Predicting GHS Hazard Classification for Eye Irritation/Corrosion Potential of Agrochemical Formulations Using Defined Approaches

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Background and Purpose

Regulators require that agrochemicals be labeled to indicate potential harmful effects caused by exposure. While in vitro methods have been developed for this purpose and are accepted by various regulatory agencies, other agencies continue to require the Draize in vivo rabbit eye irritation test ("rabbit test"). This is mainly due to discordance between direct comparisons of in vitro methods with the rabbit test. Discordance is particularly evident for substances identified as mild or moderate irritants by the rabbit test, which is also the range of irritancy where the rabbit test generates reproducible results less than 50% of the time. In 2022, the Organisation for Economic Co-operation and Development (OECD) issued Test Guideline (TG) 467, which describes defined approaches (DAs) for identifying chemicals with serious eye damage or eye irritation potential. DAs are intended to overcome limitations of individual test methods by using multiple methods in specific combinations to derive a prediction. However, the applicability of the DAs described in TG 467 are limited to non-surfactant neat liquids, and liquids and solids dissolved in water. The goal of this study was to confirm the applicability of in vitro methods to agrochemical formulations and develop DAs that leverage strengths of these methods to predict eye irritant potential.

Methods

Agrochemical formulations were selected for prospective testing based on availability of historical rabbit test data, to represent common agrochemical formulation types, and to span the full range of United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard classifications. Test methods were included based on their relevance to mechanisms of human eye irritation, and the results were assessed to determine which methods should advance to potential incorporation in a DA. Twenty-nine formulations were tested in up to five methods: bovine corneal opacity and permeability (BCOP; OECD TG 437), including histopathology, EpiOcular Eye Irritation Test (EO; OECD TG 492), SkinEthic time-to-toxicity for liquids (TTL; OECD TG 492B), in vitro depth of injury (IVDoI), and EyeIRR-IS. A preliminary analysis of alignment across these five in vitro methods and historical rabbit test data produced consensus predictions for each formulation, based on majority alignment across individual assay results. Four methods were then selected for inclusion in DAs based on their status as an OECD TG or validated, peer-reviewed method and were developed into four DAs to predict the full spectrum of GHS classifications. These DAs were based on BCOP with histopathology alone ("DA-BCOP") and EO, TTL, or EyeIRR-IS combined with BCOP with histopathology: ("DA-EO+", "DA-TTL+", and "DA-EyeIRR-IS+", respectively). For each formulation, GHS classifications predicted by the DAs and the historical rabbit test data were

assessed for concordance with the consensus prediction. Personal protective equipment (PPE) labeling associated with the predictions was also compared based on that of the consensus prediction.

Results

Consensus predictions were achieved for 27 of 29 formulations (data were insufficient for two formulations). Relative to the consensus predictions, 93% of classifications predicted by the historical rabbit test data were either equivocal or would not affect PPE labeling. The remaining 7% were underpredicted, and associated in vivo-based PPE labeling was under-protective of potential eye irritation. Classifications predicted by DA-BCOP were similar with 7% underpredicted and under-protective. For DA-EyeIRR-IS+, 100% of predicted classifications were equivocal or would not affect PPE labeling. For DA-EO+ and DA-TTL+, 93% and 89%, respectively, were either equivocal or would not affect PPE labeling. The remaining 7% and 11%, respectively, were overpredicted and associated PPE labeling was over-protective.

Conclusions

All four proposed DAs may have high utility for predicting the GHS classification of agrochemical formulations as the PPE labeling associated with the predictions are as or more protective of human health compared with the rabbit test. Furthermore, using the consensus prediction as the reference standard, some standalone in vitro methods can predict the GHS classification of agrochemical formulations as well as or better than the rabbit test. These results further support that the rabbit test may not be a suitable reference method for deriving eye irritation hazard classification information for agrochemical products, and that alternative methods such as DAs can be used instead. This project was funded in whole or in part with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.

Keywords: Alternatives to Animal Testing; Ocular Toxicity; Defined Approaches