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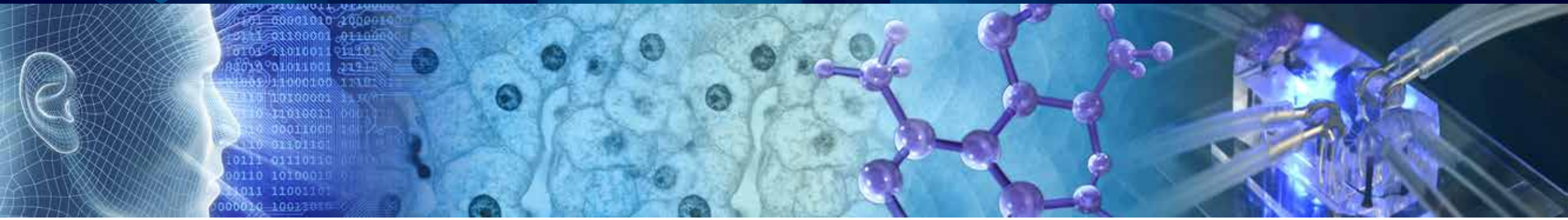


The DASS App: A Web Application to Predict Skin Sensitization Using Defined Approaches

2023 Scientific Advisory Committee on Alternative Toxicological Methods Meeting
2023-09-22

Presented by Kim To, Inotiv, contractor supporting NICEATM

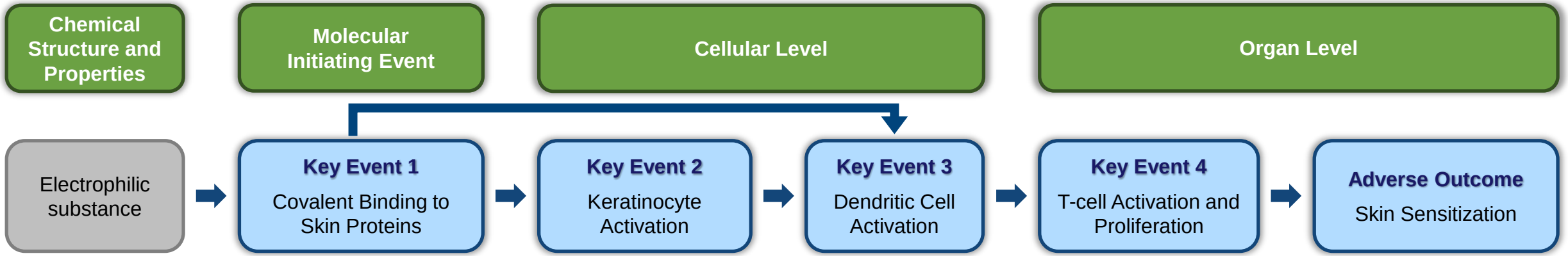
Disclaimer: Inotiv staff provide technical support for NICEATM,
but do not represent NIEHS, NTP, DTT, or the official positions of any federal agency.

Skin Sensitization

- Up to 20% of the population suffer from skin sensitization reactions[1].
- Regulatory frameworks, e.g., REACH, ask for information on predicting skin sensitization potential in **humans**.
- Opportunity: implement superior approaches based on an understanding of human biology and the adverse outcome pathway (AOP).

Adverse Outcome Pathway for Skin Sensitization

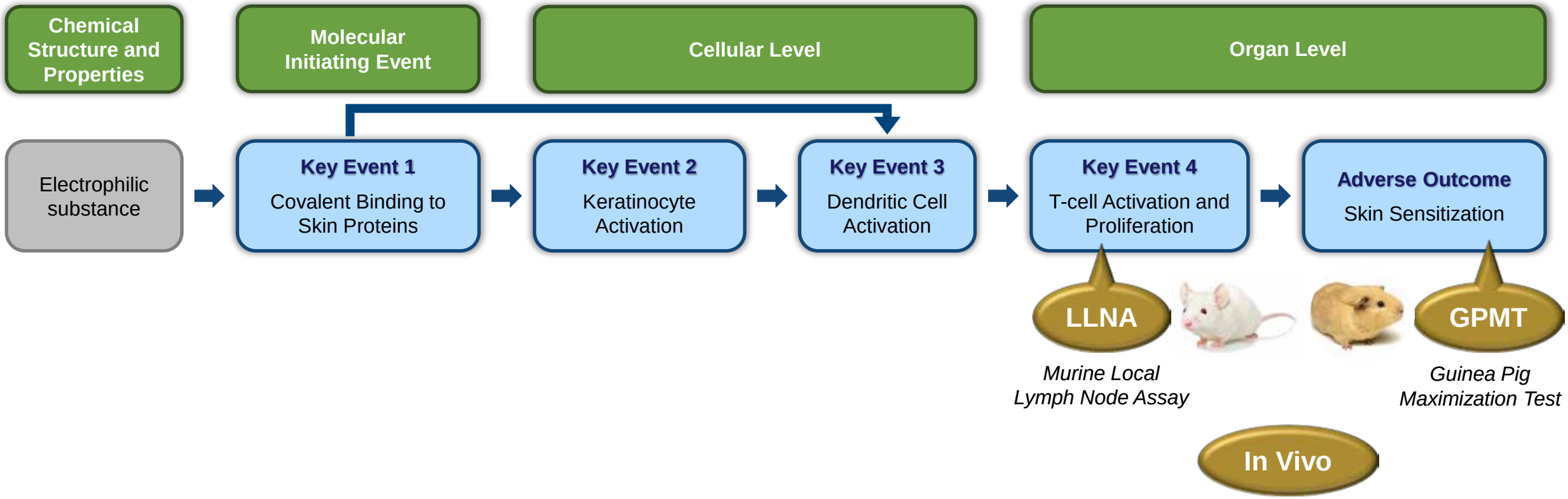
For sensitization initiated by covalent binding to proteins



