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

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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

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
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

Chemical Structure and Properties

Molecular Initiating Event

Key Event 1: Covalent Binding to Skin Proteins

DPRA

Direct Peptide Reactivity Assay

Electrophilic substance

Cellular Level

Key Event 2: Keratinocyte Activation

KeratinoSens

Key Event 3: Dendritic Cell Activation

h-CLAT

Human Cell-Line Activation Test

Key Event 4: T-cell Activation and Proliferation

LLNA

Murine Local Lymph Node Assay

Key Event 5: Skin Sensitization

GPMT

Guinea Pig Maximization Test

In Vitro / In Chemico

In Vivo

Organ Level

Adverse Outcome

Skin Sensitization

AOP Wiki. AOP 40
Adverse Outcome Pathway for Skin Sensitization

For sensitization initiated by covalent binding to proteins

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

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

Chemical Structure and Properties

Electrophilic substance

Key Event 1
Covalent Binding to Skin Proteins
DPRA
Direct Peptide Reactivity Assay

Key Event 2
Keratinocyte Activation
KeratinoSens

Key Event 3
Dendritic Cell Activation
h-CLAT
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Key Event 4
T-cell Activation and Proliferation
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.

• **Defined approaches for skin sensitization (DASS)** 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.
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

<table>
<thead>
<tr>
<th>Method</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLNA</td>
<td>74.20%</td>
</tr>
<tr>
<td>KS</td>
<td>75.80%</td>
</tr>
<tr>
<td>h-CLAT</td>
<td>78%</td>
</tr>
<tr>
<td>DPRA</td>
<td>73.40%</td>
</tr>
<tr>
<td>2o3 (KS + h-CLAT + DPRA)</td>
<td>77.20%</td>
</tr>
<tr>
<td>KE 3/1 STS (h-CLAT + DPRA)</td>
<td>80.20%</td>
</tr>
<tr>
<td>IT Sv1 (h-CLAT + DPRA + DEREK*)</td>
<td>85%</td>
</tr>
</tbody>
</table>

### Potency

<table>
<thead>
<tr>
<th>Method</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLNA</td>
<td>59.4%</td>
</tr>
<tr>
<td>KE 3/1 STS (h-CLAT + DPRA)</td>
<td>63.5%</td>
</tr>
<tr>
<td>IT Sv1 (h-CLAT + DPRA + DEREK*)</td>
<td>69.2%</td>
</tr>
</tbody>
</table>

*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

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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Step 1: Select the Defined Approaches to Apply

To begin, select the DAs to be implemented. Click on the green information buttons to view a description of the DA and the test methods required to implement the DA.

Select All | Deselect All

- 2 out of 3 (2o3)
- Integrated Testing Strategy (ITS)
- Key Event 3/1 (KE 3/1) Sequential Testing Strategy (STS)

Step 2: Upload Data

Step 3: Select Data Columns for Predictions

Step 4: Review Selection

Step 5: Results

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

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• 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.

Step 5: Results

Download Results

- Excel (.xlsx)
- Tab-Delimited (.txt)

https://github.com/NIEHS/DASS

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.
The NICEATM Group

NIEHS/DTT Contributors

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

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