National Institute of Environmental Health Sciences
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DASS App: Web Application to Predict Skin Sensitization Using Defined Approaches

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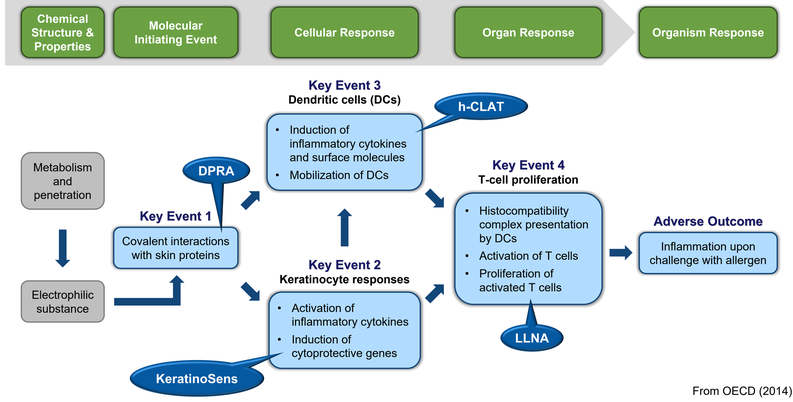
Introduction

- Defined approaches (DAs) combine data from a pre-determined set of information sources via fixed data interpretation procedures to derive toxicity predictions.
- Multiple defined approaches for skin sensitization (DASS) have been internationally accepted by regulatory agencies (OECD 2021) to identify potential skin sensitizers by integrating non-animal test methods that represent key events in the skin sensitization adverse outcome pathway (Figure 1; OECD 2012).
  - **Hazard identification** characterizes a chemical as either a sensitizer or non-sensitizer.
  - **Potency classification** assigns a chemical to a category in an established classification scheme. In this case, classifications are established by the United Nations Globally Harmonized System for Classification and Labelling of Chemicals (GHS) (UN 2021).
- We created the DASS App, an open-source web application that allows users to apply DAs to their own data to derive skin sensitization hazard and potency predictions.
- To support the evaluation of new approach methodologies, the latest DASS App release introduced the ability to derive performance metrics against user-supplied reference data.

Figure 1. Adverse Outcome Pathway for Skin Sensitization

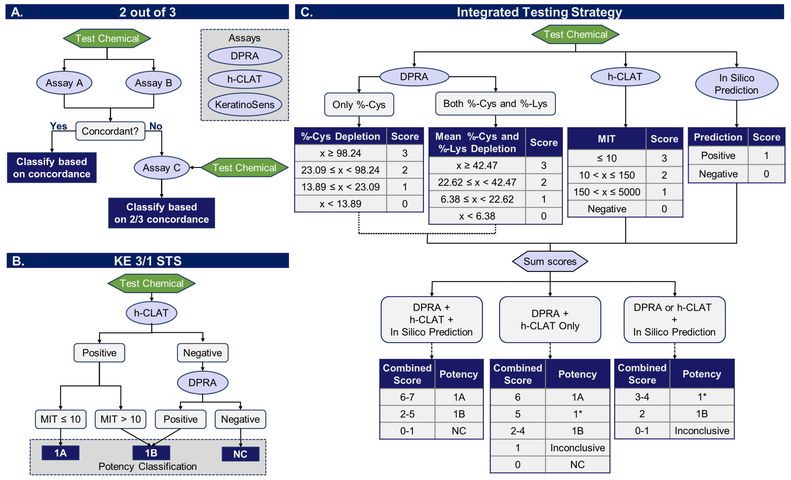
Across the DAs, three unique in vitro information sources are used, each representing a key event (KE) in the skin sensitization adverse outcome pathway:
KE1. Direct Peptide Reactivity Assay (DPRA)
KE2. KeratinoSens Assay
KE3. Human Cell Line Activation Test (h-CLAT)
KE4 can be represented by the in vivo local lymph node assay (LLNA). The LLNA has been used as a reference endpoint for evaluating the predictive performance of DASS.



