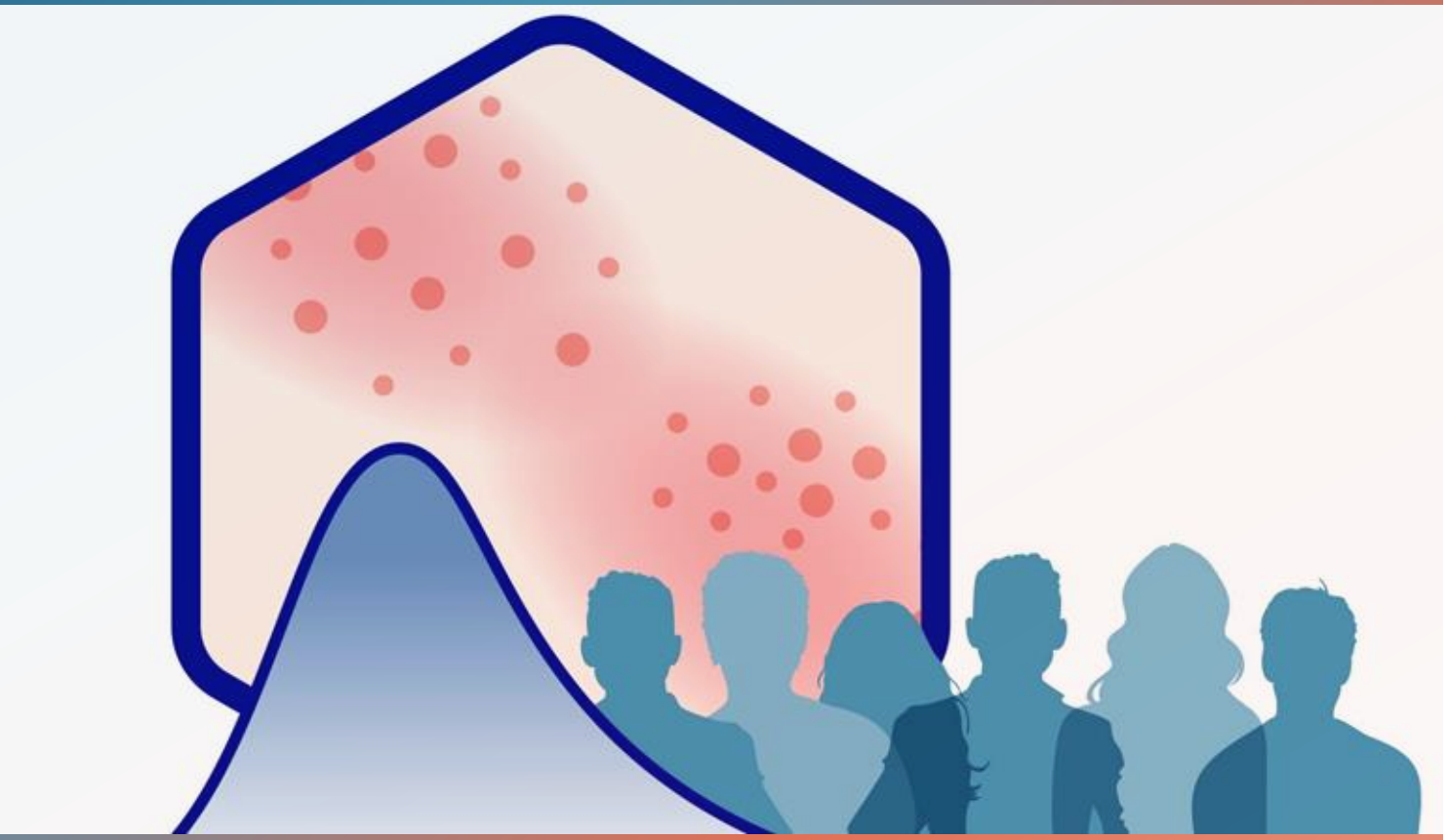
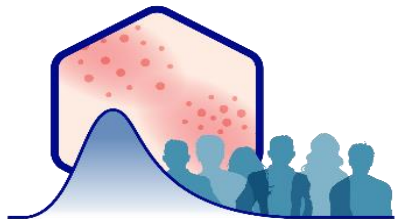


A Deep-Dive into the Application of Defined Approaches for Skin Sensitization in OECD GL 497 – SARA-ICE

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



Overview

Section 1 – SARA-ICE Basics

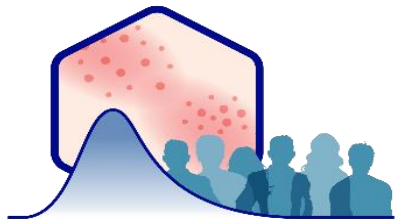
- Intro to SARA-ICE DA
- Input data options
- Data output

Section 2 – SARA-ICE Walkthrough

- Web Platform Walkthrough

Section 3 – Application of SARA-ICE in Risk Assessment

- Geraniol Case Study
- PoD NAM Acceptable MoE



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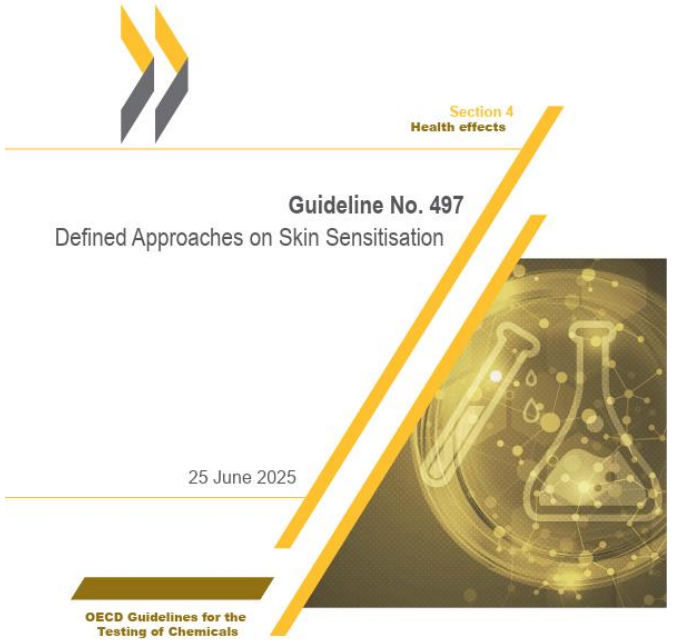
Defined Approaches for Skin Sensitisation

