



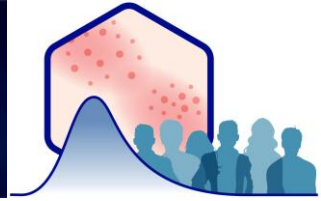
# The SARA-ICE Model for Predicting Skin Sensitizer Potency

Emily N. Reinke<sup>1</sup> and Nicola Gilmour<sup>2</sup>

<sup>1</sup>Inotiv, Inc., in support of National Toxicology Program Interagency Center for the Evaluation of Alternative Test Methods (NICEATM) and <sup>2</sup>Unilever, Safety, Environmental and Regulatory Science

**1<sup>st</sup> July 2025**

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



## Section 1 – SARA-ICE Basics

What is in the database

Input data options

Data output



## Section 2 – Using SARA-ICE

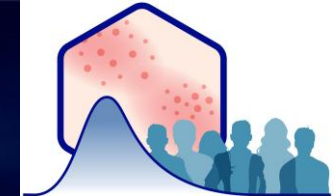
Guideline 497 PoD

Web Platform Walkthrough



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*Division of Translational Toxicology*

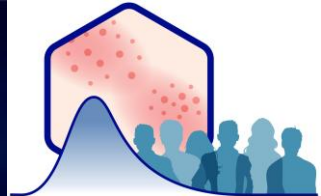
# SARA-ICE Basics



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

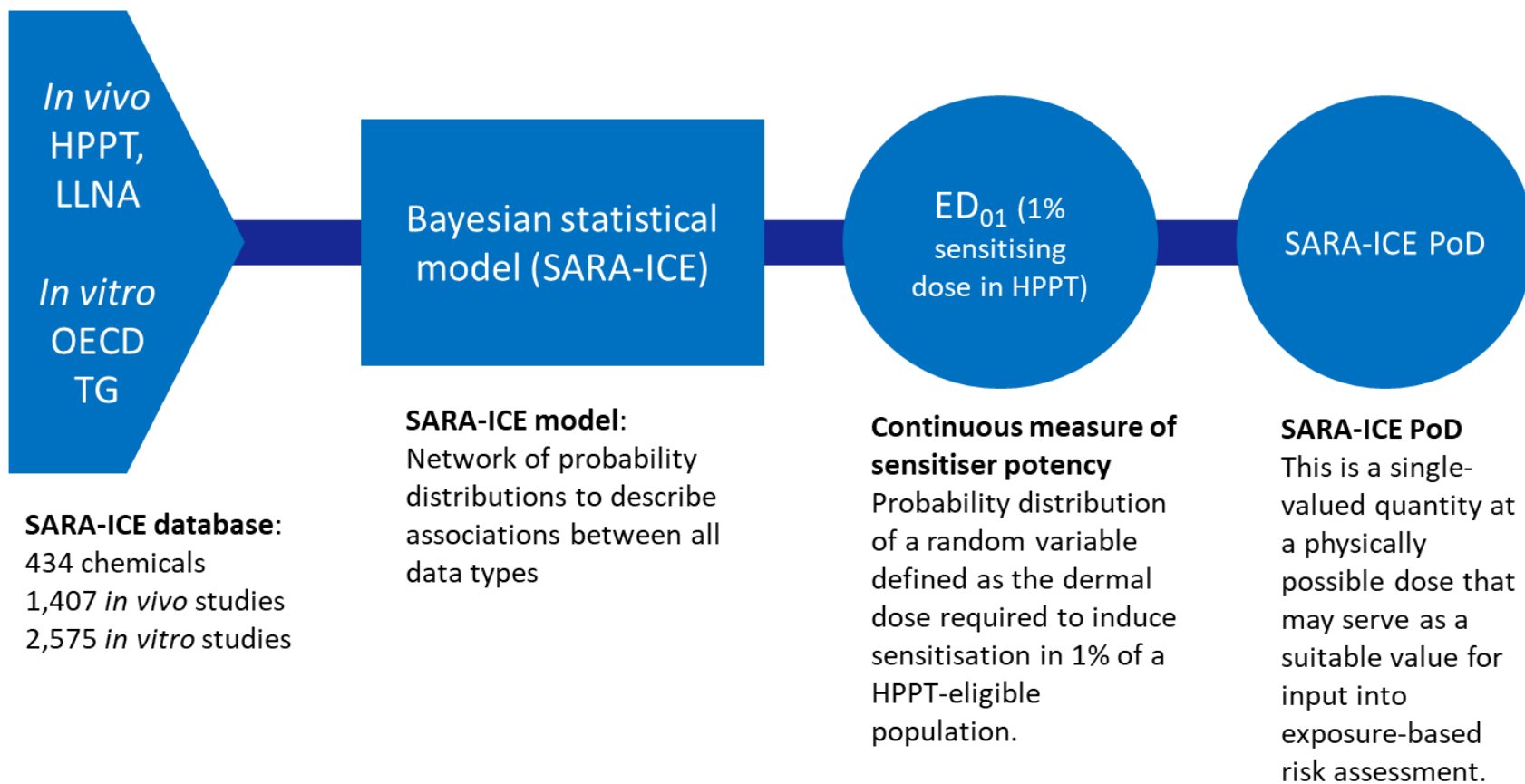
- In 2021, OECD Test Guideline 497 was adopted.
- TG 497 meets regulatory requirements for:
  - DAs that discriminate between sensitizers and non-sensitizers
  - DAs that discriminate strong from weak/moderate sensitizers (i.e., GHS potency categories)
- In 2021, the US and UK began a joint led feasibility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



