Characterizing Variability Across Rat Oral Acute Toxicity Studies: Implications for Alternative Model Evaluation

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Alternative models developed for estimating acute systemic toxicity are often evaluated using *in vivo* LD50 values as reference data. However, *in vivo* acute systemic toxicity studies conducted according to accepted test guidelines can produce results that vary significantly. This variability can make a fair assessment of alternative models difficult or impossible. To characterize the variability of *in vivo* acute systemic toxicity data, we examined LD50 values from rat oral acute toxicity studies. Data were obtained from multiple databases including the NLM's Hazardous Substances Data Bank and ChemIDplus, the OECD's eChemPortal, and the JRC's AcutoxBase, resulting in a dataset comprising a total of 28,320 oral LD50 values representing 11,686 unique chemicals. A subset of 1592 chemicals that were evaluated in at least three independent rat oral acute toxicity studies were used for assessing variability, of which 22% (343/1542) had at least one study generating an outlier LD50 value (i.e., falling outside 1.5 times the interquartile range of the distribution of LD50 values per chemical). Furthermore, 34 chemicals had LD50 values ranging across at least three orders of magnitude. Such variability resulted in 83 chemicals being classified into at least three GHS oral acute toxicity labeling categories and 53 chemicals classified into at least three different EPA categories. These findings underscore the importance of considering an appropriate margin of uncertainty when using *in vivo* oral acute toxicity data to assess the performance of alternative methods. U.S. Federal funds from NIEHS/NIH/HHS contract HHSN273201500010C supported this study.