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)

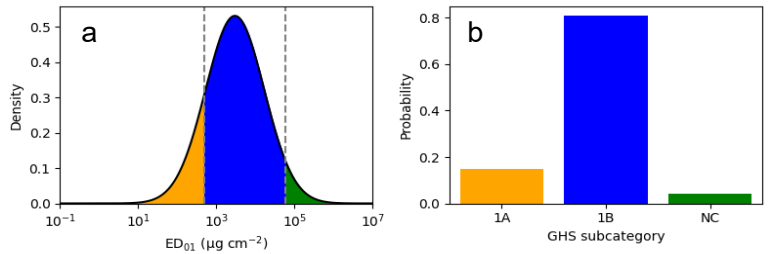


Figure (a) Example estimate of ED_{01} distribution with overlay of GHS subcategories 1A, 1B and NC defined thresholds, (b) probability of each GHS subcategory from ED_{01} distribution

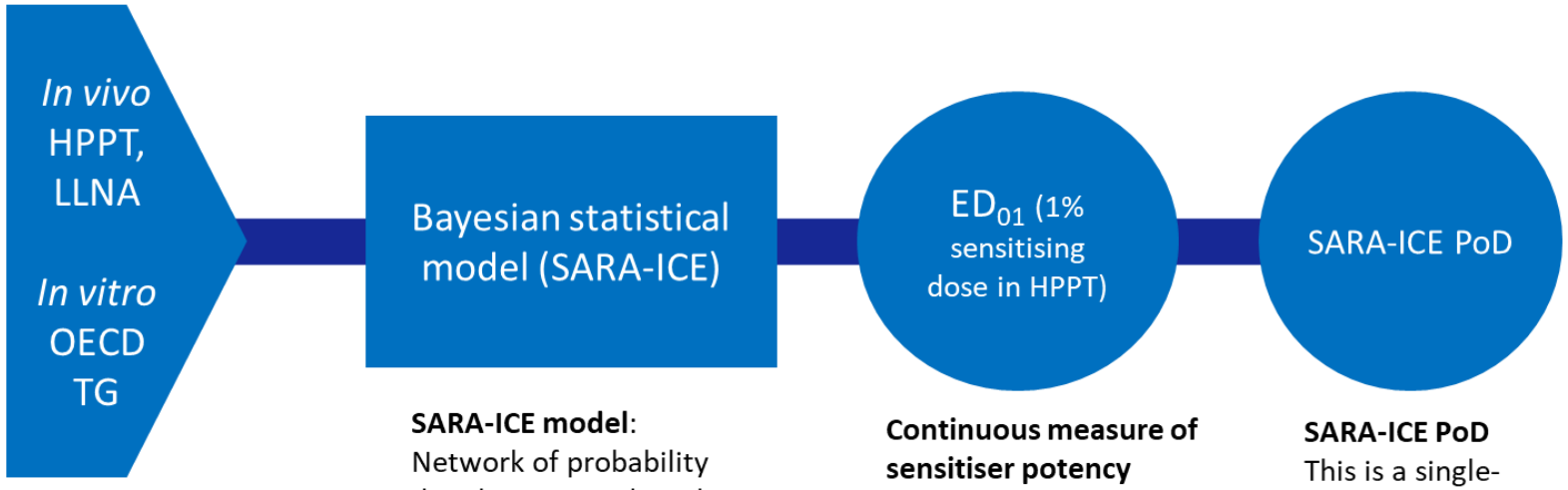
SARA-ICE Model Overview

- SARA-ICE estimates a **human-relevant metric** of sensitiser potency, the HPPT 1% sensitising dose (ED_{01}, in µg/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 database:
434 chemicals
1,407 *in vivo* studies
2,575 *in vitro* studies

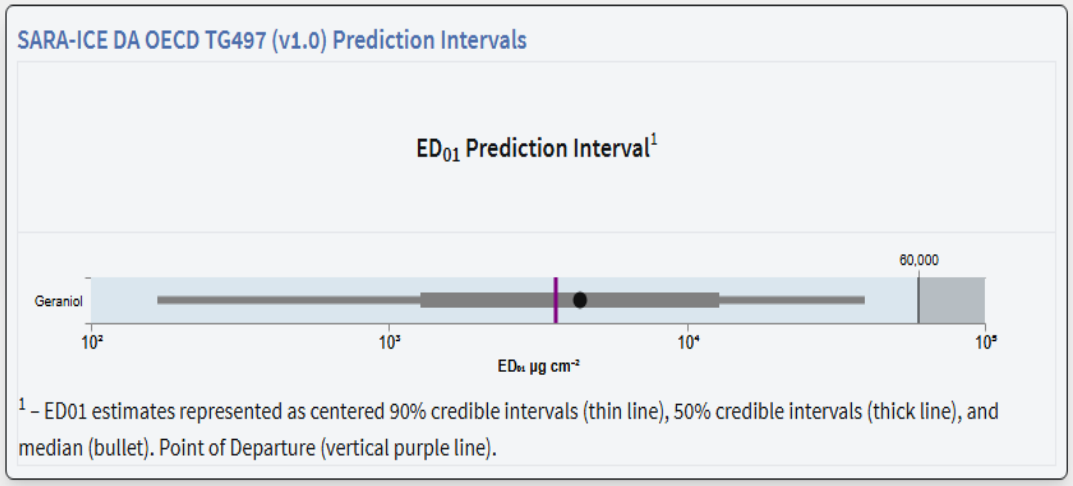
SARA-ICE model:
Network of probability distributions to describe associations between all data types

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.

