Setting Performance Expectations for New Approach Methods in Toxicity Testing: Moving from Intuition to Hard Data

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Establishing realistic performance expectations for New Approach Methods (NAMs) in toxicity testing requires moving beyond assumptions and toward empirical comparisons with human-relevant data. Traditional rodent-based toxicity tests have long been used to predict human health effects of environmental and industrial chemicals, yet their true concordance with human outcomes remains difficult to quantify—particularly in the absence of direct human testing. In recent studies, we systematically assessed the quantitative and qualitative alignment between rodent toxicity data, human clinical trial outcomes, and *in vitro* NAM-based predictions. Using lowest observed adverse effect levels (LOAELs) from rodent studies (adjusted to human equivalent doses) and comparing them with human LOAELs, we identified moderate correlation and limited predictive accuracy for matching specific adverse effects. Although rodent LOAELs were typically higher than human LOAELs, applying standard uncertainty factors rendered rodent data conservatively protective in most cases. In parallel, we evaluated *in vitro* bioactivity-based administered equivalent doses (AEDs), which also showed moderate correlation with human LOAELs—albeit with AEDs consistently lower than human values. Direct comparisons between *in vitro* AEDs and rodent LOAELs revealed greater divergence, both in correlation and magnitude. These findings underscore the importance of grounding expectations for NAMs in hard data, providing a transparent benchmark for their performance relative to both traditional animal models and observed human responses. By quantifying these relationships, we can better calibrate the role of NAMs in regulatory toxicology and prioritize approaches with demonstrable predictive value.