Application of Defined Approaches for Skin Sensitization to Agrochemical Products

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The assessment of skin sensitization potential is one of the elements included in international regulatory safety evaluation of pesticides. Several non-animal test methods have been adopted as globally harmonized test guidelines that can help to reduce animal use in these evaluations. No single assay is recommended as complete replacement for existing animal tests, such as the murine local lymph node assay (LLNA). Instead, defined approaches (DAs) that integrate data from multiple methods have been proposed to replace animal use for skin sensitization testing. However, these DAs have been evaluated using mono-constituent substances rather than mixtures or formulations (i.e., end-use products, multi-constituent substances with defined compositions). To fill this data gap, we tested 27 agrochemical formulations using the direct peptide reactivity assay (DPRA), the KeratinoSens™ assay, and the human cell line activation test (h-CLAT). Test data were used to evaluate several rule-based DAs that use these methods for hazard and/or potency categorization of skin sensitization. Balanced accuracy for the DAs for predicting skin sensitization hazard in vivo ranged from 56% to 73%. The best performing DA for GHS potency classification had a correct classification rate of 52%. By comparison, of the individual test methods, KeratinoSens had the highest performance for predicting in vivo hazard outcomes (balanced accuracy = 81% vs. 62% for DPRA and 56% for h-CLAT) and had higher balanced accuracy than any of the DAs. These results demonstrate that non-animal test methods have promising utility for evaluating the skin sensitization potential of agrochemical formulations. Further investigation will be required to determine whether DAs can outperform individual assays such as KeratinoSens for predicting in vivo sensitization hazard of pesticide formulations in general. This project was funded with federal funds from the NIEHS, NIH under Contract Nos. HHSN273201500010C and HHSN273201400017C and Corteva funds for the DPRA and KeratinoSens testing.