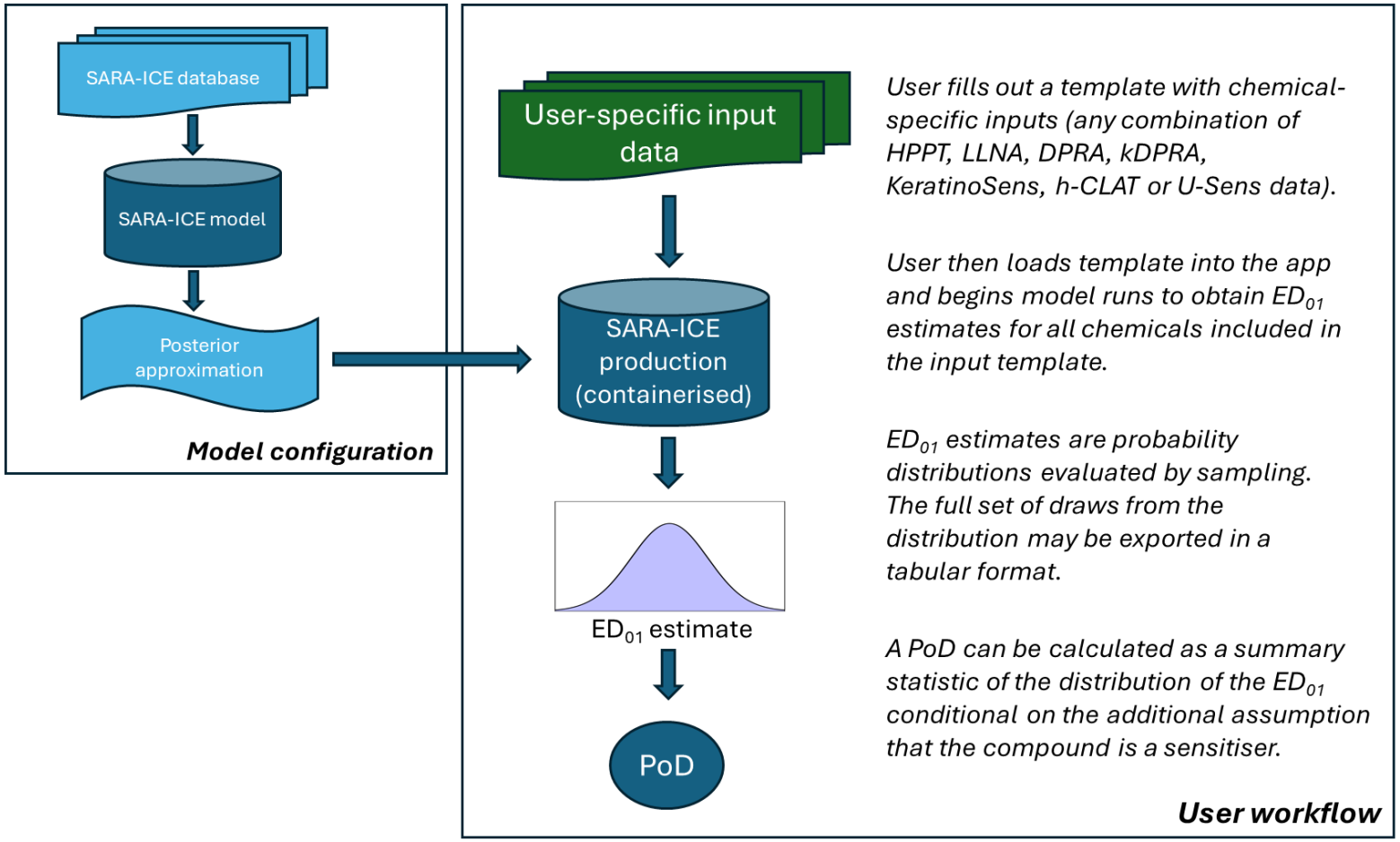
SARA-ICE DA (OECD GL 497)

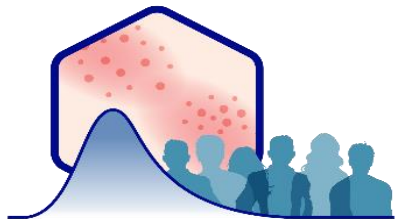
- Derives the PoD from the ED_{01} distribution for use in risk assessment.
- Presumes that the substance under evaluation by the model is a skin sensitiser.
- The ED_{01} distribution has an upper limit of 60,000 µg/cm^2 (highest dose used in an HPPT).
- Distribution is centered on the 90% credible 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.





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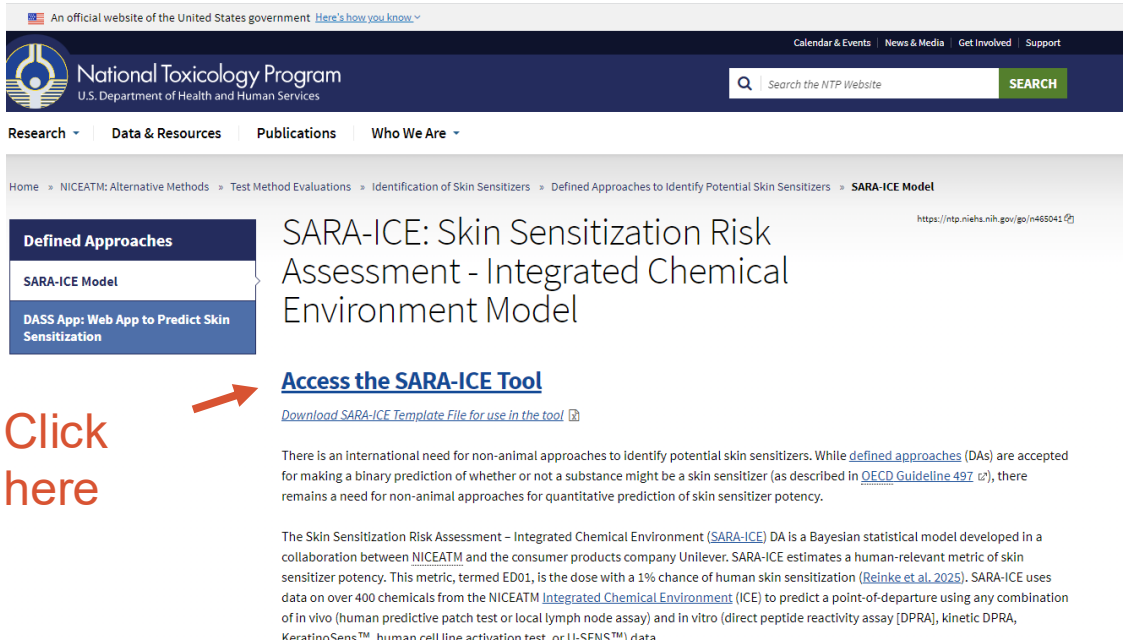
SARA-ICE Walkthrough

