in a collaboration between [NICEATM](#) and the consumer products company Unilever. SARA-ICE estimates a human-relevant metric of skin sensitizer potency. This metric, termed ED01, is the dose with a 1% chance of human skin sensitization ([Reinke et al. 2025](#)). SARA-ICE uses data on over 400 chemicals from the NICEATM [Integrated Chemical Environment](#) (ICE) to predict a point-of-departure using any combination of in vivo (human predictive patch test or local lymph node assay) and in vitro (direct peptide reactivity assay [DPRA], kinetic DPRA, KeratinoSense™ human cell line activation test, or IL-SFNS™) data.

Click here



A self-contained version of the model and user interface have been developed, accessed via the NTP website.



SARA-ICE Walkthrough

User Interface General Layout

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

Area where actions for the tool are taken.

Download templates, upload files, select models, etc.

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)'
3. After selecting a model, the analysis will automatically start running. You can [View Analysis](#) during and after processing
4. After analysis is finished, you can [Download Analysis](#)

Help & Support

Have questions or need to report an issue? Please email ICE-support@niehs.nih.gov

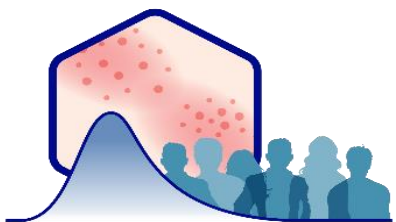
Version 0.2.5-beta

Next >

Step-by-step workflow:

- Current page is highlighted green
- White boxes are accessible (ready for use)
- Grey boxes are not accessible (require input from previous steps)

Can advance via top menu or by clicking "Next" below input field



General guidance

Steps for use:

Read the directions

Access resources if needed

To advance, click “Next” at the bottom of the page or “Select Input File” in the top menu

Resources available on this page:

[User Guide \(downloadable PDF\)](#)

Workflow instructions

Help & Support link available at ICE-support@niehs.nih.gov

The screenshot shows the SARA-ICE tool interface. At the top, there is a navigation menu with buttons for "Overview", "1 Select Input File", and "2 Select Model". Below the menu is a large grey area containing a help box titled "Steps for Using the SARA-ICE Tool". The help box contains the following text:

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:

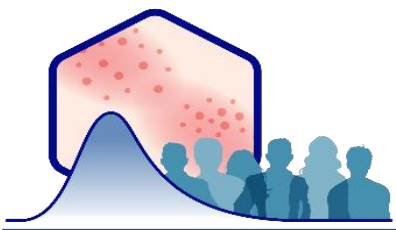
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Have questions or need to report an issue? Please email ICE-support@niehs.nih.gov
Version 0.2.5-beta

At the bottom of the help box, there is a "Next >" button.



Selecting an input file

Steps for use:

Download Template

This template provides the required formatting for data input into the models. Models will not run if this formatting is not followed.

Select Data Input File

Drag and drop completed data input file or browse to upload file.

Click “Next” or “Select Model” (top of page)

Resources available on this page:

Blank Template

Example File

Overview → 1 **Select Input File** → 2 Sele

Blank Template for Data Input

[Download Template](#)

The blank template file provides the required format of input data for analysis by the SARA-ICE model. Any adjustments to the headers/titles of the input file will result in the model failing to run. The file below provides an example dataset.

Select Data Input File

Drag and drop Data Input File here (.xlsx) or...

[Browse Files](#)

The selected Data Input File is processed locally and is not uploaded.

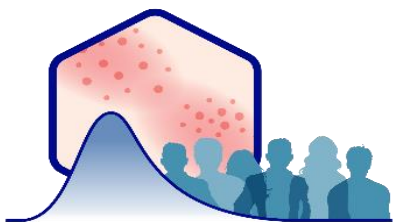
Example File for Data Input

[Download Example](#)

The example dataset file demonstrates the correct format for data entry into the blank template.