AOP Wiki. AOP 40

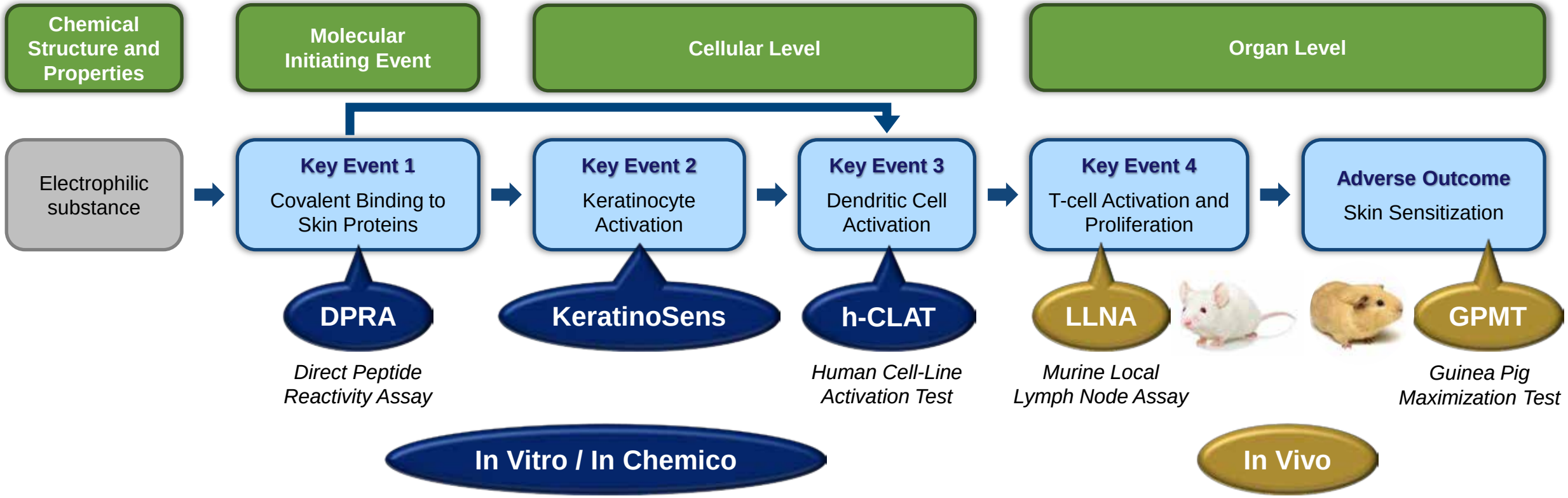
Adverse Outcome Pathway for Skin Sensitization

For sensitization initiated by covalent binding to proteins



Adverse Outcome Pathway for Skin Sensitization

For sensitization initiated by covalent binding to proteins



Adverse Outcome Pathway for Skin Sensitization

For sensitization initiated by covalent binding to proteins

Individual non-animal methods are **not** recommended as standalone replacements for animal tests.

Chemical Structure and Properties | **Organ Level**

Electrophilic substance → **Key Event 1** Covalent Binding to Skin Proteins → **Key Event 2** Keratinocyte Activation → **Key Event 3** Dendritic Cell Activation → **Key Event 4** T-cell Activation and Proliferation → **Adverse Outcome** Skin Sensitization