Accessing the Tool

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



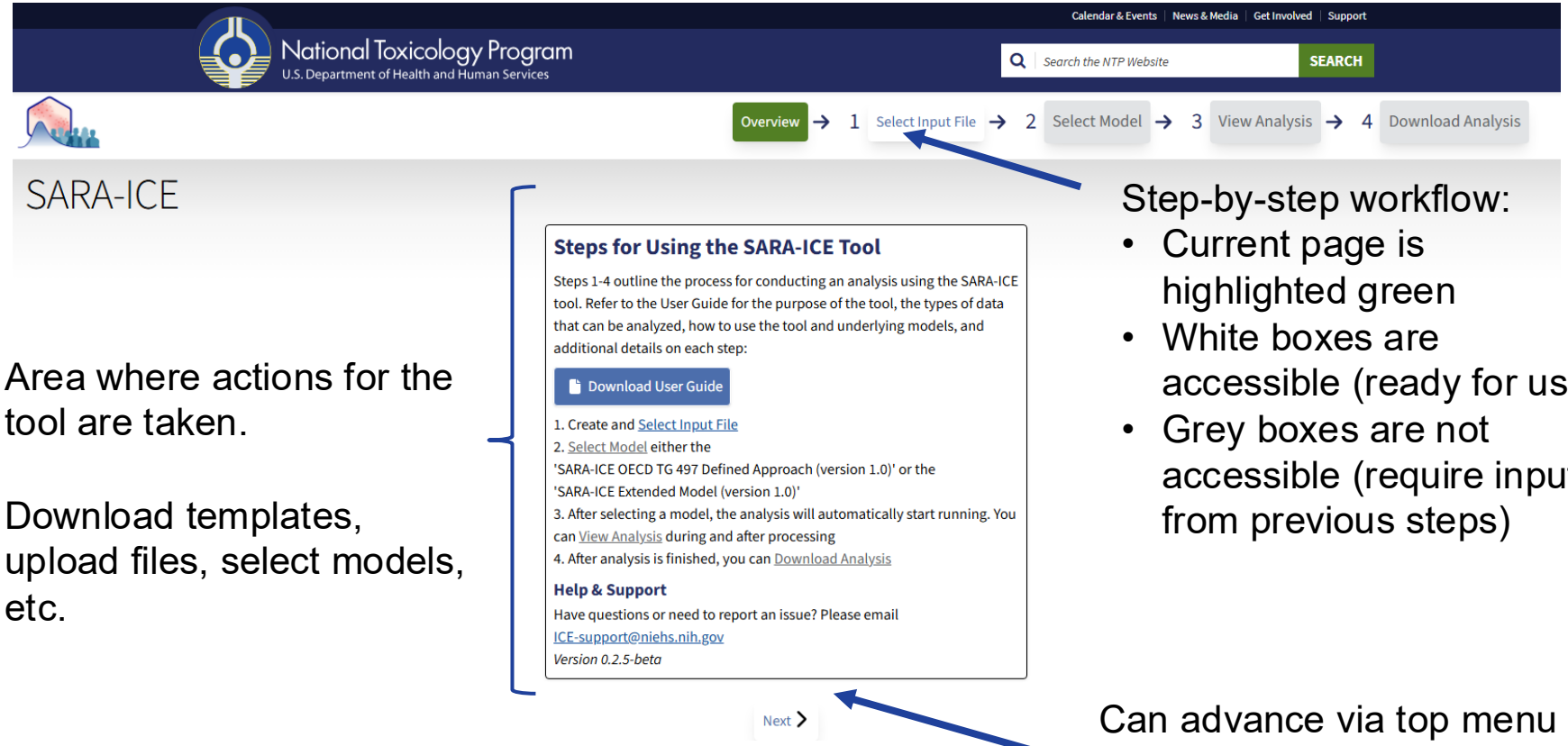
Click here

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.

