Predicting Oral Acute Toxicity using the GHS Additivity Equation

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The United Nations Globally Harmonized System for Classification and Labeling (GHS) provides a mathematical approach to estimate the acute oral toxicity of a mixture based on the combined toxicities of the individual components of the mixture. The authors evaluated how well toxicity values calculated using the GHS formula and the corresponding U.S. Environmental Protection Agency (EPA) and GHS hazard categories agreed with those obtained from in vivo acute toxicity studies of the same formulations. Data were compiled for approximately 700 agrochemical and antimicrobial product formulations, most of which were classified in the less hazardous EPA Categories III and IV and GHS Categories 4, 5, and Not Classified (NC). Although overall concordance was 54% using the EPA classification system and 72% using the GHS system, the majority of discordant results were associated with substances with measured LD_{50}s between 2000 and 5000 mg/kg that were predicted using the additivity equation as having minimal toxicity (i.e., EPA Category IV or GHS NC). Such underclassifications may be of lesser practical concern from a risk assessment perspective than underclassification of more toxic substances. However, for the few toxic substances included in the data set, the additivity equation often predicted a less toxic outcome that the in vivo test. Given the inherent variability of the animal test, it is certainly possible that similar underclassifications could also be observed if the animal test were repeated. We also subdivided the dataset based on formulation type (i.e., antimicrobial cleaning products [AMCP] and agrochemicals) and found that classification concordance was much greater for AMCP (84% and 98%) than for agrochemicals (52% and 70%). These data indicate that acute systemic toxicity of many formulations is not well represented by the sum of their ingredients' toxicities. This could be because the formulations' components may interact to result in higher toxicity than is predicted by the GHS equation or because the variability of the animal study is not adequately accounted for in the additivity calculation. This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C. The views expressed above do not necessarily represent the official positions of any federal agency.