Defined Approaches for Predicting GHS and EPA Eye Irritation Classification of Agrochemicals

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Certain regulatory frameworks require in vivo testing to determine hazard labeling for agrochemical products. We conducted prospective in vitro testing to develop defined approaches (DAs) to predict GHS and EPA eye irritation classifications without animal testing. For GHS, we determined consensus predictions based on individual assay results aligned across five in vitro methods and historical rabbit data. Consensus predictions were achieved for 93% (27/29) of formulations. We developed four DAs, comprising bovine corneal opacity and permeability with histopathology alone ("DA-BCOP+"), or combined with EpiOcular™, SkinEthic time-to-toxicity for liquids, or EyeIRR-IS ("DA-EO+", "DA-TTL+", and "DA-EyeIRR-IS+", respectively). We used consensus predictions as the GHS reference classification. In comparison, 93% of predictions based on historical rabbit data were concordant or would maintain labeling. The remaining 7% were underpredicted, with underprotective labeling. DA-BCOP+ performed similarly with 7% underpredicted and underprotective. For DA-EyeIRR-IS+, 100% of predictions were concordant or would maintain labeling. For DA-EO+ and DA-TTL+, 93% and 89%, respectively, were concordant or would maintain labeling. The remaining 7% and 11%, respectively, were overpredicted, with overprotective labeling. Finally, for both GHS and EPA, we orthogonally analyzed concordance of classification and labeling predictions across the four DAs and historical rabbit data. For both classification systems, majority orthogonal concordance was achieved for 97% (28/29) of formulations, and all four DAs were equally or more protective of human health than the rabbit test. These DAs therefore have high utility for predicting GHS and EPA classifications of agrochemical formulations. Project was funded by NIEHS under Contract No. HHSN273201500010C.