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

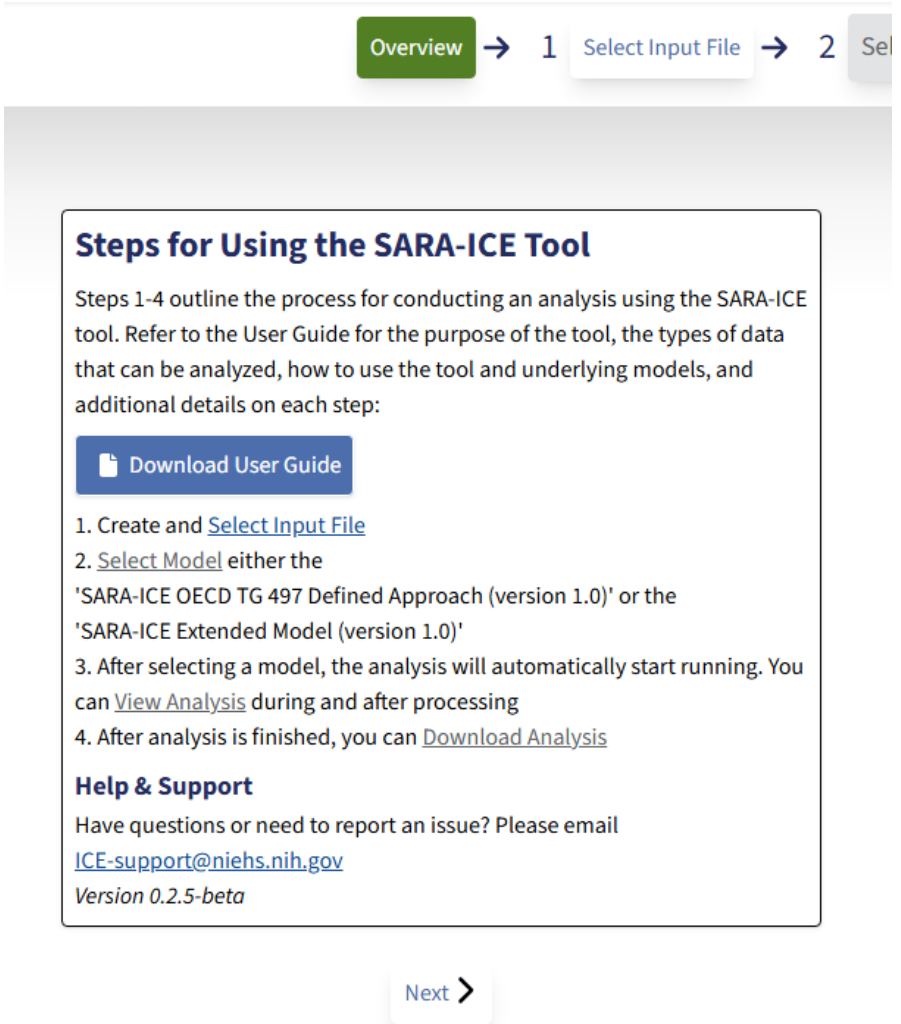
To advance, click “Next” at the bottom of the page or “Select Input File” in the top menu

Resources available on this page:

User Guide (downloadable PDF)

Workflow instructions

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



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

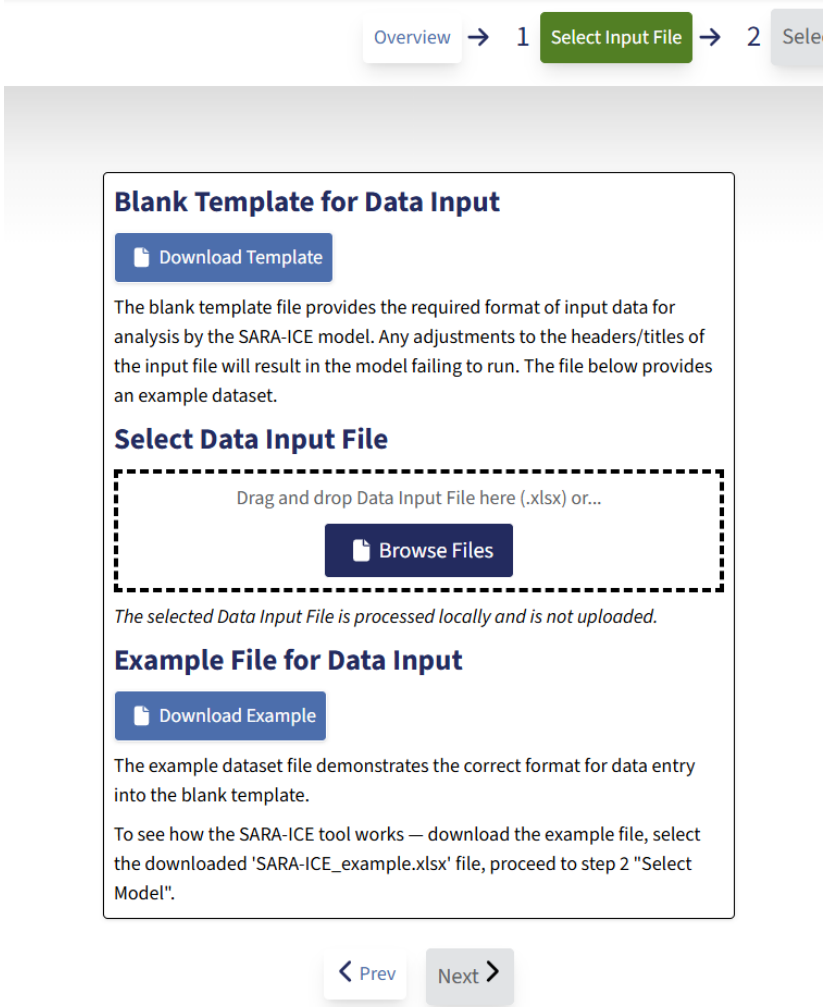
Drag and drop completed data input file or browse to upload file.

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

Resources available on this page:

