National Institute of Environmental Health Sciences
Division of Translational Toxicology

DASS App v2.0: Implementing OECD Guideline No. 497 Updates

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Background

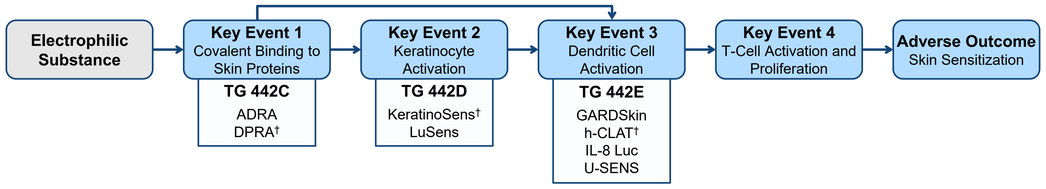
- The National Toxicology Program's DASS App (https://ntp.niehs.nih.gov/go/40498) is an open-source web application for users to apply defined approaches (DA) for skin sensitization (DASS) to their own data.
- A DA consists of a defined set of information sources (e.g., in silico predictions, in chemico, or in vitro data) used in a fixed data interpretation procedure (e.g., a mathematical model or rule-based approach) to provide predictions without the need for expert judgment.
- **Figure 1** shows the adverse outcome pathway (AOP) for skin sensitization initiated by covalent binding to proteins (OECD 2014) and assays that address the first three key events (KEs) in the AOP. The Organisation for Economic Co-operation and Development (OECD) published Test Guideline No. 497 (TG 497; OECD 2023) describing two DAs that use input data from these assays and in silico skin sensitization models.
- The DASS App implements two DAs from TG 497:
  - The Integrated Testing Strategy (ITS) DA scores results from a KE1 assay, KE3 assay, and an in silico model to generate skin sensitization hazard (sensitizer vs. non-sensitizer) and potency predictions.
  - The 2 out of 3 (2o3) DA predicts skin sensitization hazard using the majority outcome among a set of KE1, KE2, and KE3 assays.
- The ITS and 2o3 DAs were initially evaluated for TG 497 using a specific set of assays or in silico models. Additional assays and models that have a similar mechanistic basis and applicability domain are being evaluated for inclusion in TG 497.
- DASS App v2.0 introduces new features that align with pending updates to TG 497, ensuring the relevance of the web application as well as continued democratization of accepted new approach methodologies.

The latest update to the DASS App (v2.0) includes:

- Additional assay and model options for the ITS and 2o3 DAs.
- Evaluation of borderline results from assay run data for use in the 2o3 DA.
- Reference data from the Integrated Chemical Environment (ICE) for comparison with user's results.
- Interactive visualizations of user uploaded quantitative data to contextualize results.
- Newly designed graphical user interface.

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

Figure 1. Skin Sensitization AOP and Assays Included in DASS App v2.0



KE-based OECD TG (442C, D, and E) include the assays listed in the boxes under KEs 1-3, respectively.
Abbreviations: ADRA = amino acid derivative reactivity assay; DPRA = direct peptide reactivity assay; GARDskin = genomic allergen rapid detection skin assay; h-CLAT = human cell-line activation test; IL-8 Luc = interleukin-8 reporter gene assay; U-SENS = U937 Cell Line Activation Test.
†Assays included in the current DASS TG 497.

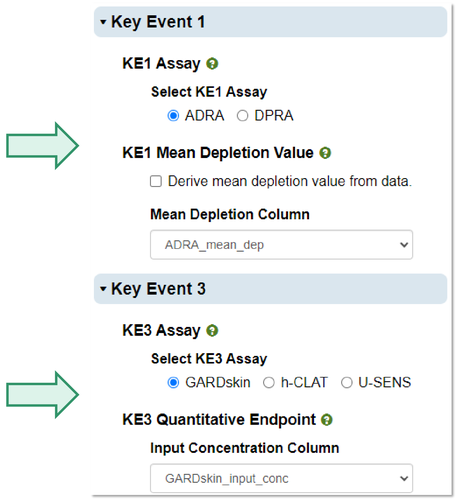
New Assay Options for the ITS

Previously limited to DPRA and h-CLAT, users can now apply the ITS using data from ADRA, GARDskin, and U-SENS.

	KE1 Assay			
	ADRA		DPRA	
Score	Mean NAC & NAL Depletion (%)	NAC Depletion (%)	Mean Cys & Lys Depletion (%)	Cys Depletion (%)
3	x ≥ 46.4	x ≥ 67.4	x ≥ 42.47	x ≥ 98.24
2	15.5 ≤ x < 46.4	17.5 ≤ x < 67.4	22.62 ≤ x < 42.47	23.09 ≤ x < 98.24
1	4.9 ≤ x < 15.5	5.6 ≤ x < 17.5	6.38 ≤ x < 22.62	13.89 ≤ x <23.09
0	x < 4.9	x < 5.6	x < 6.38	x < 13.89

NAC = N-acetyl cysteine; NAL = N-acetyl lysine

	KE3 Assay		
	GARDskin	h-CLAT	U-SENS
Score	Input Conc (µM)	MIT (µg/mL)	EC150 (µg/mL)
3	x ≤ 13.03	x ≤ 10	x ≤ 3
2	13.03 < x ≤ 56.44	10 < x ≤ 150	3 < x ≤ 35
1	x > 56.44	150 < x ≤ 5000	35 < x <200
0	Negative	Negative	Negative



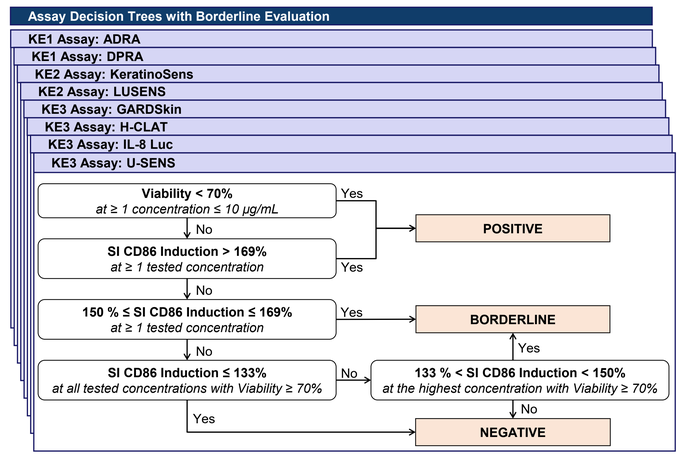
Downloadable results include individual scores and a summary of user selections.

