The Skin Allergy Risk Assessment-Integrated Chemical Environment (SARA-ICE) Model for UN GHS classification – an evaluation and application in case studies

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A collaboration between Unilever and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) has developed the Skin Allergy Risk Assessment-Integrated Chemical Environment (SARA-ICE) Model, a defined approach (DA) developed upon principles of the SARA Model. The SARA-ICE Model is designed to provide a weight-of-evidence point of departure (PoD) and United Nations Globally Harmonized System for Classification and Labelling of Chemicals (GHS) classification prediction for use in skin sensitisation assessments. The SARA-ICE core dataset utilises data within the publicly available Integrated Chemical Environment (ICE) database in addition to the published Unilever SARA database and Cosmetics Europe database. The model is constructed within the Bayesian statistical framework and allows for determination of a human relevant PoD termed the ED_{01}, defined as the dose with a 1% chance of inducing sensitisation following a human predictive patch test (HPPT) exposure. The PoD can be inferred using any combination of HPPT (human repeat insult patch test or human maximisation test), *in vivo* local lymph node assay (LLNA), and new approach methods (NAM [*in chemico* direct peptide reactivity assay and *in vitro* KeratinoSens™, h-CLAT, or U-SENS™]) data. For a chemical of interest, the model returns the probability of each GHS classification conditional on the distribution of the ED_{01}.

Here we describe initial results of an evaluation of the SARA-ICE model which pertains to a 'Feasibility Study on Inclusion of the SARA-ICE model into OECD Guideline 497 on Defined Approaches for Skin Sensitisation'. For the purpose of evaluating SARA-ICE for GHS classification, the Organisation for Economic Co-operation and Development (OECD) DA evaluation dataset (Annex II of 'Supporting document to the OECD guideline 497 on defined approaches for skin sensitisation (No 336)') was utilised. Sensitivity, specificity, and balanced accuracy conditional on making a conclusive call were calculated for binary (sensitiser versus Not Classified (NC)) and sub-category (1A, 1B, NC) GHS classifications for different tuning parameters of a decision model. For example, based upon a binary classification threshold of 0.8, a balanced accuracy of 97% was achieved for conclusive calls versus human benchmarks, but at the expense of a high inconclusive rate (36%). Based upon a sub-category classification threshold of 0.55, an average balanced accuracy of 85% (84% for sub-category 1A, 76% for sub-category 1B, 97% for subcategory NC) was achieved for conclusive calls versus human benchmarks.

The SARA-ICE model was then applied to provide GHS classifications for a number of isothiazolinones, a group of broad-spectrum preservatives, based upon each combination of HPPT, LLNA, NAM or all data. The SARA-ICE model classified all isothiazolinones as sensitisers with a probability of >0.97 using only HPPT data, only NAM data, only LLNA data or all data. All isothiazolinones were classified as 1A sensitisers with a probability of >0.62 using only HPPT data, >0.89 using only NAM data, >0.32 using only LLNA data and >0.84 using all data.

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