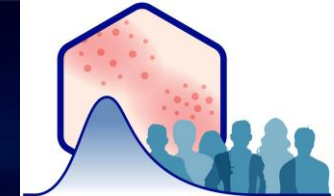


# SARA-ICE DA (OECD TG 497 Version)

## Input



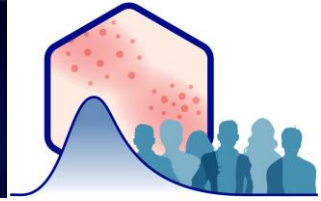




## The SARA-ICE database

Study type	HPPT	LLNA	DPRA	kDPRA	KeratinoSens	h-CLAT	U-Sens
Inputs into SARA-ICE	Dermal dose, number tested, number sensitised	EC <sub>3</sub> or maximum concentration tested if no response observed	% depletion of cysteine and lysine peptides	Log Kmax	EC <sub>1.5</sub> or maximum concentration tested IC50 or maximum concentration tested	CD86 EC <sub>150</sub> , CD50 EC <sub>200</sub> or maximum concentration tested CV <sub>75</sub> or maximum concentration tested	CD86 EC <sub>150</sub> or maximum concentration tested CV <sub>75</sub> or maximum concentration tested
Number of studies in database	871	536	650	361	972	428	164
Number of unique CASRN with this study type	276	195	251	185	258	211	90

434 distinct CASRN

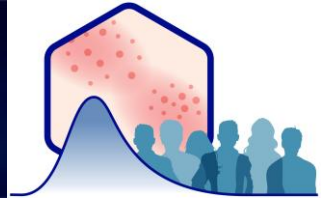


## Data Input Options

Data Type (minimum 1)	Specific Metric(s) Required*	OECD Test Guideline
Human predictive patch test (HPPT)	Dermal dose ( $\mu\text{g}/\text{cm}^2$ ), N test subjects, N test subjects sensitized	N/A
Murine local lymph node assay (LLNA)	EC3 (percent)	<a href="#">TG 429</a>
Direct peptide reactivity assay (DPRA)	Percent depletion (Cys and/or Lys)	<a href="#">TG 442C</a>
Kinetic DPRA (kDPRA)	log kmax (units/M-s)	<a href="#">TG 442C</a>
KeratinoSens™	EC <sub>1.5</sub> and IC <sub>50</sub> ( $\mu\text{M}$ ) Or maximum dose tested	<a href="#">TG 442D</a>
Human cell line activation test (h-CLAT)	EC200 (CD54), EC150 (CD86), CV75 ( $\mu\text{g}/\text{mL}$ ) Or maximum dose tested	<a href="#">TG 442E</a>
U-SENS™	EC150 and CV70 ( $\mu\text{g}/\text{mL}$ ) Or maximum dose tested	<a href="#">TG 442E</a>