To see how the SARA-ICE tool works — download the example file, select the downloaded 'SARA-ICE_example.xlsx' file, proceed to step 2 "Select Model".

[< Prev](#) [Next >](#)



SARA-ICE Walkthrough

Populating the Data Input File

“Key” tab provides instructions on what data are required for each input type.

Use the SARA-ICE Example File if unsure how data should be entered.

Do not change header names in the template: the model will not run if these are altered.

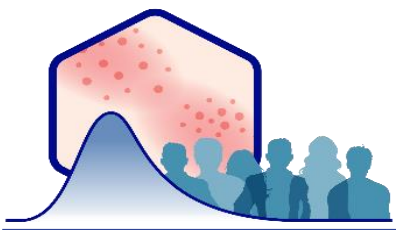
Limit entries (such as “<x”, “>x”) are permitted and should be used where relevant.

Substance short names and unique CAS RNs must be manually entered on each tab (only enter substances with data)

Molecular weight is required if kDPRA or KeratinoSens data are entered.

Field Name	Description
Substance Name	Full substance name that will appear in reports containing results.
Abbreviated Substance Name	Abbreviated substance name that is used in tables and figures.
CASRN	CASRN for the substance. This must be included alongside each datapoint on assay-specific sheets. This is used to link datapoints to the correct substance on the "Substances" sheet.
MW (g/mol)	Molecular weight of the substance. Necessary when including data on the kDPRA and KeratinoSens sheets to enable appropriate unit conversion.
Dose per Skin Area ($\mu\text{g}/\text{cm}^2$)	Dermal induction dose of the HPPT study
Number of Test Subjects	The number of test subjects in the HPPT study
Number of Positive Responses	The number of test subjects judged to be sensitised after the elicitation phase of the HPPT study
EC3 (%)	Estimated EC3 from the LLNA study. Negative studies should be entered as >X where X is the maximum concentration tested. LLNA studies with SI > 3 at the lowest tested concentration can be entered as <X where X is the lowest concentration tested.
Depletion Cys (%)	Percentage depletion of the cysteine peptide in a DPRA study
Depletion Lys (%)	Percentage depletion of the lysine peptide in a DPRA study
log Kmax (M-1 s-1)	Log Kmax value estimated from a kinetic DPRA study. When reactivity rate is too low to measure, input as <X where X is the lowest possible measurable reactivity rate. Typically X=3.5 M-1 s-1
EC1.5 (μM)	Concentration in the KeratinoSens study resulting in a 1.5 fold increase in luciferase activity
IC50 (μM)	Concentration resulting in 50% cell death in the KeratinoSens study

KEY



Selecting the correct SARA-ICE model

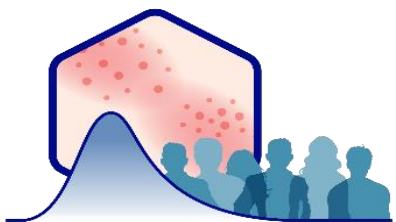
Select which model of SARA-ICE to use.

The “**OECD TG 497 Defined Approach**” model is consistent with OECD TG 497 and is acceptable under MAD.

The “**Extended Model**” provides additional functionality to determine hazard, GHS subcategorization, and additional statistics on the ED₀₁ distribution. Data derived from this model are not acceptable for use under MAD.

Click “Next” or “View Analysis” to begin analysis, which may take some time to complete.

