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Application of Skin Allergy Risk Assessment-Integrated Chemical Environment Defined Approach to a Diverse Chemical Set – a Comparative Study

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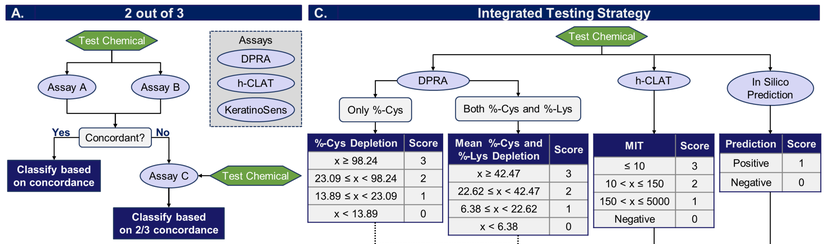
Introduction

- Current test guidelines for the assessment of skin sensitization issued by the Organisation for Economic Co-operation and Development (OECD) utilize in vitro and in chemico approaches. None of these methods can currently be used as stand-alone assays to determine skin sensitization.
- To overcome this issue, in vitro and in chemico tests are incorporated into defined approaches (DAs), which allow these new approach methods (NAMs) to be used in combination via a fixed data interpretation procedure to inform on skin sensitization potential.
- Currently accepted DAs only allow for hazard and potency classification, and do not produce a point of departure (POD) for use in quantitative risk assessment. To address this need, the Skin Allergy Risk Assessment-Integrated Chemical Environment (SARA-ICE) Model was developed based upon the principles of the Unilever SARA model (Reynolds et al., 2019; Reynolds et al., 2022). SARA-ICE is a collaboration between Unilever and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).
- SARA-ICE uses a Bayesian statistical framework and incorporates data from the publicly available ICE database, the published Unilever SARA database, and the Cosmetics Europe Database (Hoffmann et al., 2022).
- The model uses as inputs any combination of historical human predictive patch test (HPPT) and in vivo local lymph node assay (LLNA), and a variety of NAMs, including the direct peptide reactivity assay (DPRA), kinetic DPRA, KeratinoSens™ assay, human cell line activation test (h-CLAT), or U-SENS™ assay.
- The output of the model is the ED01, the dose with a 1% chance of inducing skin sensitization following a HPPT exposure. In addition to the ED01, the model also returns the probability of each GHS classification, incumbent on the distribution of the ED01.
- For this study, we applied the SARA-ICE Model to in chemico and in vitro data collected as part of a previous study that evaluated a set of chemicals with existing LLNA reference data nominated by multiple U.S. federal agencies. These 181 chemicals had previously been tested in the DPRA, KeratinoSens, and h-CLAT and evaluated within several DAs for hazard and GHS potency classification (UN, 2021).
- The ED01 derived from the SARA-ICE model was compared to existing LLNA data and predictions from three regulatory-accepted DAs (**Figure 1**):
  - A. OECD 2 out of 3 (2o3; OECD, 2022)
  - B. OECD Integrated Testing Strategy (ITS v2; OECD, 2022)
  - C. U.S. Environmental Protection Agency Key Event 3/1 Sequential Testing Strategy (KE 3/1 STS; EPA 2018)
- The SARA-ICE Model is depicted in **Figure 2**. Performance and concordance for hazard are compared in **Figure 3,** while performance and concordance for potency are provided in **Figure 4**.

Figure 1. DAs Used to Compare to SARA-ICE Predictions



%-Cys Depletion	Score
x ≥ 98.24	3
23.09 ≤ x < 98.24	2
13.89 ≤ x < 23.09	1
x < 13.89	0

Mean %-Cys and %-Lys Depletion	Score
x ≥ 42.47	3
22.62 ≤ x < 42.47	2
6.38 ≤ x < 22.62	1
x < 6.38	0

MIT	Score
≤ 10	3
10 < x ≤ 150	2
150 < x ≤ 5000	1
Negative	0

Prediction	Score
Positive	1
Negative	0

Combined Score	Potency
6-7	1A
2-5	1B
0-1	NC

Combined Score	Potency
6	1A
5	1*
2-4	1B
1	Inconclusive
0	NC

Combined Score	Potency
3-4	1*
2	1B
0-1	Inconclusive

MIT: minimum induction threshold; Cys: cysteine; Lys: lysine; 1A: strong sensitizer; 1B: weak sensitizer; NC: not classified; 1*: sensitizer, inconclusive for potency

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This project is a collaboration between NICEATM and Unilever plc.