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

Predictions can be made on partial data sets, minimum of two data types required



## SARA-ICE DA (OECD TG 497 Version)

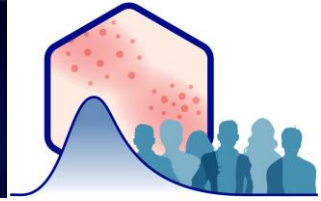
- SARA-ICE estimates a **human-relevant metric** of sensitiser potency defined as the HPPT 1% sensitising dose ( $ED_{01}$ ).
- This model derives the PoD from the  $ED_{01}$  distribution and expresses it as a value in  $\mu\text{g}/\text{cm}^2$  that can be used subsequently for a risk assessment.
  - The PoD is defined as the geometric mean of the distribution.
- Acceptable for use under MAD
- Presumes that the substance under evaluation by the model is a skin sensitizer
  - The range of the  $ED_{01}$  distribution has an upper limit of  $60,000 \mu\text{g}/\text{cm}^2$  (highest dose used in an HPPT).
  - Distribution is centered on the 90% credible interval (interval between the 5th and 95th percentiles of the distribution)





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# Using SARA-ICE




## Access to 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](#) ▾

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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/go/n465041>


**Defined Approaches**


SARA-ICE Model

DASS App: Web App to Predict Skin Sensitization

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

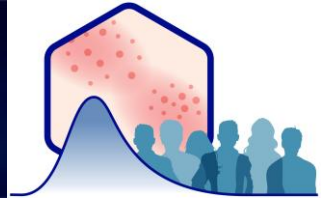
[Access the SARA-ICE Tool](#)

[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](#) ), 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, KeratinoSens™ human cell line activation test, or IL-1Sens™) data.

Click here to  
enter the tool



# General Layout

The screenshot shows the SARA-ICE tool interface. At the top is a dark blue header with the NIH logo and text. Below this is a navigation bar with the National Toxicology Program logo and a search bar. A workflow progress bar shows five steps: Overview (green), 1 Select Input File (white), 2 Select Model (grey), 3 View Analysis (grey), and 4 Download Analysis (grey). The main content area is titled 'SARA-ICE' and contains a 'Steps for Using the SARA-ICE Tool' section with a 'Download User Guide' button and a list of four steps. A 'Next >' button is at the bottom. Annotations include a blue arrow pointing to the 'Select Input File' step in the workflow bar, a blue bracket on the left pointing to the main content area, and a blue arrow pointing to the 'Next >' button.

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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)'
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](mailto:ICE-support@niehs.nih.gov)

Version 0.2.5-beta

[Next >](#)

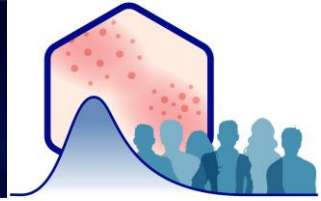
Area where actions for the tool are taken.

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



## Overview Page

- 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](mailto:ICE-support@niehs.nih.gov)

Overview → 1 Select Input File → 2 Sel

### Steps for Using the SARA-ICE Tool

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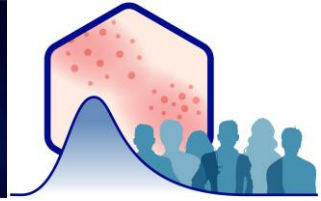
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Version 0.2.5-beta

[Next >](#)



## Select Input File Page

- 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
  - Blank Template
  - Example File - use to demonstrate tool

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

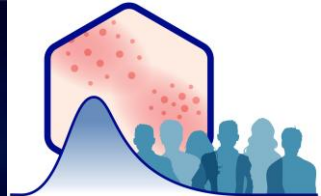
[Download Example](#)

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 >





## Populating the Data Template 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.
- Substance names/ CAS RNs must be manually entered on each tab
- Molecular weight is required if kDPRA or KeratinoSens data are entered.

