Mixture-based QSAR Models of Ocular Toxicity for Regulatory Hazard Categories

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Computational modeling can be used to design effective nonanimal approaches, if grounded in reliable experimental data. We have developed of a set of computational models to predict eye irritation and corrosion. The models were developed using a curated database of in vivo eye irritation studies from the scientific literature and stakeholder-provided data. The database contains over 500 unique substances, including many mixtures, tested at different concentrations. Substances were categorized according to Globally Harmonized System (GHS) and U.S. Environmental Protection Agency (EPA) hazard classifications. Two modeling approaches were used to predict classification of mixtures. A conventional approach generated predictions based on the chemical structure of the most prominent component of the mixture. A mixture-based approach used weighted feature averaging to consider all known components in the mixture. Ranking accuracy rates (calculated based on the area under the receiver operating curve) for EPA hazard classification of undiluted test substances were 74-81% and 75-80% for the conventional and mixture-based models, respectively. Ranking accuracy rates for EPA hazard classification of substances diluted to 10% in the conventional and mixture-based models were 90-95% and 92-96%, respectively. Ranking accuracy rates for GHS hazard classifications for undiluted test substances were 79-82% and 80-91% for the conventional and mixture-based models, respectively. Rates ranged from 89-95% for the diluted GHS classification predictions for both approaches. We observed a strong correlation between a substance's pH and activity. Our results suggest that these models are useful for screening compounds for eye irritation potential. Future efforts to increase the models' utility will focus on expanding their applicability domains and using them in conjunction with other input variables (e.g., in vitro data) to establish defined approaches for eye irritation testing. This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.