DPRA — *Direct Peptide Reactivity Assay*

KeratinoSens

h-CLAT — *Human Cell-Line Activation Test*

LLNA — *Murine Local Lymph Node Assay*

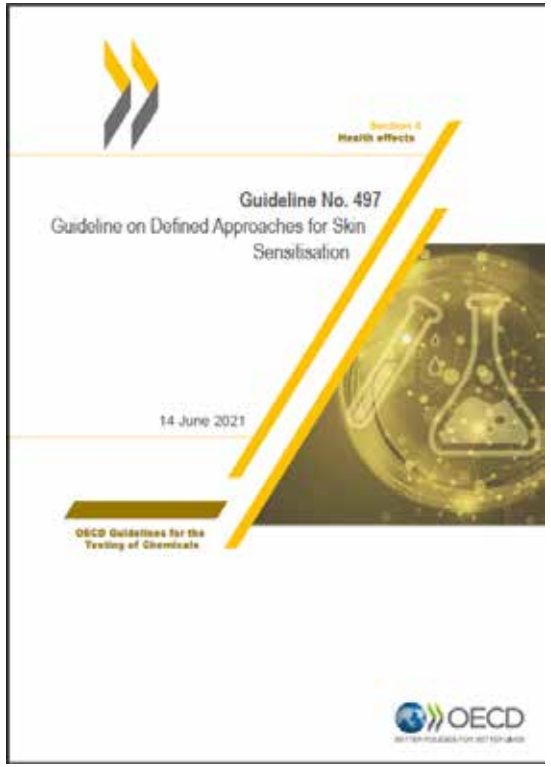
GPMT — *Guinea Pig Maximization Test*

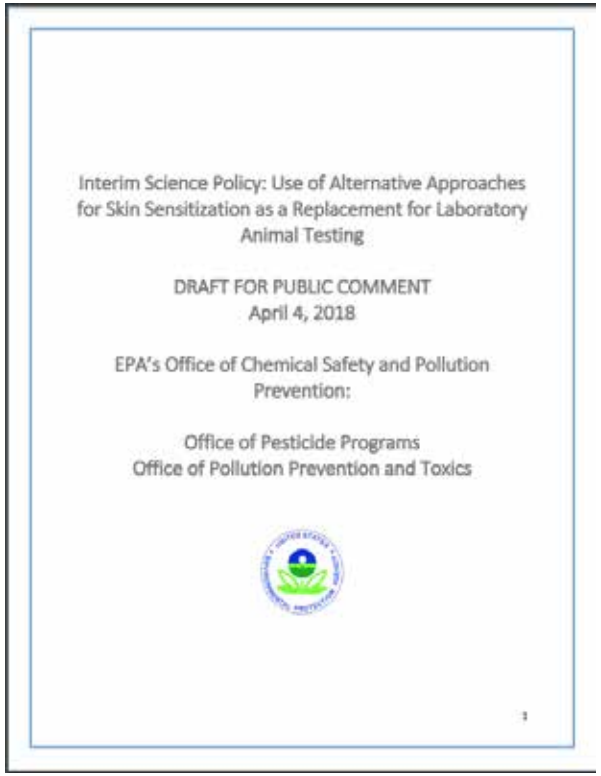
In Vitro / In Chemico

In Vivo

Defined Approaches for Skin Sensitization (DASS)

- Results from multiple assays representing KEs of the skin sensitization AOP can be combined to predict skin sensitization hazard and potency using defined approaches**.**
- **<u>Defined approaches for skin sensitization (DASS)</u>** have been developed and accepted by the OECD for hazard and potency predictions and by the U.S. EPA for hazard predictions.

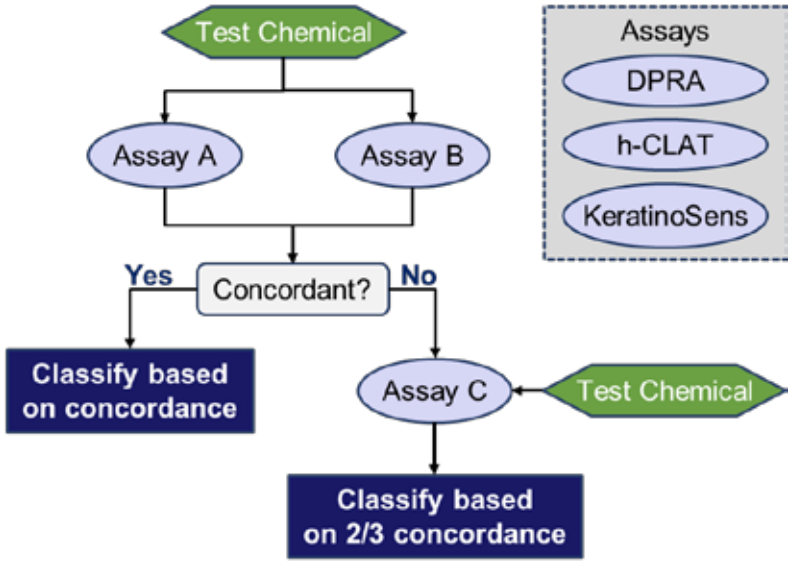




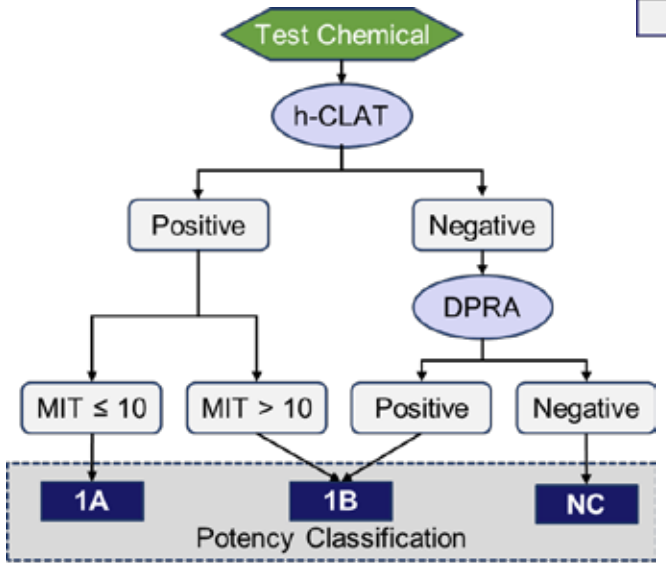
Defined Approaches for Skin Sensitization (DASS)

- DASS combine data from multiple information sources using fixed data interpretation procedures.