AutoSave Off SARA-ICE\_template (6).xlsx Saved to this PC

File Home Insert Draw Page Layout Formulas Data Review View Automate Help Acrobat

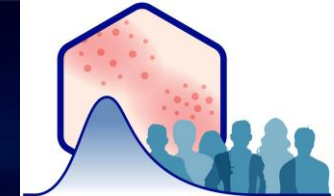
Paste Copy Format Painter Clipboard Font Alignment Number

A19 CV70 (µg/ml)

	A	B
1	<b>Field Name</b>	<b>Description</b>
2	<b>Substance Name</b>	Full substance name that will appear in reports containing results.
3	<b>Abbreviated Substance Name</b>	Abbreviated substance name that is used in tables and figures.
4	<b>CASRN</b>	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	<b>MW (g/mol)</b>	Molecular weight of the substance. Necessary when including data on the kDPRA and KeratinoSens sheets to enable appropriate unit conversion.
6	<b>Dose per Skin Area (µg/cm²)</b>	Dermal induction dose of the HPPT study
7	<b>Number of Test Subjects</b>	The number of test subjects in the HPPT study
8	<b>Number of Positive Responses</b>	The number of test subjects judged to be sensitised after the elicitation phase of the HPPT study
9	<b>EC3 (%)</b>	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	<b>Depletion Cys (%)</b>	Percentage depletion of the cysteine peptide in a DPRA study
11	<b>Depletion Lys (%)</b>	Percentage depletion of the lysine peptide in a DPRA study
12	<b>log Kmax (M-1 s-1)</b>	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	<b>EC1.5 (µM)</b>	Concentration in the KeratinoSens study resulting in a 1.5-fold increase in luciferase activity
14	<b>IC50 (µM)</b>	Concentration resulting in 50% cell death in the KeratinoSens study

Substances HPPT LLNA DPRA kDPRA KeratinoSens h-CLAT U-SENS **Key**

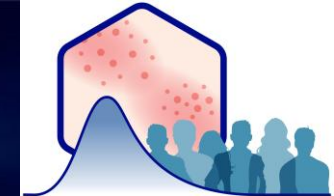




## Data Input Options

Data Type (minimum 1)	Specific Metric(s) Required*	OECD Test Guideline
Human predictive patch test (HPPT)	Dermal dose ( $\mu\text{g}/\text{cm}^2$ ), N test subjects, N test subjects sensitized	N/A
Murine local lymph node assay (LLNA)	EC3 (percent)	<a href="#">TG 429</a>
Direct peptide reactivity assay (DPRA)	Percent depletion (Cys and/or Lys)	<a href="#">TG 442C</a>
Kinetic DPRA (kDPRA)	log kmax (units/M-s)	<a href="#">TG 442C</a>
KeratinoSens™	EC <sub>1.5</sub> and IC <sub>50</sub> ( $\mu\text{M}$ )	<a href="#">TG 442D</a>
Human cell line activation test (h-CLAT)	EC200 (CD54), EC150 (CD86), CV75 ( $\mu\text{g}/\text{mL}$ )	<a href="#">TG 442E</a>
U-SENS™	EC150 and CV70 ( $\mu\text{g}/\text{mL}$ )	<a href="#">TG 442E</a>

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



## Select Model Page

- 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.

Human Services

Overview → 1 Select Input File → 2 Select M

### Select SARA-ICE Model

*Click a model to select it*

☒ **OECD TG 497 Defined Approach (DA, version 1.0)**

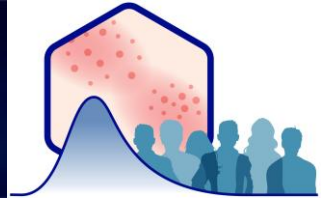
Use this SARA-ICE model with TG 497. The OECD TG 497 DA (version 1.0) uses defined input data to determine the geometric mean of the ED<sub>01</sub> distribution, which is used as the point of departure (PoD) in a quantitative risk assessment for skin sensitization. The use of the OECD TG 497 DA (version 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.