The screenshot shows a web application interface for 'Human Services'. At the top, there is a navigation bar with 'Overview' and '1 Select Input File' (highlighted in green) and '2 Select M...'. Below this is a main content area with a title 'Select SARA-ICE Model' and a sub-header 'Click a model to select it'. There are two radio button options: 'OECD TG 497 Defined Approach (DA, version 1.0)' (selected) and 'Extended Model (version 1.0)'. The selected option has a detailed description: 'Use this SARA-ICE model with TG 497. The OECD TG 497 DA (version 1.0) uses defined input data to determine the geometric mean of the ED₀₁ distribution, which is used as the point of departure (PoD) in a quantitative risk assessment for skin sensitization. The use of the OECD TG 497 DA (version 1.0) assumes that substances analyzed in this model are skin sensitizers. Outputs from this model are acceptable under the OECD Mutual Acceptance of Data system.' The unselected option has a shorter description: 'The SARA-ICE Extended Model (not for use within OECD TG 497) provides additional information and model functionality, such as predictions of skin sensitization hazard and GHS sub-categorization, as well as the distribution of the ED₀₁. Outputs from this model are not acceptable within OECD TG 497 or under the Mutual Acceptance of Data system.' At the bottom of the content area, there are 'Prev' and 'Next' navigation buttons.



During the analysis phase...

The model will analyse substances provided sequentially.

The tool will indicate which substance is under analysis by displaying “Running” next to the substance name.

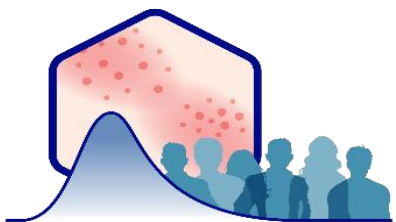
Results will auto-populate as they are determined, along with a display of the ED01 distribution as a graph.

SARA-ICE OECD TG 497 DA (version 1.0)

Results

Substance	CASRN	POD	ED ₀₁ 5th	ED ₀₁ 50th	ED ₀₁ 95th
ShortName	000-00-0	☼	Running...		
aChemical	001-00-1				

SARA-ICE OECD TG 497 DA (version 1.0) Results Key



Viewing the analysis – SARA-ICE DA (OECD GL 497)

SARA-ICE

SARA-ICE OECD TG 497 DA (version 1.0) Results

Substance	CASRN	POD	ED ₀₁ 5th	ED ₀₁ 50th	ED ₀₁ 95th
ShortName	000-00-0	4,700	780	4,900	25,000
aChemical	001-00-0	1,300	71	1,400	17,000

SARA-ICE OECD TG 497 DA (version 1.0) Results Key

- **Substance** — Name of Chemical Substance
- **CASRN** — Chemical Abstracts Service Registry Number (CAS RN or CAS Number)
- **POD** — (Point of Departure) geometric mean of the ED₀₁ predicated on being a sensitizer
- **ED₀₁ 5th** — 5th Percentile of the ED₀₁ distribution (µg/cm²)
- **ED₀₁ 50th** — 50th Percentile of the ED₀₁ distribution (µg/cm²)
- **ED₀₁ 95th** — 95th Percentile of the ED₀₁ distribution (µg/cm²)

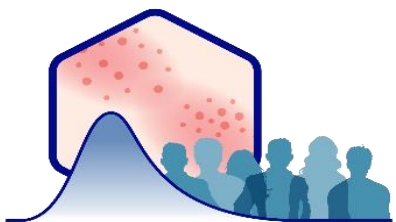
SARA-ICE OECD TG 497 DA (version 1.0) Prediction Intervals

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

POD for TG 497 DA use, in µg/cm²
Percentiles are provided as additional information on the distribution, but are not required for MAD

[< Prev](#) [Next >](#)

Click “Next” or “Download Analysis” to access Excel or .CSV files of the results.



Download your analysis

Click Download to download results as either an Excel or .CSV file.

