Variability of In Vivo Toxicology Studies: Impact on NAMs

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Test method reproducibility is critical for producing data that can be replicated, easily interpreted, and used for actionable outcomes. Guideline in vivo toxicology studies have long been the default for chemical safety assessments for regulatory decision-making and thus are the standard against which new approach methodologies (NAMs) are evaluated. However, retrospective analyses have demonstrated substantive variability in data from these studies. This variability, which has a variety of potential sources, can confound the use of these in vivo studies as reference data for establishing confidence in NAMs. With interest increasing in integrating and implementing NAMs into regulatory decision making, it becomes imperative to understand the variability of reference animal data and how that may affect the NAM evaluation process. This presentation will describe variability evaluations conducted on several different standardized in vivo toxicology test methods, including both single and repeat-dose study designs. These evaluations have shown that independent replicates of these studies can have less than 50% likelihood of yielding the same hazard classification, particularly when the original test characterizes the substance as having a mild to moderate effect. We have compiled results from variability analyses, systematic reviews, and meta-analyses of in vivo toxicological studies to characterize sources of variability across various study types. An improved characterization of in vivo variability will support a better understanding of how to set appropriate expectations when building confidence in the use and interpretation of NAMs. Project was funded by NIEHS under Contract No. HHSN273201500010C.