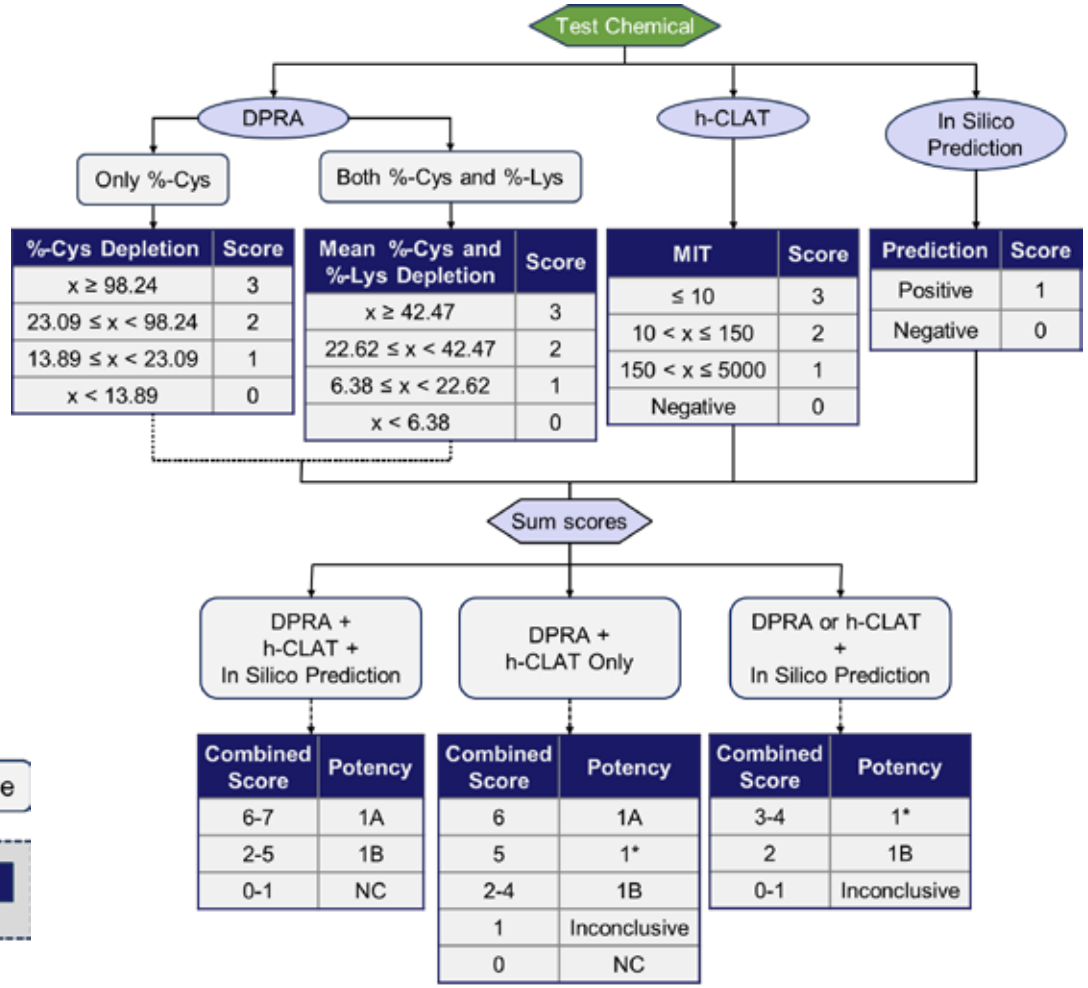
2 out of 3 (2o3)



Key Event 3/1 Sequential Testing Strategy (KE 3/1 STS)



Integrated Testing Strategy (ITS)



Accuracy of Methods Against Human Reference Data

- The DASS show higher or equivalent accuracy than the LLNA when compared to **human** reference data.

Hazard Identification

	Accuracy
LLNA	74.20%
KS	75.80%
h-CLAT	78%
DPRA	73.40%
2o3 (KS + h-CLAT + DPRA)	77.20%
KE 3/1 STS (h-CLAT + DPRA)	80.20%
ITSv1 (h-CLAT + DPRA + DEREK*)	85%

Potency

	Accuracy
LLNA	59.4%
KE 3/1 STS (h-CLAT + DPRA)	63.5%
ITSv1 (h-CLAT + DPRA + DEREK*)	69.2%