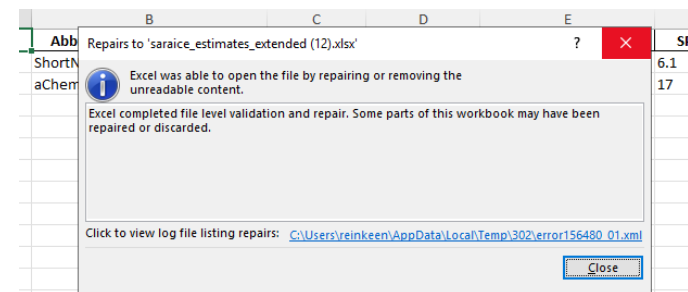
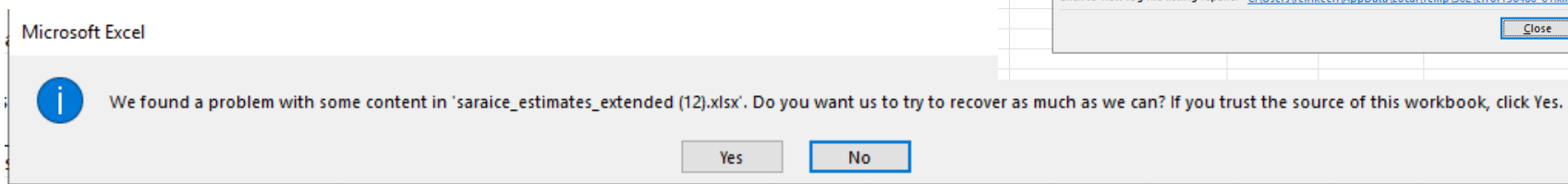
Data are populated to the “Substances” tab in the Excel file.

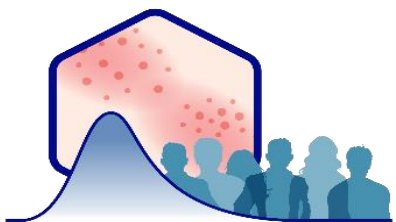
OECD TG 497 DA (version 1.0) Analysis

Download Excel Spreadsheet

Download CSV Formatted Text File

In Windows, the error shown below may appear after selecting the Excel option. Click “Yes” and Excel will recover the file. A pop-up in Excel will indicate that repairs have been made.





Troubleshooting Tips

Remember, the model can run on a single data input but a minimum of 2 input data types across KEs is required for the OECD GL 497 version to be actable under MAD.

If you get a recovery error when trying to download the data, click 'yes' to recover (or use .csv).

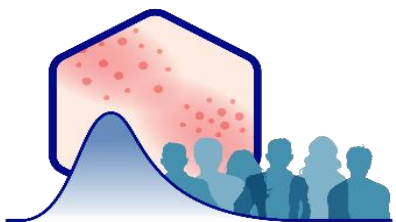
When filling in the input spreadsheet:

DO NOT

- Delete any tabs (even if you aren't using that data type)
- Add the substance name/unique CAS to tabs where you don't have that data type

DO

- Read the 'key' tab
- Fill in 'Short Name' (in each data tab) even if it's the same as the substance name
- Check your units
- Input data for all headers for each data type you have available
 - If you don't have a datapoint, use '> max. dose' tested as a surrogate or 0% for lys peptide depletion if not available



Section 1 – SARA-ICE Basics

Intro to the SARA-ICE DA
Input data options
Data output



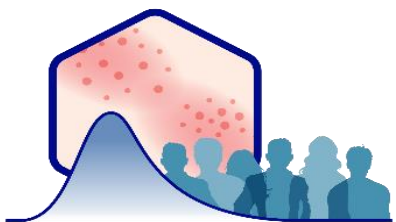
Section 2 –SARA-ICE Walkthrough

Web Platform Walkthrough



Section 3 – Application of SARA-ICE in Risk Assessment

Geraniol Case Study
PoD NAM Acceptable MoE



Example Case Study: Geraniol

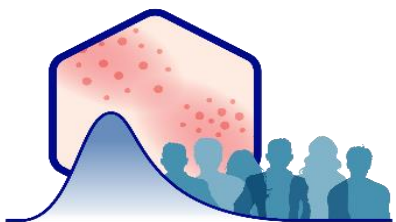
- Using NAM data only, generate a PoD (SARA-ICE DA)

SARA-ICE Input Data:

Note, although I have used a single data point from each possible NAM input type, it may be more realistic to assume you have 1 piece of evidence per key event...

