ID HESI.01

Quantitative Interpretation of In Vivo Mutagenicity Dose Response Data for Risk Assessment and Regulatory Decision-Making

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Interpretations of in vivo genotoxicity test results have traditionally involved dichotomous hazard identification. However, recent works have established a paradigm involving quantitative dose response analyses for determination of PoD (point of departure) values, followed by extrapolation below the PoD for chemical prioritization, risk assessment and regulatory decision-making. Standardized methods to analyze dose-response data have been established; the most robust approach determines the BMD (Benchmark Dose). The CES (critical effect size) is a key parameter for BMD determination; for in vivo genotoxicity endpoints, the emerging consensus value is 50%. The use of BMDs to determine health-based guidance values (HBGVs) commonly requires the application of assessment factors (AFs) to account for interspecies differences, variability in individual sensitivity, less-than-chronic treatment, and possibly effect severity. Interspecies adjustment commonly uses animal-to-human body-size scaling. AFs to adjust for variability in human sensitivity are the subject of considerable controversy. Analyses of published genotoxicity dose-response data scrutinising the effects of compensatory pathway deficiency indicate that a default AF of 10 for sensitivity differences is likely appropriate. Published dose-response data can also be used to evaluate the utility of a default AF to adjust for less-than-chronic treatment durations. An initial comparison of chronic and acute genotoxicity datasets suggests that a default AF of 10 may not be sufficient. The need of an additional AF for effect severity is also the subject of continued debate. Although the aforementioned AFs are commonly multiplied to provide a composite value, the approach can result in values that are unnecessarily conservative, particularly for substances such as aneugens. An alternative approach involves the use of the MOE (Margin of Exposure) concept that simply examines the ratio of the PoD to the estimated level of human exposure. The minimum acceptable MOE is often set at 10,000, with values below 10,000 indicating the need for intervention. Another alternative involves the use of informatic tools such as APROBA to conduct approximate probabilistic analyses, i.e., analyses that consider inherent uncertainties within the AF values used to determine HBGVs. The approach permits critical examinations of the uncertainties associated with HBGVs such as the RfD (Reference Dose).