☐ **Extended Model (version 1.0)**

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 ED<sub>01</sub>. Outputs from this model are not acceptable within OECD TG 497 or under the Mutual Acceptance of Data system.

< Prev

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## During the Analysis

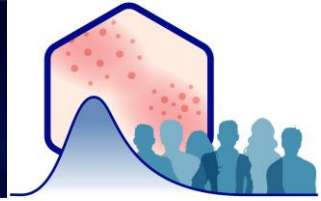
- The tool can only analyze one substance at a time, so it will step through each substance provided sequentially.
- The tool will indicate which substance is under analysis by displaying “Running” next to the substance name.
- Results will auto-populate as they are determined, along with a display of the ED<sub>01</sub> distribution as a graph.

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

#### Results

Substance	CASRN	POD	ED <sub>01</sub> 5th	ED <sub>01</sub> 50th	ED <sub>01</sub> 95th
ShortName	000-00-0	⚙ Running...			
aChemical	001-00-1				

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



## View Analysis – TG 497 DA

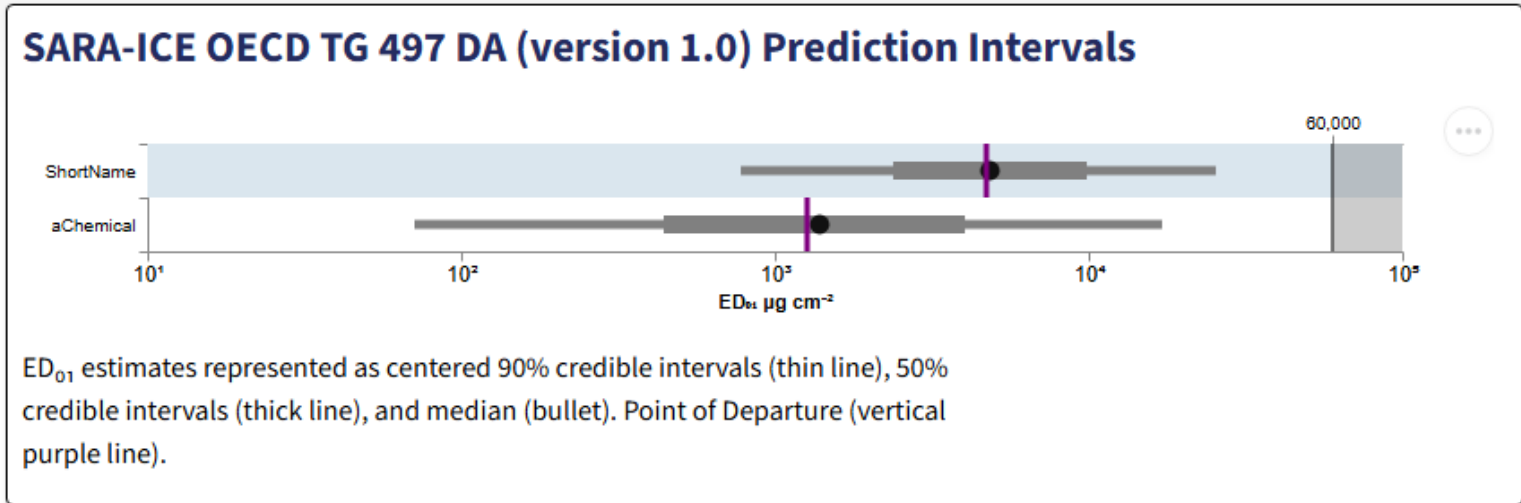
### SARA-ICE

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

Substance	CASRN	POD	ED <sub>01</sub> 5th	ED <sub>01</sub> 50th	ED <sub>01</sub> 95th
ShortName	000-000	4,700	780	4,900	25,000
aChemical	001-001	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 ED<sub>01</sub> predicated on being a sensitizer
- ED<sub>01</sub> 5th** — 5th Percentile of the ED<sub>01</sub> distribution (µg/cm<sup>2</sup>)
- ED<sub>01</sub> 50th** — 50th Percentile of the ED<sub>01</sub> distribution (µg/cm<sup>2</sup>)
- ED<sub>01</sub> 95th** — 95th Percentile of the ED<sub>01</sub> distribution (µg/cm<sup>2</sup>)

