Impact of Local Lymph Node Assay Uncertainty on Predictions of a Bayesian Network Integrated Testing Strategy for Skin Sensitization Potency

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As toxicity testing moves away from traditional animal models towards cell-based assays and in silico methods, computational models integrating such data are being developed and improved. An example is the Bayesian network (BN) model used to predict local lymph node assay (LLNA) potency classification of substances in the NICEATM LLNA database. Datasets used to build such models may include multiple values for some combinations of assays and compounds. Using standard Bayesian network methods, it is difficult to build a model that makes use of all the available data. Instead, the data are either collapsed or selected from to produce a single value, which eliminates all distributional information. Using a published BN integrated testing strategy (ITS-2) for skin sensitization, we compare predictions of the original model and those of two methods that incorporate multiple LLNA values. In the first method, the potency class probabilities assigned by the BN are modified using an empirically derived conditional distribution. In the second method, Markov chain Monte Carlo is used to calculate results for a large number of BNs generated under distributional assumptions on the LLNA variable. This method propagates the uncertainty through all model building steps. On a test set of 21 compounds, agreement on the most probable class prediction was 81% for the two new methods, 86% for the original BN ITS and the second method, and 95% for the original model and the first method. The most probable class predictions were similar, but the distributions of the predictions differed. These more transparent methods enhance risk assessment by describing the uncertainty from the data and the model and better represent the reliability of the predictions. *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract Nos. HHSN27320140003C and HHSN273201000086U.*