Application of Defined Approaches for Skin Sensitization for Chemicals of Federal Agency Interest

J. Strickland[1] J. Truax[1], K.T. To[1], E.N. Reinke[1], T. Gulledge[2], V.J. Johnson[2], D.G. Allen[1], N. Kleinstreuer[3], D. Germolec[3]

[1]Inotiv, RTP, NC, United States; [2]Burleson Research Technologies, Inc., Morrisville, NC, United States;[3]NIH/NIEHS/DTT/PTB/NICEATM, RTP, NC, United States

Multiple U.S. federal agencies require the assessment of skin sensitization potential for their chemical evaluation and management programs. Although these agencies have historically relied on skin sensitization data from animal testing, several non-animal methods have been internationally adopted as test guidelines. While none are considered complete replacements for animal tests, one approach to improve performance is to combine the results of non-animal methods that represent multiple key events of the adverse outcome pathway for skin sensitization using defined approaches (DAs). However, the DAs for regulatory use described in the Organisation for Economic Co-operation and Development's Guideline 497 have been evaluated using primarily chemicals that are relevant to the cosmetics industry. This project aimed to evaluate DAs relevant to the chemical evaluation and management programs of federal agencies who were requested to nominate substances to be tested in three non-animal skin sensitization assays: the direct peptide reactivity assay, the KeratinoSens™ assay, and the human cell line activation test. In vitro, in silico, and in vivo data were collected on 185 substances nominated by the National Toxicology Program, the U.S. Environmental Protection Agency (EPA) and the Consumer Product Safety Commission (CPSC). The results from each individual assay and the DAs were pooled by agency and the hazard and/or potency categorization for skin sensitization potential was determined. For each set of agency-nominated substances, local lymph node assay (LLNA) results were used as reference data to evaluate the individual test methods and DAs. When adequate in vitro, in silico, and in vivo data for predicting sensitization hazard were available, the accuracy of the individual assays, based on LLNA results and grouped by agency, ranged from 40% to 80% depending on the assay evaluated. Accuracy for predicting hazard using the 2 out of 3 DA ranged from 46% to 89%, the Integrated Testing Strategy (ITS)v2 DA ranged from 41% to 100%, and the Key Event 3/1 Sequential Testing Strategy (STS) DA ranged from 31% to 100%. The lowest number in each range of the individual or DA results was from the EPA Office of Pesticide Program nominations in which the heterogeneity of the pesticide products or mixtures in that group and their solubility may have impacted performance. The best accuracy among the DAs was for the substances nominated by CPSC, but it should be noted that there were no LLNA non-sensitizers available in that group. The accuracy for potency prediction was based on the Globally Harmonized System of Classification and Labelling of Chemicals (NC = non-sensitizer, 1B = weak sensitizer, 1A = strong sensitizer). Concordance of potency classification of the ITSv2 DA ranged from 37% to 53% and the 3/1 KE STS DA ranged from 27% to 67%. Results from in vitro testing and application of DAs may provide a useful alternative to animal testing for predicting skin sensitization hazard and potency of substances relevant to a wide range of federal agency programs. This project was funded in whole or in part with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C and HHSN27320140017C.

Keywords: chemical allergy, chemical hazard assessment, alternatives to animal testing