From OECD (2014)

Figure 2. Defined Approach Data Interpretation Procedures

- Two DAs from Guideline 497 of the Organisation for Economic Co-operation and Development (OECD 2021) are available in the DASS App:
  - The 2 out of 3 (2o3) DA predicts skin sensitization hazard (not potency) using the majority outcome among the DPRA, h-CLAT, and KeratinoSens assays (Fig. 2A). The 2o3 DA is also accepted by the U.S. Environmental Protection Agency (EPA) for hazard prediction.
  - The Integrated Testing Strategy (ITS) DA predicts skin sensitization hazard and potency by scoring results from the DPRA and h-CLAT as well as in silico predictions (Fig. 2C). ITS version 1 uses in silico predictions from Derek Nexus. ITS version 2 uses in silico predictions from the OECD QSAR Toolbox. ITS includes multiple scoring schemes to derive predictions when data are available from only two of the information sources.
- The DASS App also includes a DA that has been accepted by EPA for predicting hazard (EPA 2018):
  - The Key Event 3/1 Sequential Testing Strategy (KE 3/1 STS) DA (Nukada 2013, Takenouchi 2015) predicts skin sensitization hazard and potency by first evaluating results from the h-CLAT and then evaluating results from the DPRA if the h-CLAT result is negative (Fig. 2B). EPA accepts results from the KE 3/1 STS only for hazard classification, but the DASS App also provides potency classification predictions.



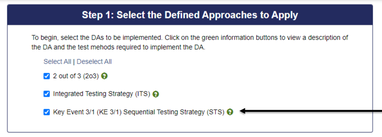
MIT: minimum induction threshold; Cys: cysteine; Lys: lysine; 1A: strong sensitizer; 1B: weak sensitizer; NC: not classified; 1*: sensitizer, inconclusive for potency

The DASS App

- The DASS App enables users to apply the KE 3/1 STS DA, the 2o3 DA, and both versions of the ITS DA to their own data.
- The web application supports upload and analysis of user-provided data, includes steps to identify inconsistencies and formatting issues, and provides hazard and potency predictions in a downloadable format.
- The DASS App can be accessed from anywhere via the web with no account creation required. No data are retained by the app.
- The DASS App was developed using the R Shiny package. Code, including functions for applying the DAs, is available online.

Access the DASS App
https://ntp.niehs.nih.gov/go/952311

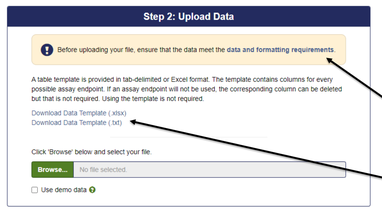
Step 1: Select DAs



- The DASS App is organized into step-by-step modules.
- In the first step, the user selects the defined approaches to be applied.

Information buttons display pop-ups with details about the DAs and links to relevant documentation.

Step 2: Upload Data



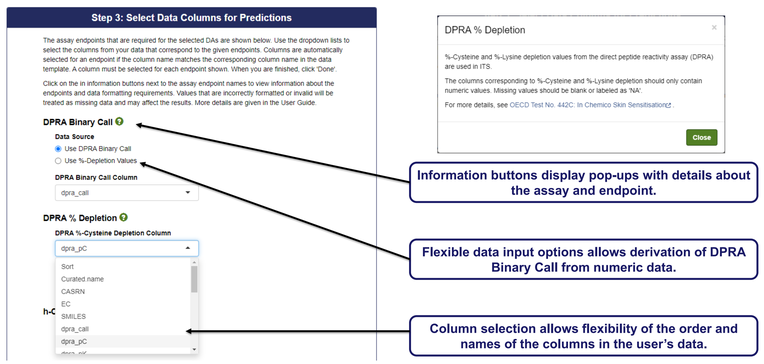
- In the second step, the user uploads their data.
- Three file formats are accepted:
  1. Tab-delimited
  2. Comma-delimited
  3. Excel workbook

The app provides detailed guidance to assist users with data preparation.

Optional data templates can be used. Templates can be customized with additional metadata columns at the user's discretion.

