**Defined Approaches for Skin Sensitization for Diverse Chemical Sets**

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While several non-animal methods have been accepted to identify potential skin sensitizers, none is considered a full replacement for animal tests. Defined approaches (DAs) combining multiple assays representing key events from the skin sensitization adverse outcome pathway have been accepted internationally under OECD Guideline 497 for hazard and potency prediction. This project evaluated 185 chemicals nominated by federal agencies with mandates for skin sensitization assessments: NTP, EPA, and the U.S. Consumer Product Safety Commission. We tested chemicals using three DAs that combine results from three assays: the direct peptide reactivity assay, the KeratinoSens™ assay, and the human cell line activation test. Local lymph node assay results were used as reference data. Individual test method accuracy for hazard (sensitizer vs. nonsensitizer) ranged from 40% to 80%. Accuracy for hazard classification using the 2 out of 3 DA was 46% to 89%, the Integrated Testing Strategy (ITS)v2 DA was 41% to 100%, and the Key Event 3/1 Sequential Testing Strategy (STS) DA was 31% to 100%. Accuracy was lower for classification of pesticide products, possibly due to heterogeneity and insolubility of some products. Potency prediction was based on GHS categories. Correct potency classification using the ITSv2 DA ranged from 37% to 53%, while the 3/1 KE STS DA ranged from 27% to 67%. DAs based on in vitro methods may provide useful alternatives to animal testing for predicting skin sensitization hazard and potency of substances relevant to multiple U.S. agency programs. Project was funded by NIEHS under Contract Nos. HHSN273201500010C and HHSN27320140017C.