Substance Name	CASRN	MW (g/mol)	KeratinoSens	
Geraniol	8007-13-4	154.25	EC1.5 (uM)	209.8
DPRA		hCLAT		
Depletion Cys (%)	Depletion Lys (%)	CD54, EC200 (ug/ml)	CD86, EC150 (ug/ml)	
12.3	2.6	>168	123	
kDPRA		USENS		
log Kmax (M-1 s-1)		CD86, EC150 (ug/ml)	53.6	
-3.4				






Generating a PoD for Geraniol: SARA-ICE DA (GL 497)

An official website of the United States government [Here's how you know](#)

Calendar & Events | News & Media | Get Involved | Support

 National Toxicology Program
U.S. Department of Health and Human Services

Search the NTP Website [SEARCH](#)

SARA-ICE [Overview](#) > [Load Input File](#) > [Select Model](#) > [View Analysis](#) > [Download Analysis](#)

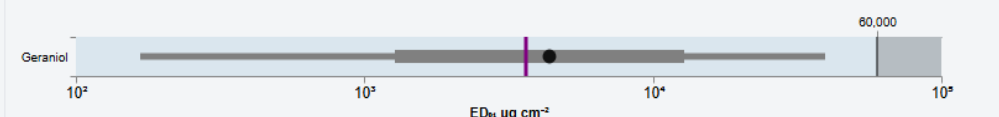
SARA-ICE DA OECD TG497 (v1.0) Results

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

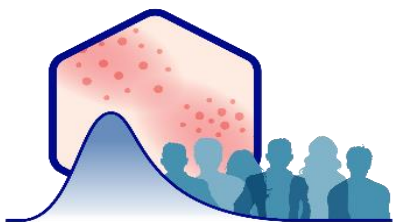
ED₀₁ Prediction Interval¹



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).

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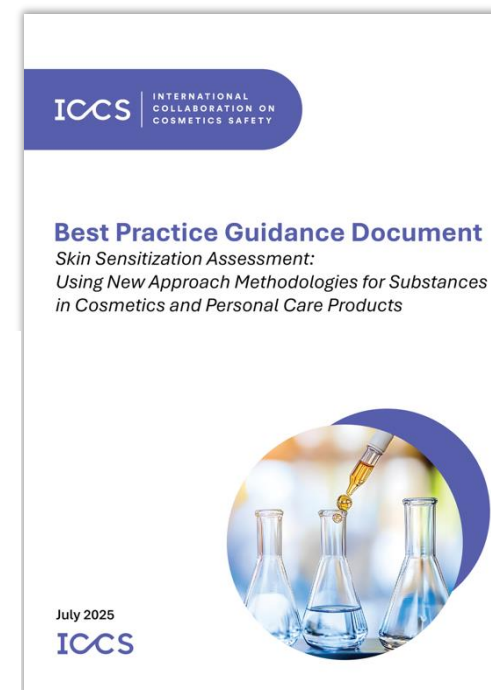
NAM PoD Margin of Exposure (MoE) in Risk Assessment

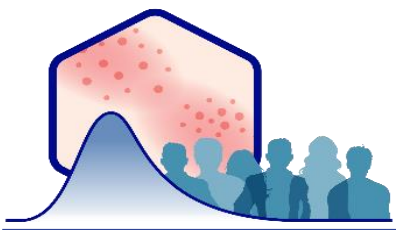
Acceptable Margin of Exposure (acceptable MoE) = a value above which a risk assessor may usually conclude low risk for their safety assessment.

An approach to define NAM PoD equivalent acceptable MoEs has been published in the **ICCS Best Practice Guidance 2025** so that SARA-ICE PoDs can be applied in current risk assessment methodologies such as QRA. This is beyond the scope of the OECD GL.



