Evaluating Defined Approaches to Testing and Assessment of Skin Sensitization Potential

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Skin sensitization is a toxicity endpoint of widespread concern for which the mechanistic understanding and concurrent necessity for non-animal testing approaches have evolved to a critical juncture, with many available options for predicting chemical sensitization potential without using animals. The International Cooperation on Alternative Test Methods (ICATM) held a workshop in October 2016 on acceptance of non-animal test methods for assessing skin sensitization potential which was attended by regulators from around the world. A product of the ICATM workshop was the development of an assessment framework for integrated non-animal approaches that could serve as replacements for the current animal test, the local lymph node assay (LLNA). A set of criteria were proposed by the workshop participants and further developed by ICATM to facilitate the evaluation of a number of existing alternative approaches, based on key elements such as biological plausibility, accessible data interpretation procedures, and performance against reference chemicals. The thresholds for acceptable performance were derived from the LLNA assay, based on its reproducibility and its accuracy against human data, where available. The cosmetics sector was used as an example, given the broad coverage of chemical ingredients with in vitro data in many assays, including the three test methods adopted as Test Guidelines by the Organization for Economic Cooperation and Development (OECD), and the existence of well-characterized in vivo data/classifications in both animals and humans. Multiple 'defined approaches' that were submitted as case studies to the OECD for predicting both hazard and potency were assessed to demonstrate how this framework and the associated performance standards can be applied. Defined approaches examined include consensus methods, artificial neural networks, support vector machine models, and decision trees. Multiple non-animal testing strategies incorporating *in vitro, in chemico,* and *in silico* inputs demonstrated comparable or superior performance to the LLNA, fulfilled the criteria in the ICATM assessment framework, and should be considered as acceptable replacements for regulatory purposes.

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