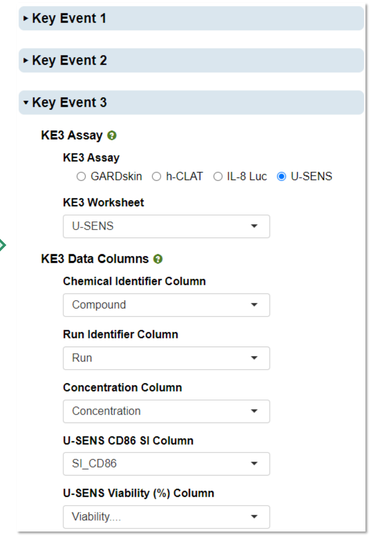
ITS.ke1_score	ITS.ke3_score	ITS.insil_score	ITS.total_score	ITS.hazard	ITS.potency
3	1	1	5	Positive	1B
0	NA	0	0	Inconclusive	Inconclusive
NA	NA	1	1	NA	NA
2	NA	1	3	Positive	Inconclusive
1	NA	0	1	Inconclusive	Inconclusive
0	0	1	1	Negative	NC
3	3	1	7	Positive	1A
0	NA	1	1	Inconclusive	Inconclusive
3	3	1	7	Positive	1A
1	2	1	4	Positive	1B
0	2	1	3	Positive	1B
1	1	1	3	Positive	1B
0	NA	1	1	Inconclusive	Inconclusive

Required Endpoint	Selection	Flagged
DA	ITS	
KE1 Assay	ADRA	
KE3 Assay	GARDskin	
KE1 Mean Depletion	ADRA_mean_dep	FALSE
KE3 Quantiative Value	GARDskin_input_conc	FALSE
In Silico Call	Derek_prediction	FALSE
In Silico Applicability Domain	Derek_ad	FALSE

New Assay Options and Borderline Evaluation for the 2o3

Users can now apply assay-specific decision trees to identify results within borderline range of the assay decision thresholds.





2o3 Results

Show 10 entries

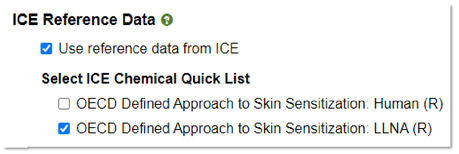
Compound ID	DPRA	KeratinoSens	U-SENS	DA 2o3 Hazard
All	All	All	All	All
A	Positive	Positive	Positive	Positive
B	Borderline	Negative	Borderline	Borderline
C	Borderline	Borderline	Negative	Borderline
D	Negative	Negative	Positive	Negative
E	Inconclusive	Positive	Borderline	Inconclusive

The results of the borderline evaluation are used to generate 2o3 hazard predictions.

Downloadable results include individual and overall borderline evaluation outcomes, 2o3 hazard predictions, and a summary of user selections.

New Features for Evaluating Performance

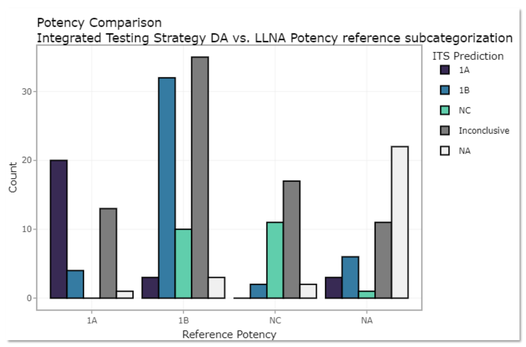
DA results can be compared to harmonized reference chemical lists from OECD, available on ICE.



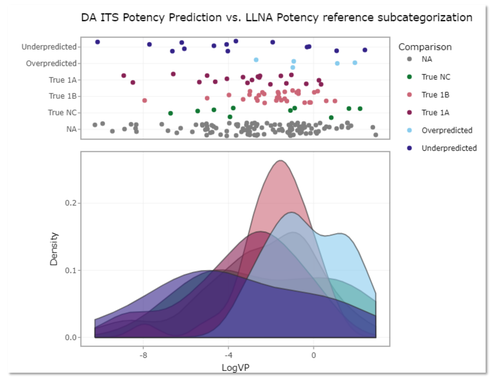
Confusion Matrix and Performance Metrics
Reference Column: LLNA Potency reference subcategorization
Prediction Column: Potency

		Reference		
		1A	1B	NC
Predicted	1A	20	3	0
	1B	4	32	2
	NC	0	10	11
	Inconclusive	13	35	17

Bar charts provide a visual summary of the comparison.



Users can upload quantitative data, such as physicochemical property data, to contextualize DA performance with interactive visualizations.



References

OECD 2014. Guidance Document No. 168. https://doi.org/10.1787/9789264221444-en.
OECD 2023. Guideline No. 497: Defined Approaches on Skin Sensitisation. https://doi.org/10.1787/b92879a4-en.

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