Figure 2. SARA-ICE Model

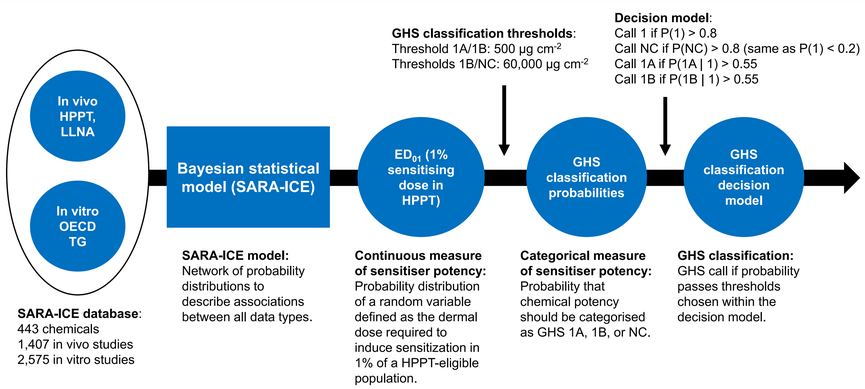
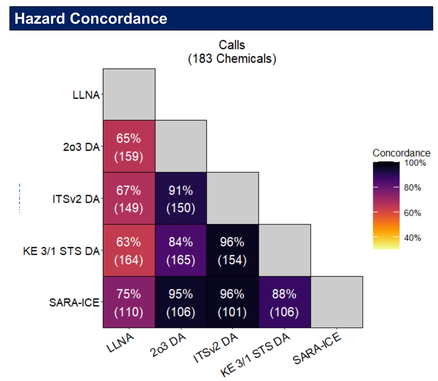


Figure 3: Performance of Chemical Set for Hazard

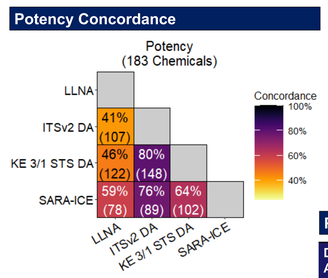


- Percent concordance was calculated based on total number of chemicals that shared a prediction (positive or negative) over the total number of chemicals shared between the assay or DA.
- Numbers in parentheses indicate the numbers of chemicals predicted by both comparators.
- LLNA data have been shown to be less predictive of human responses than AOP-based DAs. However, human data were not available for these chemicals.

Hazard Performance Compared to LLNA

Defined Approach	Sensitivity	Specificity	Balanced Accuracy	False Positive Rate	False Negative Rate	Number of Chemicals Predicted	Inconclusive (LLNA GHS 1/NC)
2o3	76.00%	47.46%	61.73%	53%	24%	159	9 (6/3)
ITSv2	84.69%	33.33%	59.01%	67%	15%	149	18 (8/10)
KE 3/1 STS	87.38%	22.95%	55.16%	77%	13%	164	0
SARA-ICE	83.33%	53.13%	68.23%	47%	17%	110	63 (33/30)

Figure 4: Performance of Chemical Set for Potency



- Percent concordance was calculated based on total number of chemicals that shared a prediction (positive or negative) over the total number of chemicals shared between the assay or DA.
- Numbers in parentheses indicate the numbers of chemicals predicted by both comparators.

Potency Performance Compared to LLNA

Defined Approach	Accuracy	Underpredicted	Overpredicted	Number of Chemicals Predicted	Inconclusive (LLNA GHS 1A/1B/NC)
ITSv2	41%	26%	33%	102	19 (4/6/9)
KE 3/1 STS	46%	21%	33%	122	0
SARA-ICE	59%	18%	23%	78	51 (7/18/26)

Results

- Binary classification performance of the SARA-ICE Model with P > 0.8 decision thresholds resulted in an inconclusive rate of around 20% for Class 1 and 17% for Not Classified against LLNA benchmarks. Sensitivity, specificity, and balanced accuracy for conclusive predictions were 83%, 53%, and 68%, respectively, versus LLNA benchmarks.
- Comparatively, hazard prediction of the other DAs against the LLNA ranged from 76-87%, 23-47%, and 55-62% for sensitivity, specificity, and balanced accuracy. Concordance (e.g., how many times two models agreed on an outcome) between the models ranged from 63–96%, with highest concordance between SARA-ICE and ITS. Against all the DAs, SARA-ICE was at least 88% concordant, as compared to 75% concordant with the LLNA (**Figure 3)**.
- Using the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS), classification of the SARA-ICE model against LLNA benchmarks resulted in an inconclusive rate of around 5% for Category 1A, 14% for Category 1B, and 20% for NC. Accuracy for LLNA GHS classification was 59% for the SARA-ICE Model, as compared to 41 – 46% for the ITSv.2 or KE 3/1 STS.
- SARA-ICE underpredicted GHS categories 18% of the time and overpredicted GHS categories 23% of the time. SARA-ICE had the highest concordance against the LLNA as compared to the ITSv.2 and KE 3/1 STS. When compared to the other DAs, SARA-ICE demonstrated 76% and 64% concordance (**Figure 4**).

Discussion

- SARA-ICE is a probabilistic model that integrates multiple skin sensitization data inputs in various combinations.
- SARA-ICE supports classification of skin sensitizers according to the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS), and provides a human-relevant point of departure, with quantified uncertainty, for quantitative risk assessment.
- Currently, SARA-ICE is undergoing evaluation via the OECD Defined Approach Skin Sensitisation (DASS) Expert Group for potential inclusion in Guideline 497: Defined Approaches on Skin Sensitisation (OECD, 2021).
- Ultimately, the SARA-ICE Model will be publicly available as a containerized version available in GitHub and eventually housed on the NICEATM ICE platform (https://ice.ntp.niehs.nih.gov/).
- These data were compiled for chemicals or substances that were nominated by multiple U.S. federal agencies with the intention of understanding their skin sensitization potential. SARA-ICE provides additional confidence in assessing these chemicals, at least when compared to LLNA benchmark data, as compared to the already accepted OECD guideline DAs.
- The use of this diverse range of substances aids in further characterizing the applicability of NAMs to skin sensitization assessments.

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