**ITSv1 uses in silico hazard predictions from Derek Nexus software*

Kleinstreuer et al. 2018 Crit Rev Tox
Hoffmann et al. 2018 Crit Rev Tox

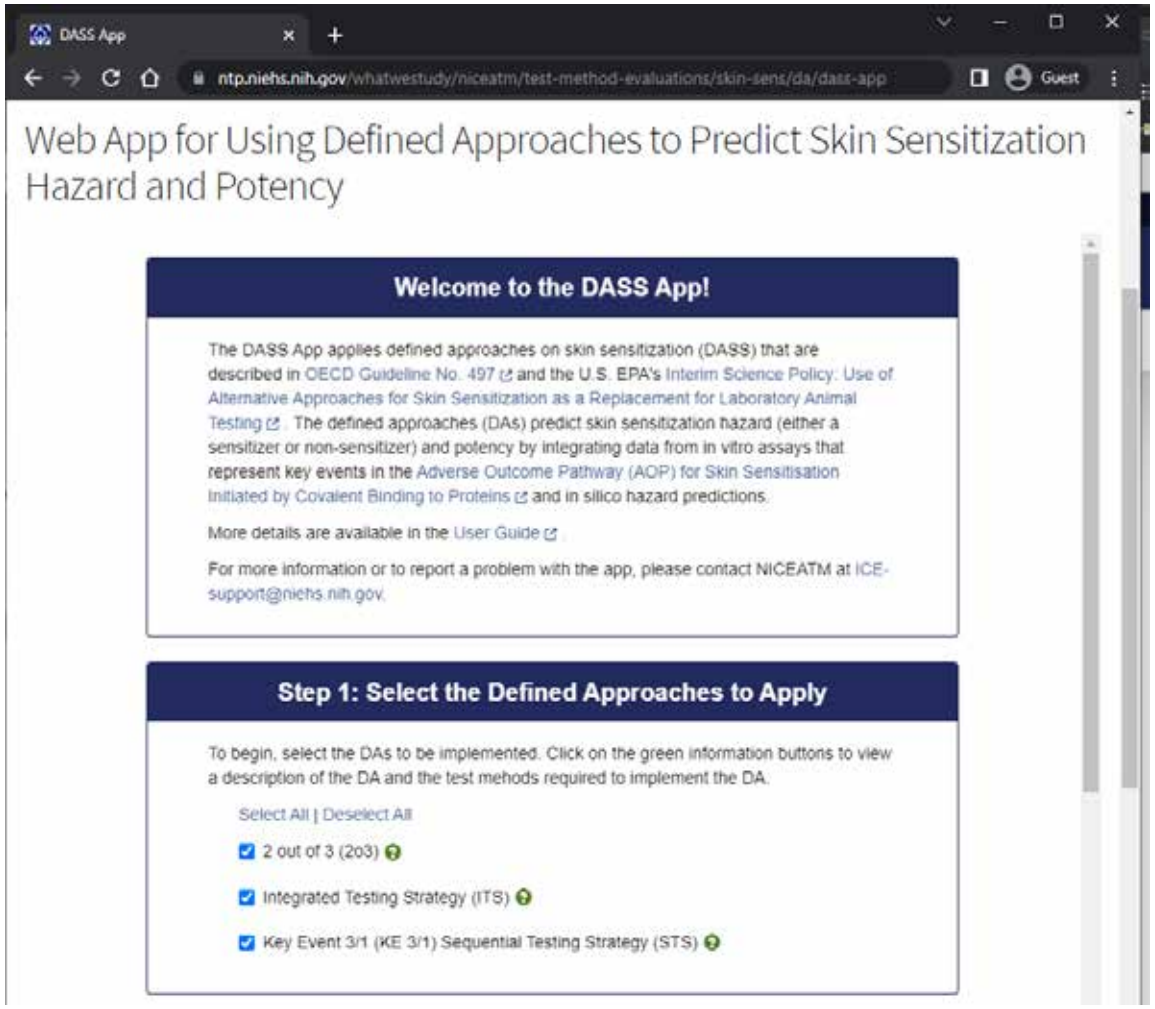
Defined Approaches for Skin Sensitization (DASS)

- DASS are non-animal approaches that can be used to fully replace an animal test to identify skin sensitizers.
- DASS logic can be difficult to implement or error-prone when applied manually.

The DASS App

- We created the DASS App, an open-source web application that allows users to apply DASS 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. No data are retained by the app.

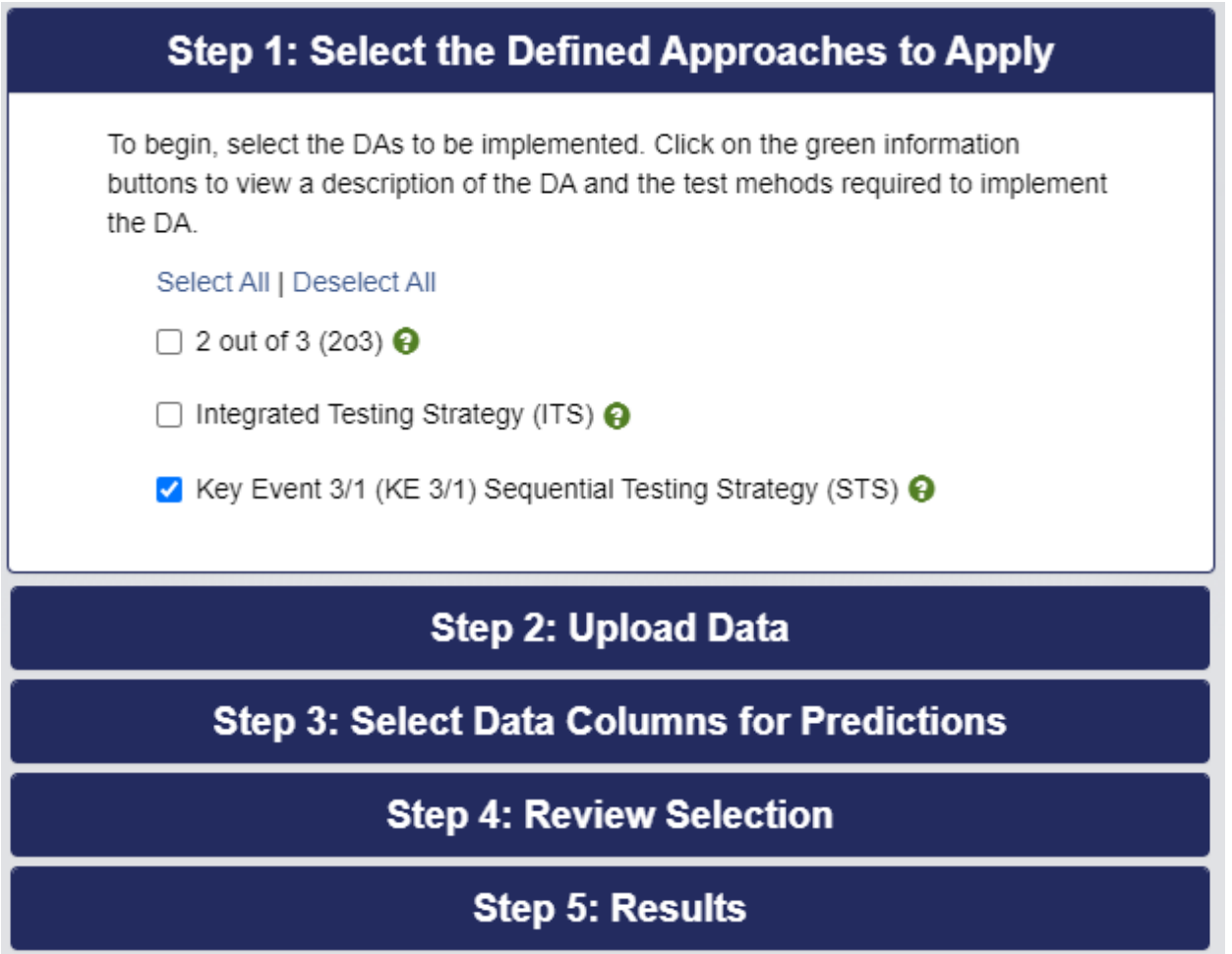
Access the DASS App
https://ntp.niehs.nih.gov/go/952311



