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Defining the Edge: A Case Study in Expert Review of *In Silico* Hazard Predictions to Identify Activity Cliffs and Improve Chemical Risk Assessment

New approach methodologies for chemical safety assessments are seeing increased regulatory acceptance and use across multiple contexts, including medical device and pharmaceutical safety, chemical registration, and product stewardship initiatives. Expert review of predictive methods is a critical step in making informed hazard and risk conclusions. Often, these methods rely on data for structurally similar chemicals either directly *via* read-across or indirectly through nearest-neighbor *in silico* models. While chemicals may be similar in molecular weight, relevant functional groups, and chemical character, they may not behave similarly *in vivo*. In this case study, we investigated a test set of structurally similar compounds selected from established databases of local lymph node assay (LLNA) results. All the compounds in the test set share a carbonyl moiety and trigger the "Schiff base formation" alert for sensitization in Toxtree (v3.1.0). Lastly, the test set was filtered through a binning clustering model to ensure a reasonable degree of quantitative structural similarity (ChemMine similarity cutoff = 0.4). The resulting set consisted of 12 substituted benzenes of similar molecular weight (106-190 g/mol), and predicted physiochemical properties relevant to skin sensitization (water solubility > 100 mg/L; K_{ow} range 0-3). The test set represented a range of experimental results, from non-sensitizing to moderately sensitizing, and a false-positive hazard prediction rate based on the Schiff base formation alert alone of 25%. Further review of these compounds' chemical structures suggests that the distance of the carbonyl moiety from the benzene ring is a possible contributing factor with respect to sensitization potential. The nine test set compounds with experimental data for mutagenicity were also evaluated *via in silico* methods in accordance with guidelines for assessing mutagenic impurities (ICH M7 guidelines). The expert-rule-based program Toxtree falsely predicted eight out of nine compounds to be potential mutagens. In contrast, the (Q)SAR program VEGA (v1.1.5) and expert-rule-based program Derek Nexus (v2.2) accurately predicted all nine compounds to be non-mutagenic. This case study demonstrates the importance of expert review when applying predictive toxicology methods and highlights a possible activity cliff with regards to Schiff base formation and skin sensitization potential.