

ICCVAM Integrated Decision Strategy for Skin Sensitization

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One of the top priorities currently being addressed by ICCVAM is the identification and validation of non-animal alternatives for skin sensitization testing. Although it is a complex process, the key biological events leading to skin sensitization have been well characterized in an adverse outcome pathway (AOP) proposed by OECD. Accordingly, ICCVAM is working to develop an integrated decision strategy based on the OECD AOP using *in vitro*, *in chemico*, and *in silico* information on skin sensitization. Data were compiled for 120 chemicals tested in the local lymph node assay (LLNA), direct peptide reactivity assay (DPRA), human cell line activation test (h-CLAT), and KeratinoSens assay. Data for six physicochemical parameters (octanol:water partition coefficient, water solubility, vapor pressure, molecular weight, melting point, and boiling point) were collected and OECD QSAR Toolbox predictions for skin sensitization were calculated for each chemical. These data were combined into a variety of potential integrated decision strategies to predict LLNA outcomes using a training set of 94 chemicals and an external test set of 26 chemicals. Thirty-six models were built using six different machine learning approaches and six groups of predictor variables. A support vector machine model using 10 variables provided the best performance: accuracy = 98% (92/94), sensitivity = 99% (66/67), and specificity = 96% (24/25) for the training set; and accuracy = 92% (24/26), sensitivity = 90% (17/19) and specificity = 100% (7/7) for the test set. The performance of this model was better than any of the *in vitro*, *in chemico*, or *in silico* tests alone and better than a simple test battery approach using these methods. These data suggest that computational approaches 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. HHSN27320140003C.*