https://github.com/NIEHS/DASS
To et.al 2023. Cambridge Open Engage. Preprint.

The DASS App

- The DASS App is organized into step-by-step modules.
- In the first step, users select the defined approaches to apply.
  - The app includes the 2o3, KE 3/1 STS and ITS approaches



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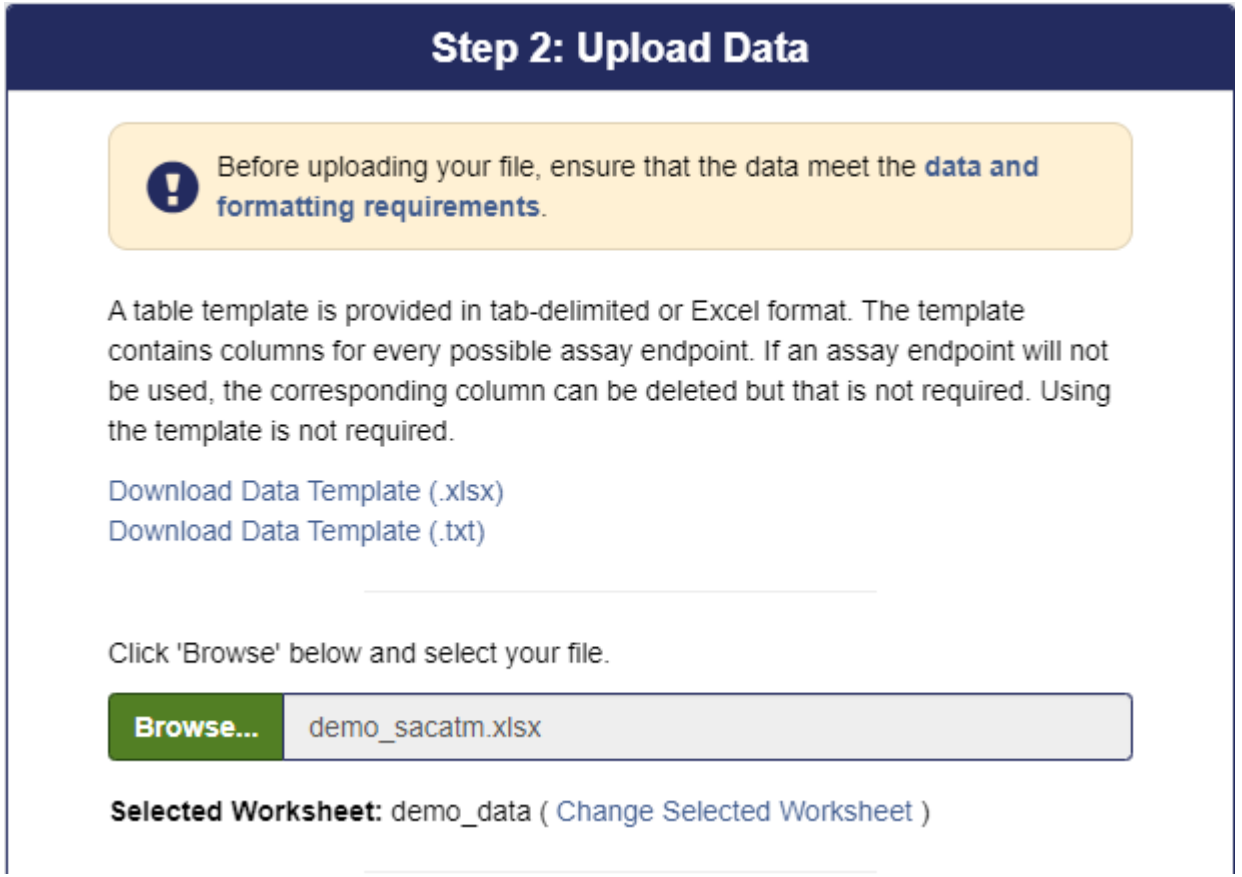
The DASS App