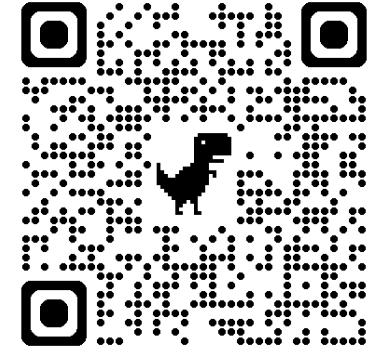
ICCS BPG





NAM PoD Margin of Exposure (MoE) in Risk Assessment

- Traditionally, values of 100 or above have been used as acceptable MoE.
- To convert **acceptable MoE for a human derived NESIL** → **acceptable MoE for NAM PoDs**, Reynolds et al., 2025 statistically analysed
 - a) differences between NESILs vs benchmark exposures
 - b) differences between NESILs and NAM PoD.



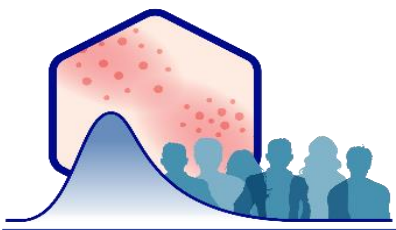
Reynolds et al., 2025

$$\log_{10}(\text{NAM MoE}) = \begin{cases} \beta + \beta_{\text{NAM}} + (S - \beta) \sqrt{1 + \frac{\sigma_{\text{NAM}}^2}{\sigma^2}} & \text{if } S > \beta + \frac{\beta_{\text{NAM}}}{1 - \sqrt{1 + \frac{\sigma_{\text{NAM}}^2}{\sigma^2}}}, \\ S & \text{if } S \leq \beta + \frac{\beta_{\text{NAM}}}{1 - \sqrt{1 + \frac{\sigma_{\text{NAM}}^2}{\sigma^2}}}. \end{cases}$$

Table 11. Side by Side Comparison of the Acceptable MoE from a Traditional NESIL-Based Risk Assessment to that for PoD_{NAM} from SARA-ICE

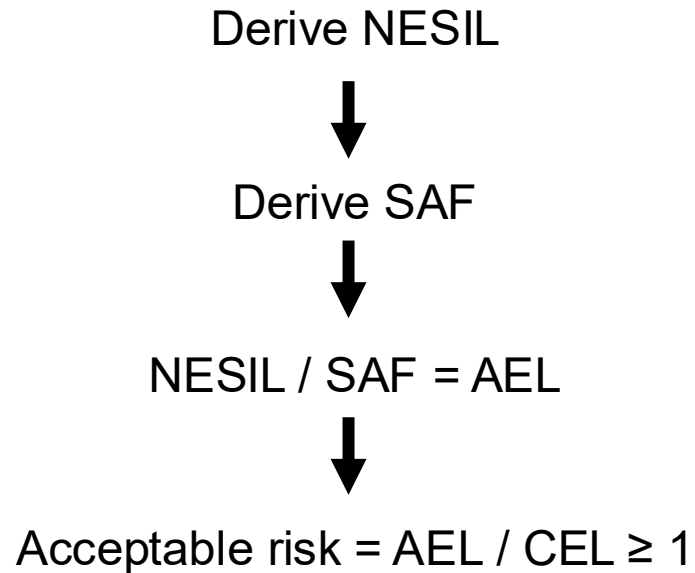
Acceptable MoE for traditional, NESIL-based risk assessment	Median of the distribution for the acceptable MoE for SARA-ICE PoDs
3	3
10	10
30	30
100	100
300	360
1,000	1,700