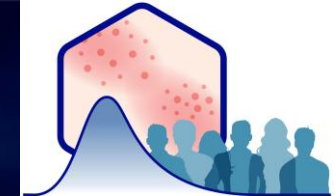


POD for TG 497 DA use, in µg/cm<sup>2</sup>

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.




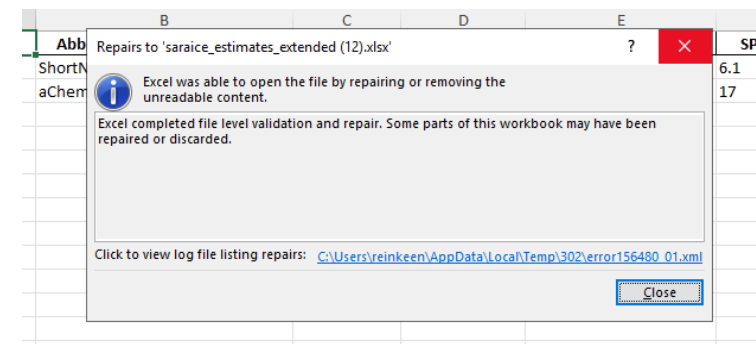
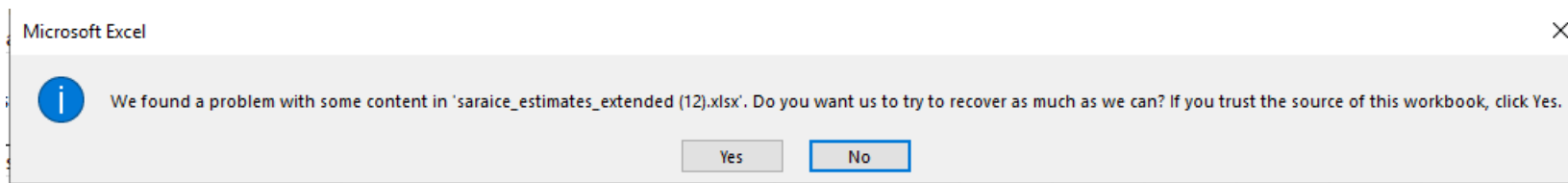
## Download Analysis

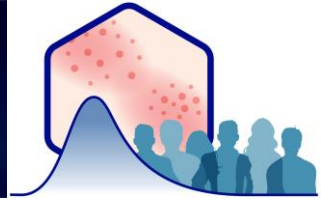
- Click Download to download results as either an Excel or .CSV file.
- Data are populated to the “Substances” tab in the Excel file.
- In Windows, the error shown below may appear after selecting the Excel option. Click “Yes” and Excel will recover the file. A pop-up in Excel will indicate that repairs have been made.

### OECD TG 497 DA (version 1.0) Analysis

 Download Excel Spreadsheet

 Download CSV Formatted Text File





## Resources and Help

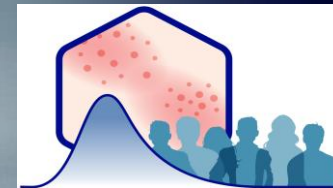
- Email [ICE-support@niehs.nih.gov](mailto:ICE-support@niehs.nih.gov) for assistance.
- SARA-ICE Publication: Reinke et al., 2025: <https://doi.org/10.1016/j.crttox.2024.100205>
- OECD Guideline 497: Defined Approaches on Skin Sensitisation: <https://doi.org/10.1787/b92879a4-en>.





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# Acknowledgments



## The NICEATM Group



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**Integrated  
Chemical  
Environment**



[emily.reinke@inotivco.com](mailto:emily.reinke@inotivco.com)

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