

Web Application to Predict Skin Sensitization Using Defined Approaches

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Introduction/Summary

- 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 2014).
 - 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 of Classification and Labelling of Chemicals (GHS) (UN 2023).
- 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.
 - The DASS App can be accessed from anywhere via the web with no account creation required.
 - User support resources include context-appropriate pop-up boxes and a downloadable user guide.

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

Figure 1. Adverse Outcome Pathway for Skin Sensitization

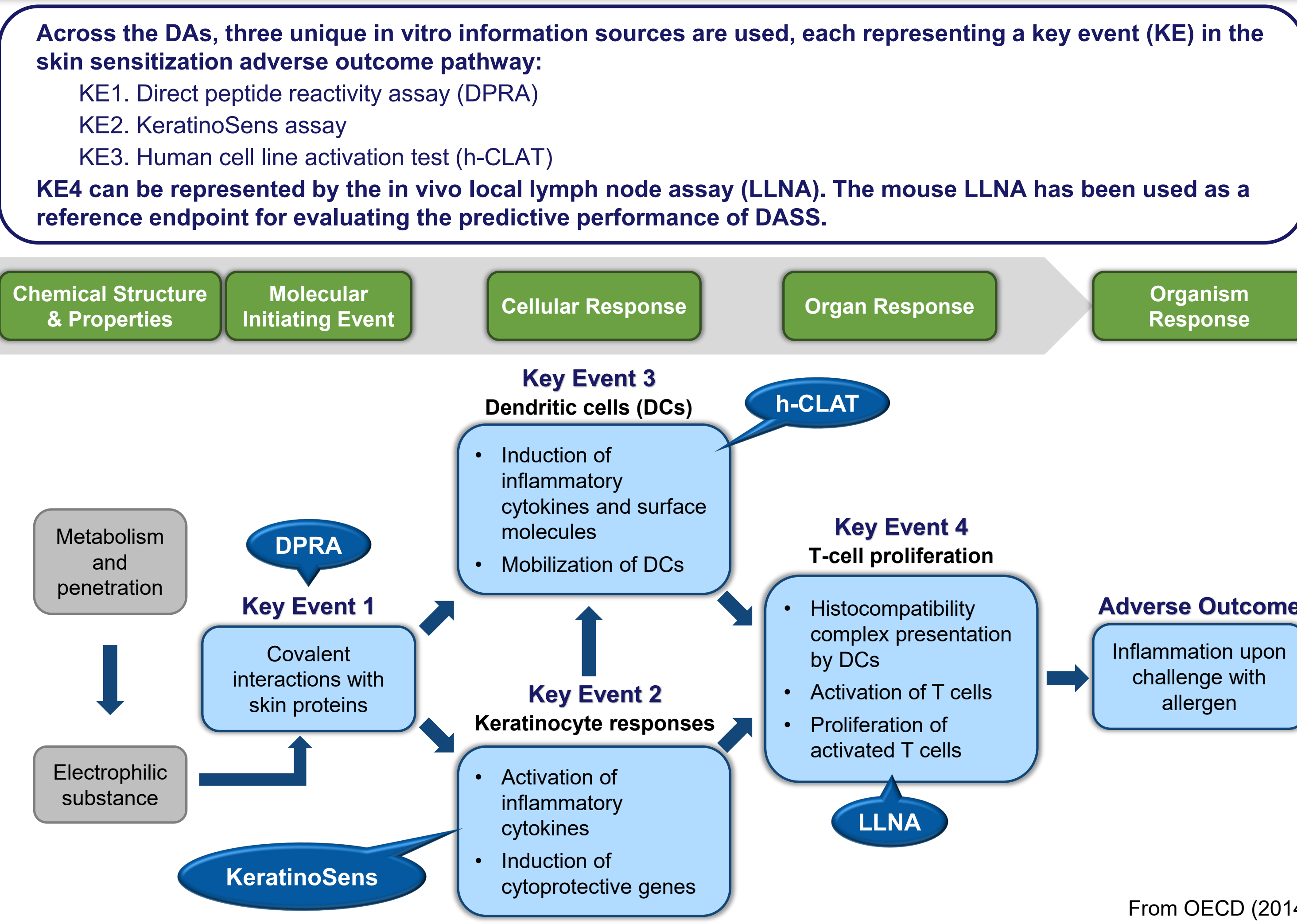
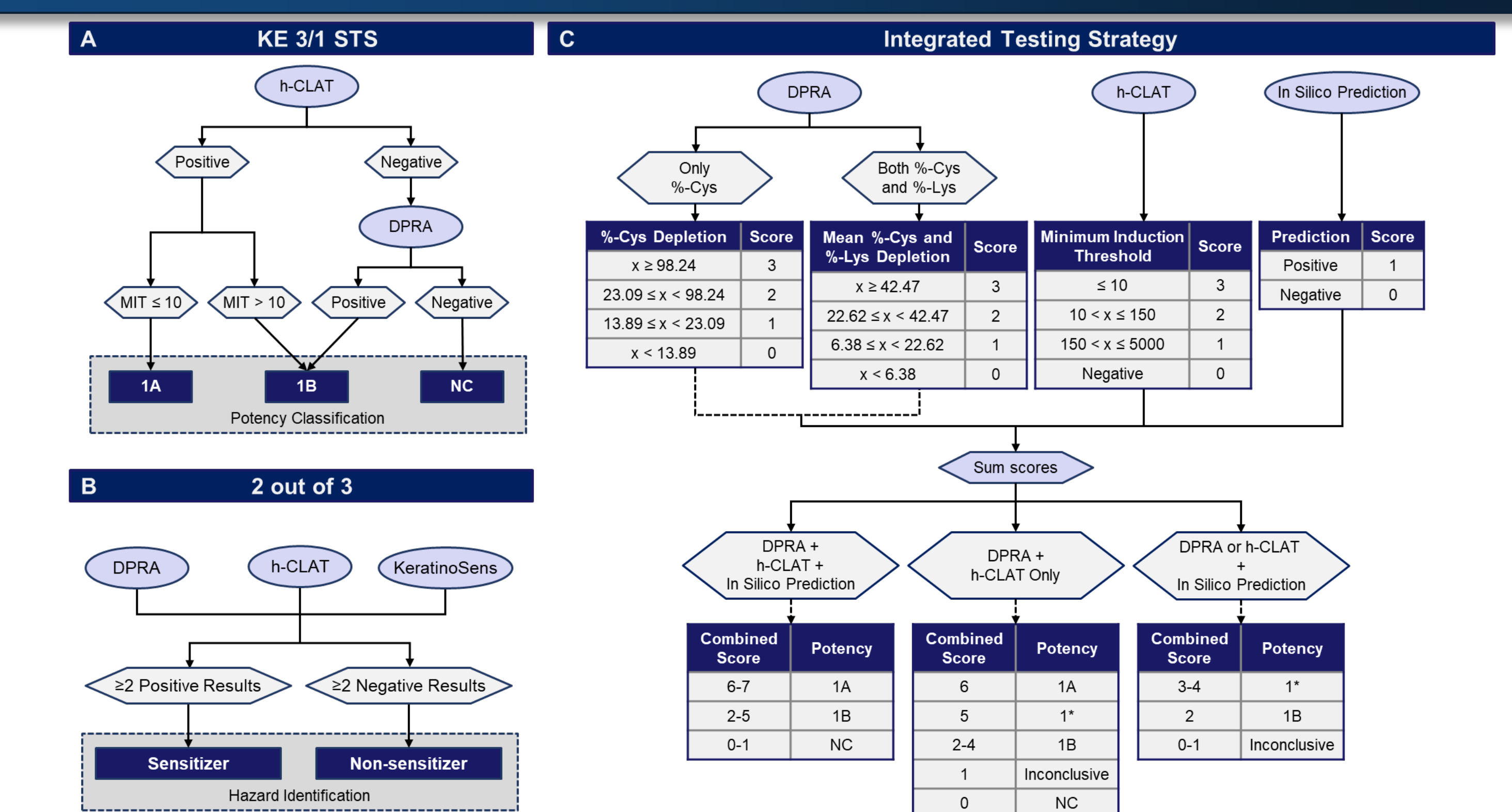