Source: Reynolds et al. 2025

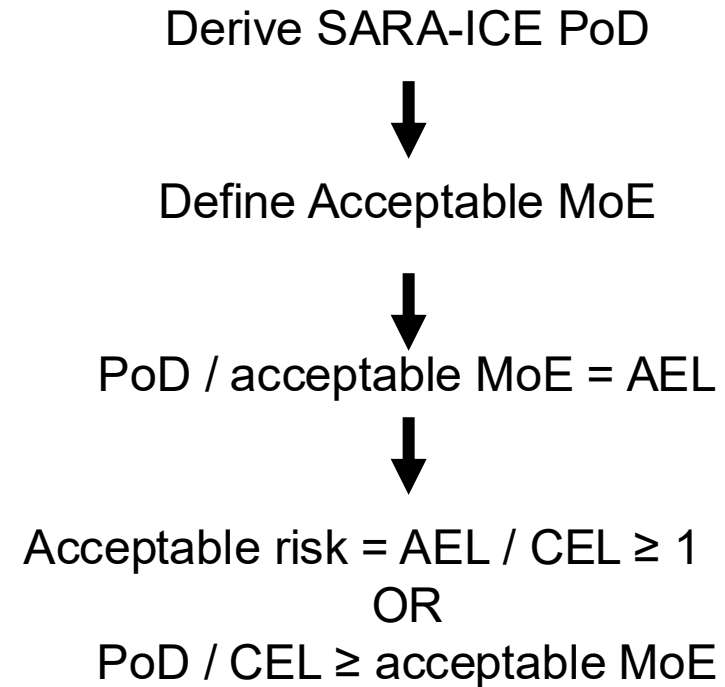


NAM PoD Margin of Exposure (MoE) in Risk Assessment

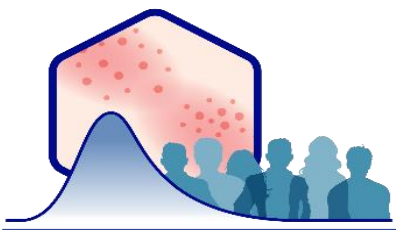
Traditional Quantitative Risk Assessment*



SARA-ICE DA Risk Assessment



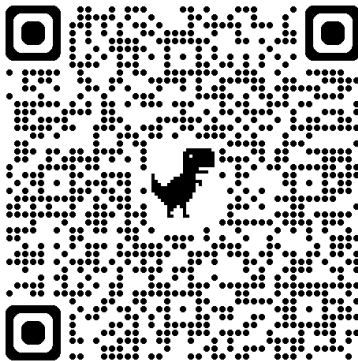
* e.g. Api et al., 2020



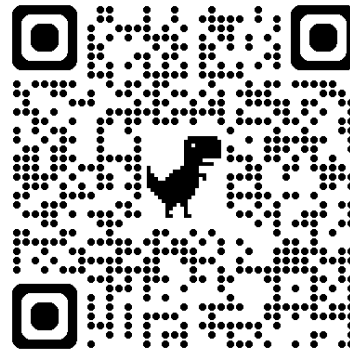
Summary

- SARA-ICE allows flexible use of a range of OECD TG NAMs (as well as historical LLNA/Human data)
- SARA-ICE DA fulfils a gap in the current OECD TG 497 on defining a PoD for risk assessment
- SARA-ICE DA PoDs are acceptable under MAD and can be applied in current skin sensitisation risk assessment methods

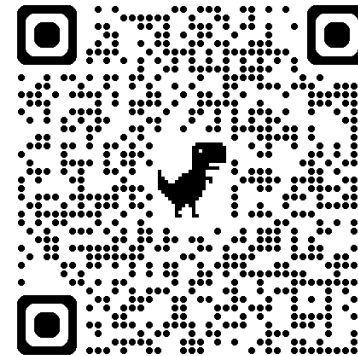
OECD GL 497



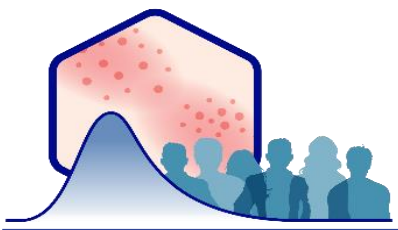
SARA-ICE Evaluation (Annex 11)



SARA-ICE User Interface



With special thanks to Unilever and NICEATM teams who were instrumental to the development of SARA-ICE.



THANK YOU!