Blank Template

Example File



Populating the Data Input File

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

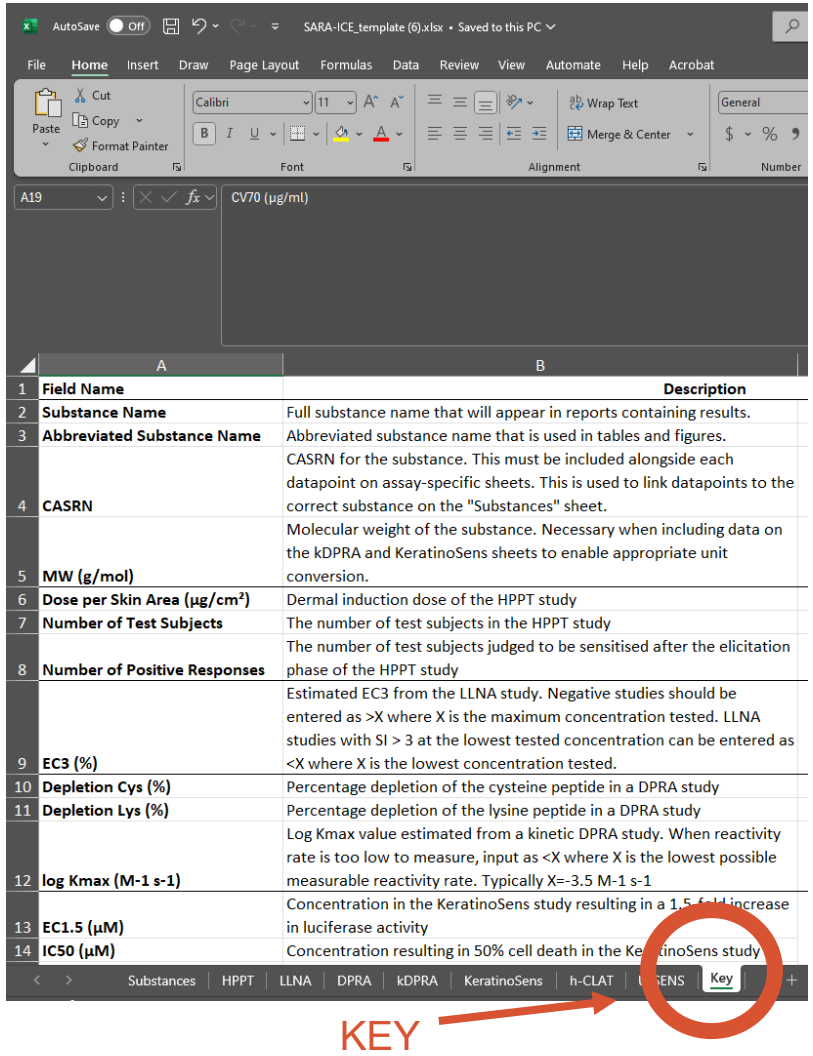
Use the SARA-ICE Example File if unsure how data should be entered.

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.



	A	B
1	**Field Name**	**Description**
2	**Substance Name**	Full substance name that will appear in reports containing results.
3	**Abbreviated Substance Name**	Abbreviated substance name that is used in tables and figures.
4	**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.
5	**MW (g/mol)**	Molecular weight of the substance. Necessary when including data on the kDPRA and KeratinoSens sheets to enable appropriate unit conversion.
6	**Dose per Skin Area (µg/cm²)**	Dermal induction dose of the HPPT study
7	**Number of Test Subjects**	The number of test subjects in the HPPT study
8	**Number of Positive Responses**	The number of test subjects judged to be sensitised after the elicitation phase of the HPPT study
9	**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.
10	**Depletion Cys (%)**	Percentage depletion of the cysteine peptide in a DPRA study
11	**Depletion Lys (%)**	Percentage depletion of the lysine peptide in a DPRA study
12	**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
13	**EC1.5 (µM)**	Concentration in the KeratinoSens study resulting in a 1.5-fold increase in luciferase activity
14	**IC50 (µM)**	Concentration resulting in 50% cell death in the KeratinoSens study

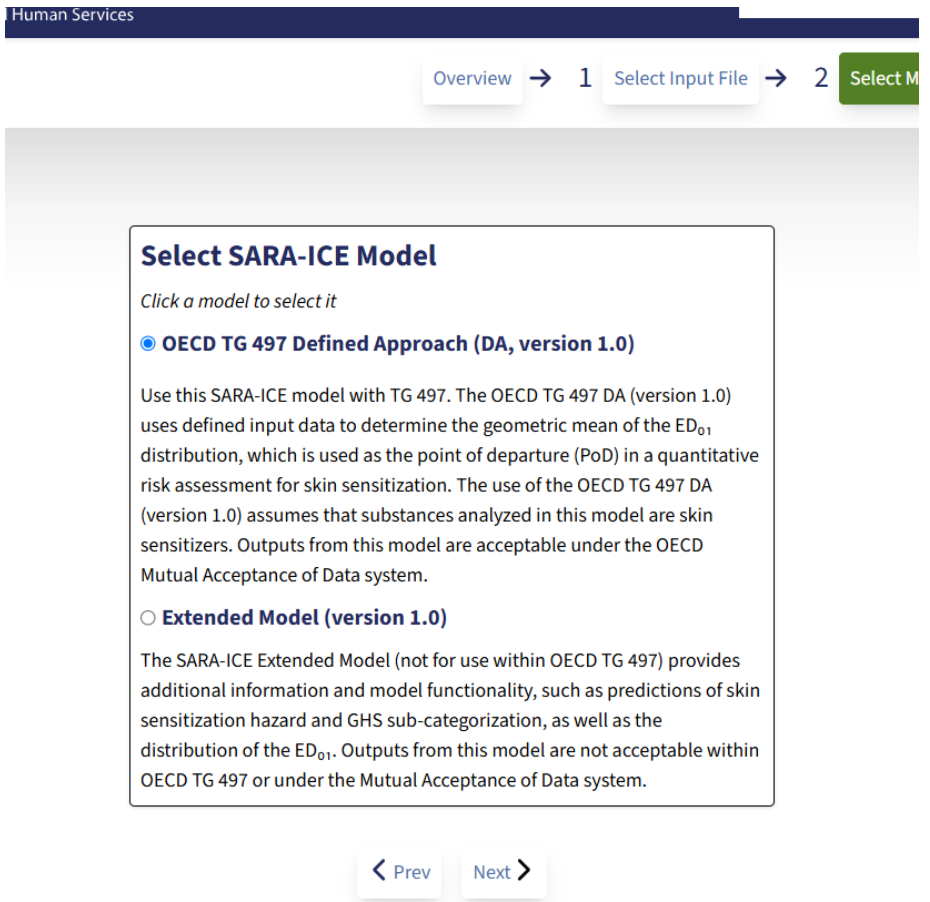
Selecting the correct SARA-ICE model

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.