Step 3: Select Data Inputs

- The app evaluates the DA selections and populates the Step 3 module with the required endpoints and dropdown selection lists.
- In the third step, the user specifies the columns in their data corresponding to the required endpoint data.

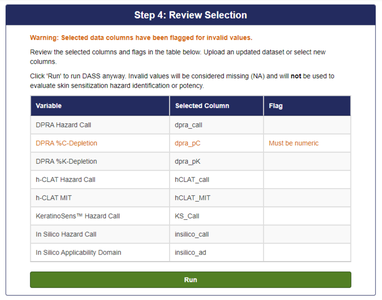


Information buttons display pop-ups with details about the assay and endpoint.

Flexible data input options allows derivation of DPRA Binary Call from numeric data.

Column selection allows flexibility of the order and names of the columns in the user's data.

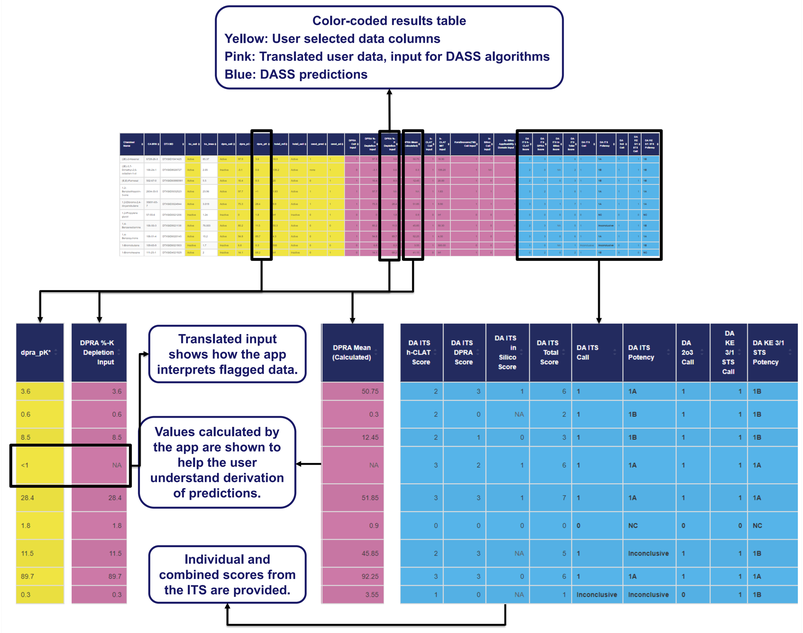
Step 4: Review Selection



- The app evaluates the values in the user-selected columns against the data and formatting requirements and flags any columns that have invalid values.
- In the fourth step, the user reviews their column selections.
- The user may choose to derive predictions with flagged data, in which case invalid values are treated as missing data.

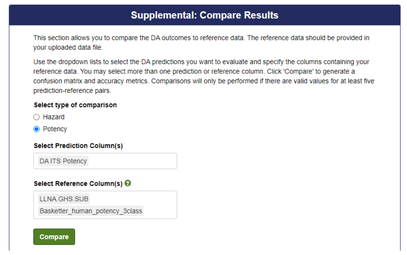
Step 5: View Results

- In the final step, the user is shown a results table that can be downloaded as a tab-delimited or Excel file.
- The results table contains the user's data with DA predictions appended, along with columns that help the user to understand their results.



Performance Metrics

- To support the evaluation of new approach methodologies, the latest DASS App release introduced a supplemental module for deriving performance metrics.
- Performance metrics can be derived for DA call and potency predictions against user-uploaded reference data.
- Results can be downloaded as a PDF.



Confusion Matrix and Performance Metrics

Reference Column: Basketter_human_potency_3class

Prediction Column: DA ITS Potency

		Reference		
		1A	1B	NC
Predicted	1A	18	6	0
	1B	5	33	6
	NC	0	2	19
	Inconclusive	2	2	3

Metric	Value
N	96
Accuracy	79%
Overpredicted	13%
Underpredicted	8%

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Acknowledgments and More Information

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