Variability in the Rabbit Skin Irritation Assay

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The in vivo rabbit skin test is the benchmark against which new approach methodologies (NAMs) for skin irritation testing are compared. Guideline in vitro methods for assessing skin irritation potential are accepted as partial replacements for the in vivo test, but none are capable of classifying moderate and mild irritants. A limiting factor in identifying a full replacement could be the variability inherent to the subjective scoring of erythema and edema responses in the rabbit test. This is particularly relevant for mild and moderate irritants, which NAMs have difficulty differentiating. To characterize the reproducibility of the in vivo assay, we assessed variability in animal study results from chemicals tested multiple times. We compiled and curated a dataset of 3291 test records representing 1071 unique chemicals, each tested at least twice. Where possible, primary dermal irritation indexes were estimated from the available data and used to classify chemicals according to the U.S. Environmental Protection Agency skin irritation criteria. Conditional probabilities were used to evaluate the reproducibility of hazard classifications resulting from the in vivo assay. Chemicals classified as moderate irritants at least once had a greater than 50% probability of being classified as mild- or non-irritants when tested repeatedly. This analysis indicates that variability present in the rabbit skin irritation test should be taken into consideration when evaluating the performance of NAMs.

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