Machine Learning Approaches for Predicting Human Skin Sensitization Hazard

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One of ICCVAM's top priorities is the development and evaluation of non-animal approaches to identify potential skin sensitizers. The complexity of biological events necessary for a substance to elicit a skin sensitization reaction suggests that no single *in chemico*, *in vitro*, or *in silico* method will provide a complete replacement for currently accepted animal tests. Thus, ICCVAM is evaluating machine learning approaches to integrate relevant data based on the OECD adverse outcome pathway for skin sensitization to predict human skin sensitization hazard. Models were built and tested using input variables derived from public data for 96 chemicals with human skin sensitization hazard information. Data were obtained from three *in chemico* or *in vitro* methods (direct peptide reactivity assay [DPRA], human cell line activation test [h-CLAT], and KeratinoSens assay) and six physicochemical properties (octanol:water partition coefficient [log P], water solubility, vapor pressure, molecular weight, melting point, and boiling point). A read-across prediction of skin sensitization hazard for each substance, produced using OECD QSAR Toolbox, provided an additional input. All of these data were used as potential features to predict human hazard using two machine learning approaches, support vector machine and logistic regression, applied to 12 combinations of features. Models were trained on a set of 72 substances and tested on an external set of 24 substances. The feature set containing DPRA, h-CLAT, KeratinoSens, OECD QSAR Toolbox, and log P produced the best performing model by either approach: accuracy = 99% (71/72), sensitivity = 98% (50/51), and specificity = 100% (21/21) for the training set; and accuracy = 96% (23/24), sensitivity = 93% (14/15), and specificity = 100% (9/9) for the test set. The performance of this integrated approach was better at predicting human skin sensitization hazard than the local lymph node assay or any of the *in chemico*, *in vitro*, or *in silico* methods alone. These data suggest that computational methods are promising tools to effectively identify potential skin sensitizers without testing in animals. *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C*.