Variability of LD50 Values from Rat Oral Acute Toxicity Studies: Implications for Alternative Model Development

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Alternative models developed for estimating acute systemic toxicity are generally evaluated using in vivo LD50 values. However, in vivo acute systemic toxicity studies can produce variable results, even when conducted according to accepted test guidelines. This variability can make assessment of alternative models extremely challenging. To characterize the variability of in vivo acute systemic toxicity data, we examined a large compilation of LD50 values reported in rat oral acute toxicity studies. Data were obtained from multiple curated databases including the NLM’s Hazardous Substances Data Bank and ChemIDplus, the OECD’s eChemPortal, and the JRC’s AcutoxBase. The resulting dataset comprised a total of 21,210 rat oral LD50 values representing 15,698 unique chemicals. A subset of 1,118 chemicals that had been evaluated in at least three independent rat oral acute toxicity studies were used to assess variability. Of this subset, 20% (234 chemicals) had at least one study generating an “extreme” LD50 value (i.e., falling outside 1.5 times the interquartile range of the LD50 distribution for that chemical). Furthermore, 30 chemicals had LD50 values ranging across at least two orders of magnitude, with seven of these chemicals having LD50 values ranging across at least three orders of magnitude. This degree of variability can confound hazard categorization: LD50 values from 47 chemicals fell into at least three different Globally Harmonized System (GHS) oral acute toxicity labeling categories, and values from 28 chemicals fell into at least three EPA hazard 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 and provide a reference dataset to ensure that appropriately representative LD50 data are routinely used for the development and validation of alternative models. This project does not necessarily reflect EPA policy and was funded in whole or in part with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.

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