Figure 2. Defined Approach Data Interpretation Procedures



- Potency categories are based on the GHS: 1A: strong sensitizer, 1B: weak sensitizer; NC: not classified (non-sensitizer). 1* indicates a conclusive sensitizer hazard prediction and an inconclusive potency prediction.
- The DASS App includes a DA that has been accepted by the U.S. Environmental Protection Agency (EPA) for hazard classification (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. 2A). EPA accepts results from the KE 3/1 STS only for hazard classification, but the DASS App also provides potency classification predictions.
- Two DAs from Guideline 497 of the Organisation for Economic Co-operation and Development (OECD 2021) are also 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. 2B). The 2o3 DA is also accepted by the EPA for hazard classification.
 - 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 includes multiple scoring schemes to derive predictions when data are available from only two of the information sources.

Acknowledgments

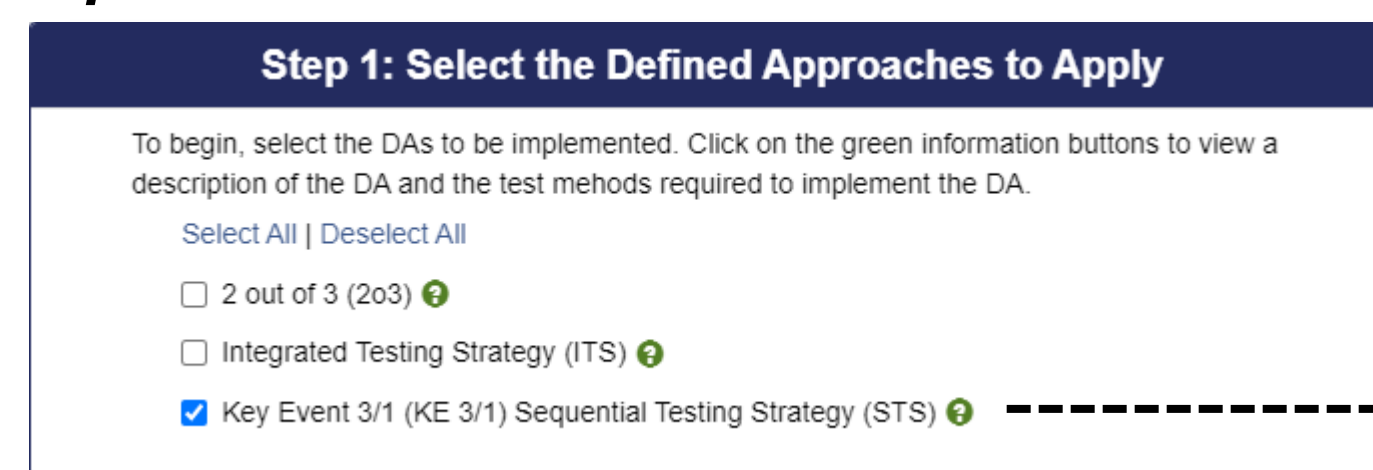
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Using the DASS App

