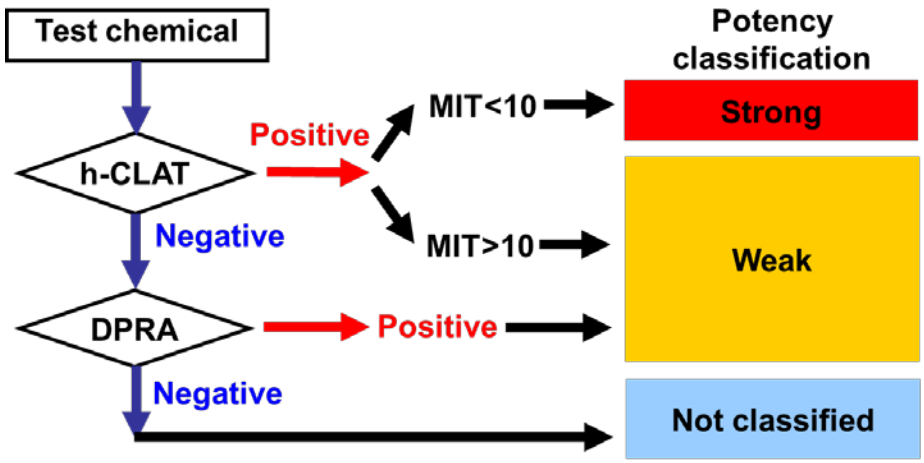
Case Study: Evaluating a Non-Animal Defined Approach for Skin Sensitization

Is this non-animal defined approach ready to replace the LLNA?

Consider the example non-animal defined approach below for replacement of the LLNA. Seven criteria categories are listed below with questions to guide your evaluation.

Example: Sequential Testing Strategy (STS) Defined Approach (DA)

The figure below summarizes a DA that is currently being considered as an alternative approach to replace the LLNA. The DA's output is a potency classification (i.e., chemical is categorized for likelihood as a strong or weak skin sensitizer, or is not classified as a skin sensitizer). The minimum induction threshold (MIT) is the quantitative readout of the h-CLAT assay, and determines the potency for chemicals that are positive in the h-CLAT. Chemicals that are negative in the h-CLAT are then run in the DPRA to either confirm their lack of sensitization activity, or classify them as weak sensitizers.



Adapted from Takenouchi et al. 2015

1. Structure: Components, Information Provided

- This DA is a simple decision tree
- Outputs are hazard and potency predictions
- This DA depends on two OECD Test Guideline methods: hCLAT, DPRA

➢ **What are advantages/disadvantages to this STS approach?**

2. Relevance: Mechanistic Coverage

- This DA integrates data from two OECD Test Guideline assays representing key events (including molecular initiating event) of the AOP

➢ **Would this DA be acceptable with other assays if they addressed the same key events in the AOP (i.e., same framework but using assays other than h-CLAT or DPRA)? If so, under what conditions?**

3. Predictive Accuracy: Performance Compared to Reference Data

Test Method:	*Non-animal: STS DA*	*Animal: LLNA*
Accuracy:*	80%	74%

*Accuracy was assessed vs. human data (n = 128)

➢ **In the absence of human data, would the reproducibility of the animal test be a reasonable threshold for predictive performance of a DA?**

4. Reliability: Reproducibility

- Decision tree is rule-based, i.e., 100% reproducible
- Depends on the reproducibility of the assays input (>80% for *in vitro* assays)

➢ **What else does the reliability of this DA depend on?**

5. Applicability: Technical Limitations, Chemical Space

- Depends on the technical limitations of the data sources (assays).

➢ **How would you characterize the applicability domain of a DA that depends on multiple assays, with different limitations?**

6. Complexity: Data Interpretation Procedure

- Simple decision tree, straightforward to apply.

➢ **Consider more complex DAs. For example, would a machine learning algorithm be an acceptable replacement? If so, under what conditions?**

7. Transparency: Proprietary Elements

- Fully transparent, third-party assessment performed (Kleinstreuer et al. 2018).

➢ **Do the information sources/assays in the DA need to be widely available, or can they be proprietary? What conditions would apply to each?**