Rat Acute Systemic Toxicity Testing: Evaluating Reproducibility and Inherent Variability

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Regulatory agencies rely upon rodent in vivo acute oral lethality data to determine hazard categorization, assign appropriate precautionary labeling, and perform quantitative risk assessments. As the field of toxicology moves towards animal-free new approach methodologies (NAMs), there is a pressing need to develop reliable and robust reference data sets to contextualize results, to set expectations regarding NAM performance, and for training and evaluating computational models. To meet these needs, rat acute oral LD50 (dose corresponding to 50% lethality) data from multiple databases were compiled and curated. These data were analyzed to characterize variability and reproducibility of results across a set of more than 2400 chemicals with multiple independent study records. We did not have sufficient study metadata to evaluate the impact of specific protocol components such as species/strain, age, sex of rat, feed used, treatment vehicle, etc. However, we assumed studies had followed standard test guidelines, and thus evaluated several chemical-based possible sources of variability, including chemical structure, physiochemical properties, and functional use. We could not attribute the observed variability to any chemical-specific characteristics, and thus concluded that inherent biological or protocol variability is likely underlying the variance in the results. By bootstrapping across computed chemical-specific standard deviations, quantified variability was used to define a 95% confidence interval of ±0.25 log10(mg/kg). This confidence interval was used to define the uncertainty associated with discrete in vivo rat acute oral LD50 values, and may serve as a benchmark to apply to future NAM performance assessments. This project was funded with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C. This abstract does not necessarily reflect EPA policy.