Evaluating Skin Sensitization Hazard of Diverse Chemicals Using GARDskin

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Multiple U.S. agencies require that chemicals be assessed for skin sensitization potential, although specific requirements vary based on the remit of an agency's chemical evaluation and management programs. Determination of skin sensitization hazard and potency using data from non-animal models adopted by OECD is gaining interest. The recently accepted GARDskin is the first assay based on genomics and machine-learning algorithms to make hazard predictions. Validation of the GARDskin required openness and transparency to verify the performance of the prediction model. NICEATM and collaborators tested 30 "challenging" chemicals in the GARDskin assay to potentially expand the applicability domain of the assay. Chemicals were nominated by NTP, EPA, the U.S. Consumer Product Safety Commission, and FDA. Results were compared to historical data from the mouse local lymph node assay (LLNA). Concordance of hazard classifications based on the LLNA was determined for classifications based on outcomes from three in vitro tests: the human cell line activation test (h-CLAT), direct peptide reactivity assay (DPRA), and KeratinoSens assay (KS). Against the LLNA, the GARDskin had sensitivity of 86%, specificity of 42%, and accuracy of 64%. Comparatively, the DPRA, h-CLAT, and KS performance metrics ranged from 40-54% for sensitivity, 22-47% for specificity, and 31-50% accuracy. Overall, the GARDskin predicted LLNA-based classifications with higher concordance than the other in vitro assays and appears to be useful for predicting skin sensitization hazard. Assessment of the suitability of GARDskin to be included in OECD Test Guideline 497 is ongoing. Project funding provided under NIEHS Contract Nos. HHSN273201500010C and HHSN27320140017C.