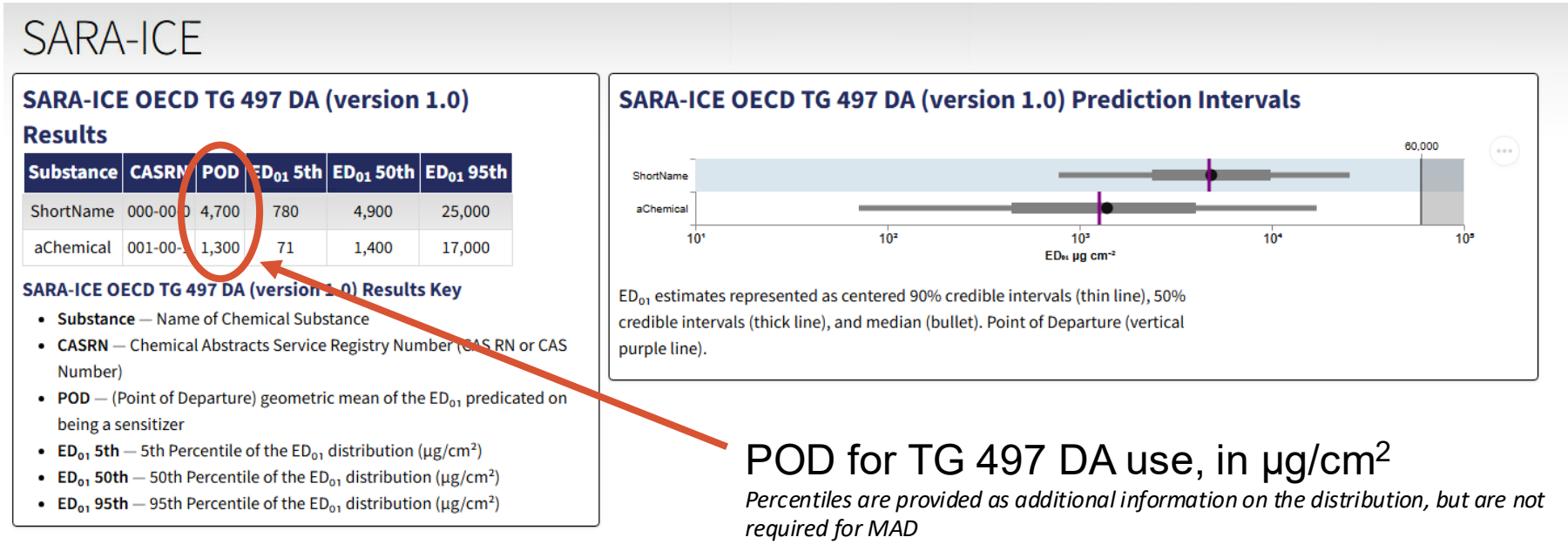
During the analysis phase…

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.

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



POD for TG 497 DA use, in µg/cm^2

Percentiles are provided as additional information on the distribution, but are not required for MAD

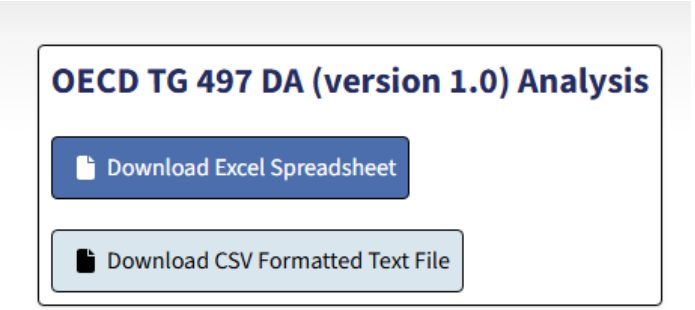
Prev Next

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

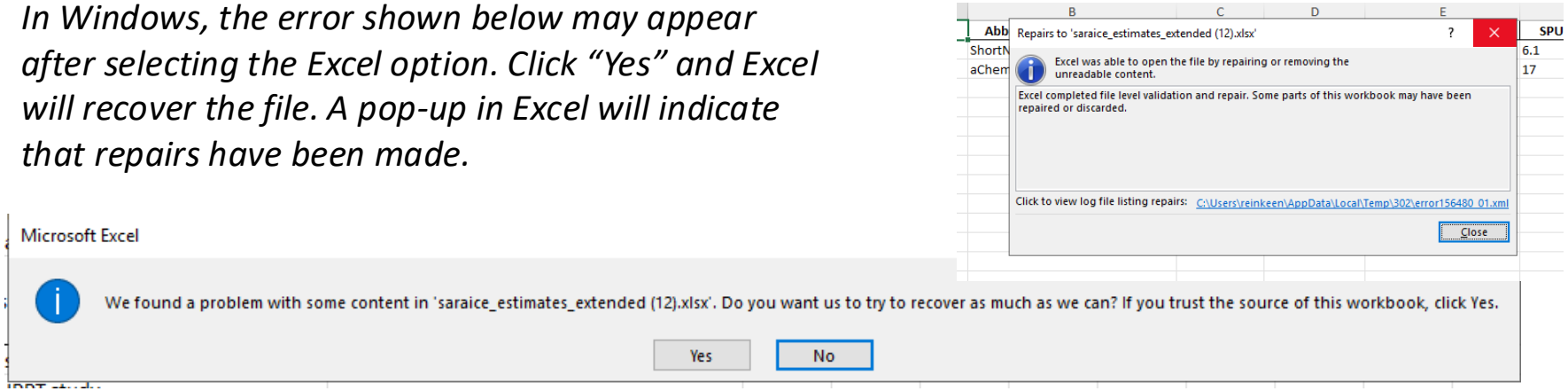
Download your analysis

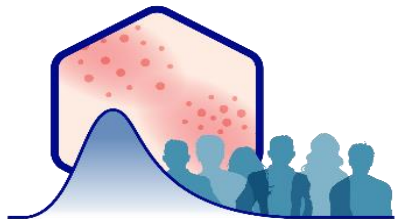
Click Download to download results as either an Excel or .CSV file.