- File formats accepted: txt, csv, xlsx
- Detailed guidance to assist users with data preparation
- No specific column names or order required



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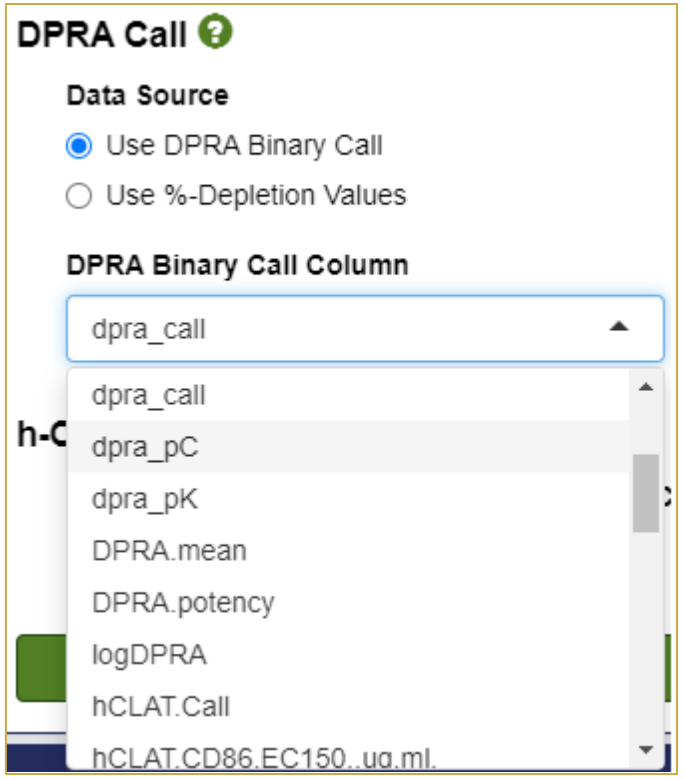
The DASS App

- In Step 3, users specify which columns correspond to a given assay endpoint.



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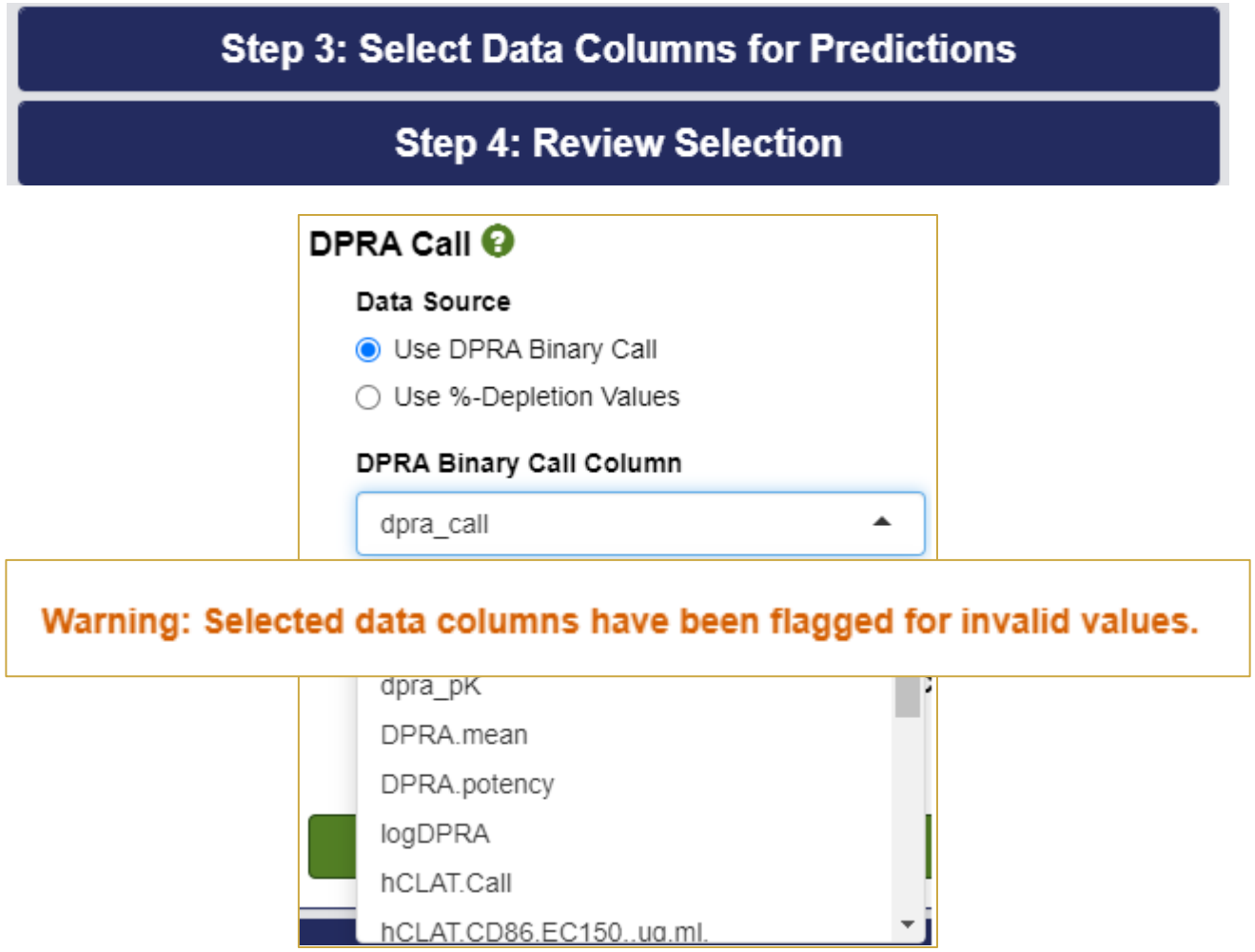
The DASS App

