Application of the SARA-ICE Skin Sensitization Defined Approach to a Diverse Chemical Set – a Comparative Case Study

Emily N. Reinke[1], Tripp LaPratt[1], Judy A. Strickland[1], Dori Germolec[2], James Truax[1], Joe Reynolds[3], Georgia Reynolds[3], Nicola Gilmour[3], David G. Allen[1], Gavin Maxwell[3], Nicole C. Kleinstreuer[2]

[1]Inotiv, Research Triangle Park, NC, United States; [2]NIH/NIEHS/DTT/NICEATM, Research Triangle Park, NC, United States; [3]SEAC Unilever, MK44 1LQ, United Kingdom

Background and Purpose

A collaboration between Unilever and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) has resulted in the development of the Skin Allergy Risk Assessment-Integrated Chemical Environment (SARA-ICE) Model. This Bayesian statistical model is a defined approach (DA) designed to provide a human-relevant weight-of-evidence based point-of-departure (POD) for skin sensitization. The POD, the ED_{01}, is the dose with a 1% chance of inducing sensitization across the population following a human predictive patch test (HPPT) exposure. SARA-ICE can predict the ED_{01} using any combination of data from the HPPT, local lymph node assay (LLNA), or specific in vitro assays for skin sensitization. These assays include the (kinetic) direct peptide reactivity assay (kDPRA or DPRA), KeratinoSens™, human cell line activation test (h-CLAT), or the U-SENS™. SARA-ICE also provides a United Nations Globally Harmonized System for Classification and Labelling of Chemicals (GHS) classification prediction for sensitization potency.

The SARA-ICE model uses publicly available data on 443 chemicals (1,407 *in vivo* studies and 2,575 *in vitro* studies) from the ICE database and Unilever SARA and Cosmetics Europe databases and has been applied in several case studies focused on different chemical classes. Here we describe the application of SARA-ICE to a diverse set of chemicals nominated by multiple U.S. federal agencies for testing in the DPRA, the KeratinoSens, and the h-CLAT. The output of SARA-ICE can be compared to previous applications of the same data to existing DAs found within the Organisation for Economic Cooperation and Development (OECD) Guideline 497 or those accepted by the U.S. Environmental Protection Agency.

Methods

Multiple U.S. federal agencies nominated 185 test chemicals for testing in the DPRA, KeratinoSens, and h-CLAT methods. Data were generated on 181 chemicals, and reference LLNA data were compiled for 172 chemicals. Data were then used as information sources within the SARA-ICE model, and an ED_{01} was derived for each test chemical. The ED_{01} was used to assign a GHS classification, which was compared to the LLNA reference data. The SARA-ICE results were also compared to those from the OECD DAs 2 out of 3 (2o3) and Integrated Testing Strategy (ITS)v2, as well as the Key Event 3/1 Sequential Testing Strategy (STS).

Results

The SARA-ICE model had the highest concordance for hazard against the LLNA (75%) as compared to the other DAs (63-67% concordance). When compared to the other DAs directly, SARA-ICE concordance ranged from 88% to 96%. For GHS potency categorization, SARA-ICE was 59% concordant with the LLNA, compared to 41-46% concordance against the LLNA for

the STS and ITSv2 respectively. When concordances of all DA combinations were compared, SARA-ICE was less concordant with the ITSv2 (76%) and the STS (64%) than the ITSv2 and STS were with each other (80%). SARA-ICE also had a sensitivity of 83% and a specificity of 53%, with a balanced accuracy of 68% for hazard when compared to the LLNA reference set. Comparatively, the other DAs had a sensitivity range of 76-87%, a specificity range of 23-47%, and a balanced accuracy range of 55-62%. SARA-ICE had an underprediction of 18% for GHS category, and an overprediction of 23%, compared to the other DAs with 21-26% underprediction and 33% overprediction.

Conclusions:

This study showed that for this challenging chemical set the SARA-ICE DA performs as well as or better than other skin sensitization DAs that are already accepted for regulatory use. These data demonstrate that results from in vitro testing, when combined with comprehensive, human-relevant probabilistic prediction models, can provide a useful alternative to animal testing for predicting skin sensitization hazard and potency, as well as advancing the field by providing a point of departure for quantitative risk assessment applications. This project was funded in whole or in part with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C and HHSN273201400017C.

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