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



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).

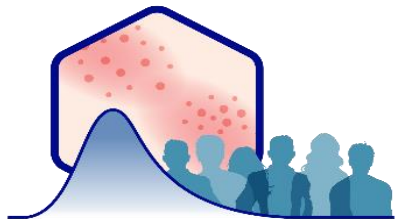
When filling in the input spreadsheet:

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



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Example Case Study: Geraniol

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

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…

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

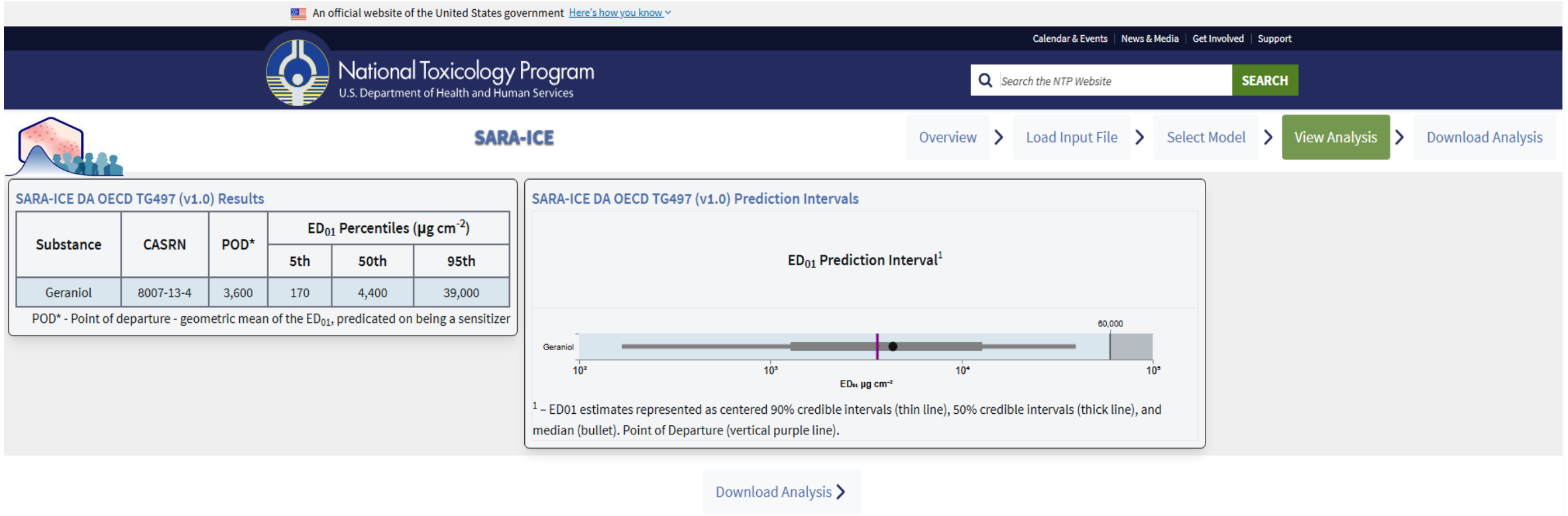
kDPRA
log Kmax (M-1 s-1)
-3.4

KeratinoSens
EC1.5 (uM)
209.8

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

USENS
CD86, EC150 (ug/ml)
53.6

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

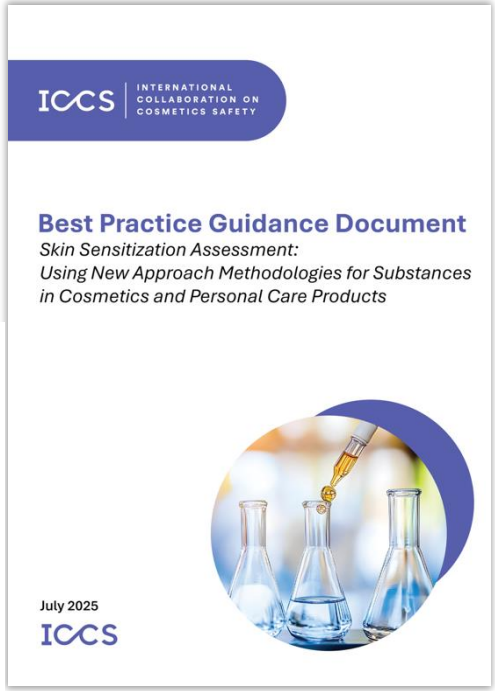


NAM PoD Margin of Exposure (MoE) in Risk Assessment

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

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

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*

Derive NESIL

↓

Derive SAF

↓

NESIL / SAF = AEL

↓

Acceptable risk = AEL / CEL ≥ 1

SARA-ICE DA Risk Assessment

Derive SARA-ICE PoD

↓

Define Acceptable MoE

↓

PoD / acceptable MoE = AEL

↓

Acceptable risk = AEL / CEL ≥ 1
OR
PoD / CEL ≥ acceptable MoE

** e.g. Api et al., 2020*

Example Geraniol Risk Assessment

PoD	Value (µg/cm²)	Acceptable MoE
Quantitative (SARA-ICE)	3600	100

Product and inclusi (%)
Face cream

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

1,000 1,700

Source: Reynolds et al. 2025

36µg/cm² (AEL) / 54.5µg/cm² (CEL) = **0.66**

AEL / CEL = **0.66 is <1** therefore **Inadequate MoE / High Risk**

SARA-ICE Risk Assessment

Derive SARA-ICE PoD

↓

Define Acceptable MoE

↓

PoD / acceptable MoE = AEL

↓

Acceptable risk = AEL / CEL ≥ 1

OR

PoD / CEL ≥ acceptable MoE

AEL = acceptable exposure level
CEL = consumer exposure level

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!