- In Step 3, users specify which columns correspond to a given assay endpoint.
- In Step 4, the app reviews the selected data and flags invalid values.



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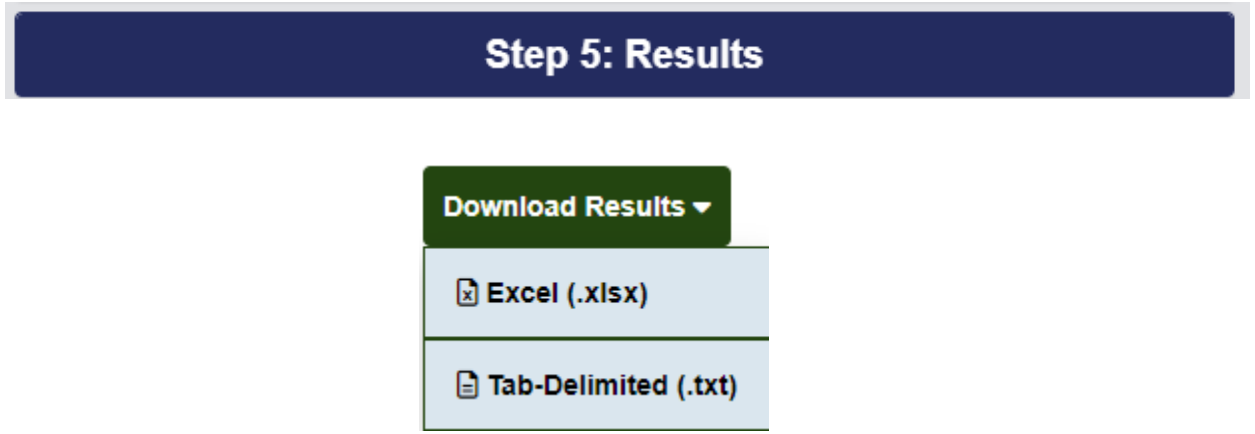
The DASS App

- Results are displayed to the user and can be downloaded as an .xlsx or .txt file.
- DASS predictions are appended to the user's uploaded data.



Curated.nam	CASRN	SMILES	dpra_call*	dpra_pC	dpra_pK	DPRA.mean	hCLAT.Call	hCLAT.MIT*	DPRA Call Input	h-CLAT MIT Input	DA KE 3/1 STS Call	DA KE 3/1 STS Potency
Abietic acid	514-10-3	CC(C)C1CC[C	1	99.9	16.3	58.1	0	Inf	1	Inf	1	1B
Acetanisole	100-06-1	COc1ccc(cc1)	0	4.723885562	0.1	2.411942781	0	Inf	0	Inf	0	NC
2-Acetylcyclo	874-23-7	CC(=O)C1CC(	0	5	0	2.5	1	109.7	0	109.70	1	1B
4-Allylanisole	140-67-0	COc1ccc(CC=	1	20.62541583	0	10.31270792	1	207.5967652	1	207.60	1	1B
Allyl phenoxy	7493-74-5	C=CCOC(=O)(	0	0.61	4.08	2.345	0	Inf	0	Inf	0	NC
4-Aminobenz	150-13-0	Nc1ccc(cc1)C	0	10.7	0.4	5.55	0	Inf	0	Inf	0	NC
4-Amino-m-c	2835-99-6	Cc1cc(O)ccc1	1	90	28.8000031	59.40000155	1	11.50004363	1	11.50	1	1B
5-Amino-o-cr	2835-95-2	Cc1ccc(N)cc1	1	89.1999998	12.5	50.8499999	1	113.2362193	1	113.24	1	1B
2-Aminopher	95-55-6	Nc1ccccc1O	1	96.2	18.1	57.15	1	1.1	1	1.10	1	1A

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Summary

- We created the DASS App to facilitate the use of accepted DASS to integrate data from non-animal methods and provide skin sensitization hazard and potency predictions.
- The DASS App enables users to leverage computational methods to efficiently apply DAs through a user-friendly interface.

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Acknowledgments

The NICEATM Group

NIEHS/DTT Contributors

UNITED STATES ICCVAM
Advancing Alternatives to Animal Testing

https://ntp.niehs.nih.gov/go/2021iccvamreport

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