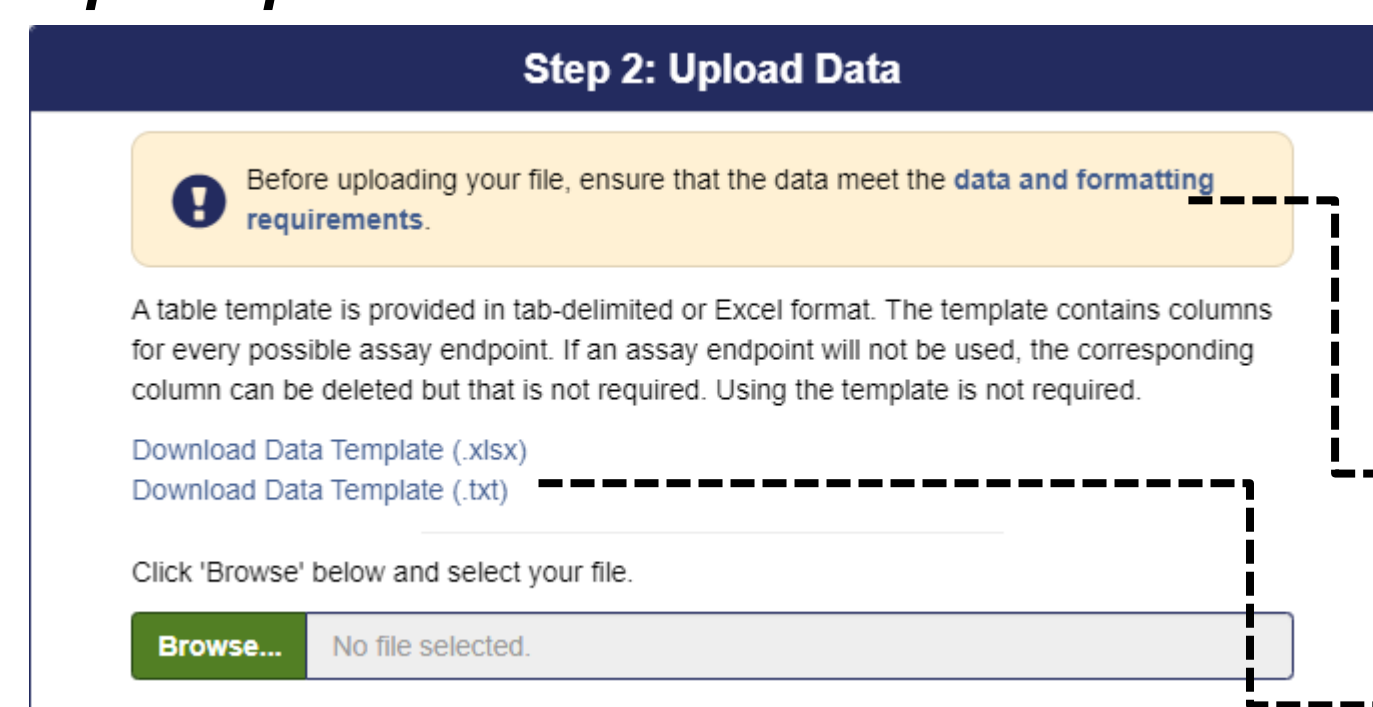
Step 1: Select DAs



- 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

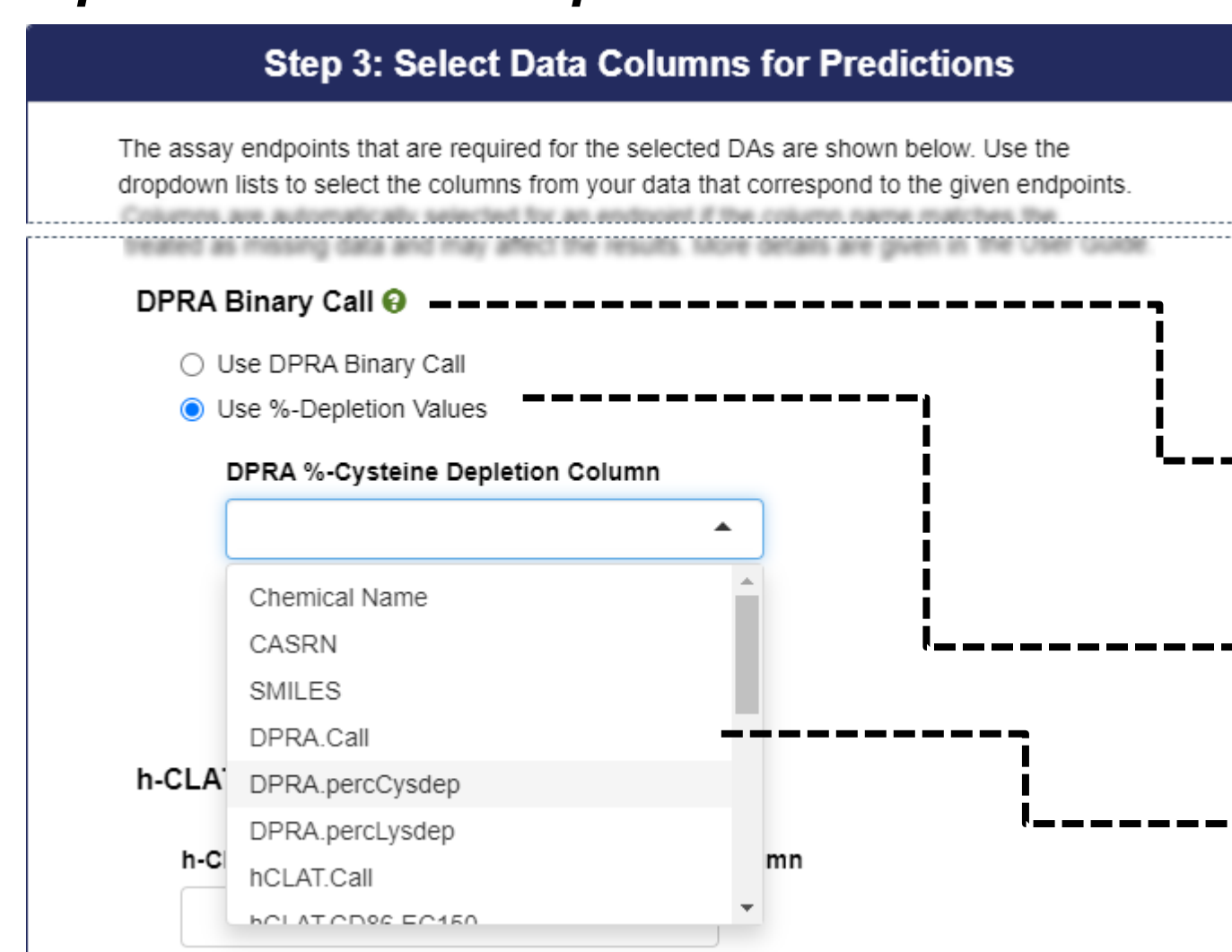


- In the second step, the user uploads their data.
- Three file formats are accepted:
 - Tab-delimited
 - Comma-delimited
 - Excel workbook

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



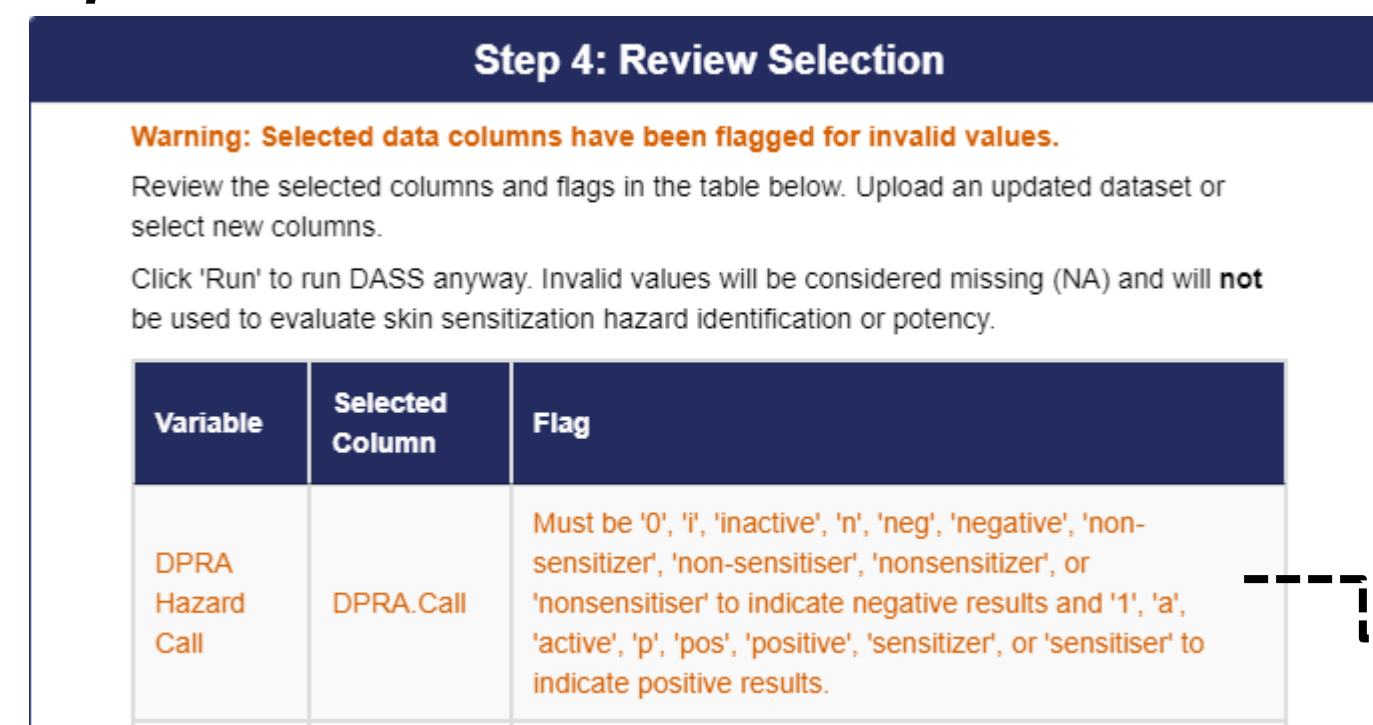
- The app evaluates the DA selections and populates the Step 3 module with the required endpoints and dropdown selection lists.
- In the third step, the user specifies the columns in their data corresponding to the required endpoint data.

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 Selections



- 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.

Broad set of accepted terms for binary outcomes reduces data preparation needs for the user.

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.

