Application of Skin Allergy Risk Assessment-Integrated Chemical Environment Defined Approach (SARA-ICE DA) to Assess Skin Sensitization Potency of Isothiazolinone Compounds

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Background and Purpose

The Skin Allergy Risk Assessment-Integrated Chemical Environment (SARA-ICE) Model, a defined approach (DA) that expands upon the previously published SARA Model, has been developed through collaboration between Unilever and the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). The SARA-ICE Model is designed to provide a weight of evidence point of departure (PoD), hazard prediction and United Nations Globally Harmonized System for Classification and Labelling of Chemicals (GHS) classification prediction for use in skin sensitisation assessments. Here we describe the development and results of a case-study evaluation to determine the feasibility of inclusion of the SARA-ICE model into OECD Guideline 497 on Defined Approaches for Skin Sensitisation.

Methods

The SARA-ICE model uses data on 443 chemicals (1,407 *in vivo* studies and 2,575 *in vitro* studies) 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 across the population 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 methodologies (NAM [direct peptide reactivity assay (DPRA), kinetic DPRA (kDPRA), 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}.

Results

For the purpose of evaluating SARA-ICE for hazard and GHS classification, the OECD DASS 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 non-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, balanced accuracies of 86% and 97% were achieved for conclusive calls versus human and LLNA OECD DASS benchmark data, respectively (inconclusive rates: human = 20%; LLNA = 21%). Based upon a sub-category classification threshold of 0.55, average balanced accuracies of 85% and 90% were achieved for conclusive calls versus human and LLNA benchmarks, respectively (inconclusive rates: human = 22%; LLNA = 26%). The SARA-ICE

model was then applied to provide ED_{01} estimates and GHS classifications for six isothiazolinones (MIT, CMIT, BIT, OIT, DCOIT, BBIT), a group of broad-spectrum preservatives, based upon combinations of historical LLNA and NAM data. The SARA-ICE model classified all isothiazolinones as sensitisers with a probability of >0.97 using only NAM data, only LLNA data, or all data. They were sub-classified as Category 1A sensitisers with a probability of >0.94 using only NAM data; >0.34 using only LLNA data, and >0.80 using all data.

Conclusions

The SARA-ICE model shows good concordance with sensitizer binary and GHS sub-category classifications against OECD DASS benchmark data. The case study with isothaizolinone chemicals demonstrates that the SARA-ICE DA can accurately categorize skin sensitization hazard and potency using in vitro and in vivo data inputs and provide quantitative estimates of human potency (ED_{01}) that include uncertainty. This model is an important tool to assess the probability that exposure to a chemical of interest is “low risk” and to support diverse regulatory decision frameworks.

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