CASRN	dpra_call*	hclat_mit*	DPRA Call Input	h-CLAT MIT Input	DA KE 3/1 STS Call	DA KE 3/1 STS Potency
6728-26-3	Active	18.9	1	18.90	1	1B
2634-33-5	Active	1.83	1	1.83	1	1A
57-55-6	Inactive	Negative	0	Inf	0	NC
101-86-0	Inactive	Negative	0	Inf	0	NC
431-03-8	Active	94	1	94.00	1	1B
5910-85-0	Active	6.9	1	6.90	1	1A
615-50-9	Active	116	1	116.00	1	1B
637-07-0	Inactive	< 1000.0	0	NA	NA	NA
97-90-5	Active	563.6	1	563.60	1	1B

Inf, infinity, numeric value to indicate a negative outcome; MIT, minimum induction threshold; NA, not applicable, indicates missing or invalid values.

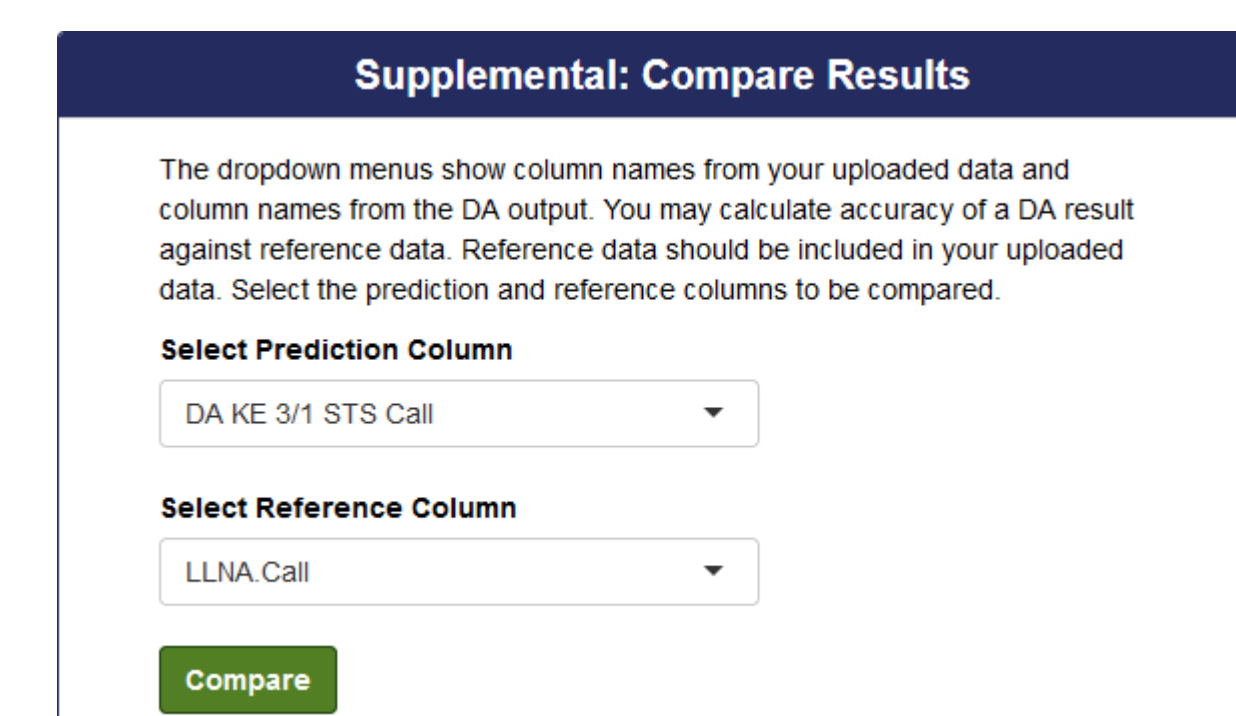
Yellow columns indicate the user selected data.

Pink columns indicate how the app interprets user data.

Blue columns contain the DA results.

Supplemental Module: Performance Metrics

- To support the evaluation of new approach methodologies, a new module is under development and will enable users to derive performance metrics against their own reference data or results from another DA.



Predicted	Reference	
	Positive	Negative
Positive	123	14
Negative	11	19

Metric	Value
N	167
Accuracy	85%
Balanced Accuracy	75%
F1 Score	91%
True Positive Rate	92%
False Positive Rate	42%
True Negative Rate	58%
False Negative Rate	8%

References

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