**Quantitative Interpretation of in vitro Genotoxicity Data**

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The evaluation of genotoxicity (i.e., mutagenicity, clastogenicity and aneugenicity) plays a critical role in the assessment of chemical hazard. Traditionally, genotoxicity assessment results have been used mainly for hazard identification purposes in order to classify chemicals as genotoxic or non-genotoxic. However, there is increasing use of quantitative approaches (i.e., dose-response analyses) to determine Point-of-Departure (PoD) metrics that can be used for risk assessment.

Under many regulatory frameworks, chemicals require both in vitro and in vivo genotoxicity assays. However, there is a growing international movement away from rodent studies in favor of non-animal approaches that can serve as human-relevant alternatives. Thus, there is a need to develop strategies to optimally use in vitro concentration-response data to quantify the genotoxic risk that chemicals pose to human and environmental health. We are focused on addressing this issue through collaborative case studies and workshops that strive to develop standardized approaches and strategies for improved quantitative interpretation of in vitro genotoxicity data.

One strategy for determination of human relevant PoD values from in vitro genotoxicity data is in vitro to in vivo extrapolation (IVIVE). Specifically, IVIVE models can be used to estimate the administered equivalent dose in humans (i.e., the human AED) that would result in an internal concentration in the plasma or tissues equivalent to the concentration observed to be genotoxic in vitro. Thus, a PoD for risk assessment can be established. To demonstrate the utility of the IVIVE approach for quantitative interpretation of genotoxicity assessment results, the Genetic Toxicology Technical Committee, under the auspices of the Health and Environmental Sciences Institute, conducted a case study using 31 reference chemicals (https://doi.org/10.1002/em.22521). The results demonstrated that PoDs derived from in vitro concentration-response data and IVIVE are generally protective of human health. Furthermore, chemicals classified as misleading positives (i.e., positive in vitro despite negative in rodent studies), were found to have very high AEDs deemed to be of low biological relevance. The results support preclusion of confirmatory rodent studies.

To support the paradigm shift in genotoxicity assessment that favors non-animal alternatives, an Expert Working Group (EWG) of the 8th International Workshop on Genotoxicity Testing (IWGT) further evaluated the utility of quantitative interpretation of in vitro concentration-response data for risk assessment (https://doi.org/10.1002/em.22582). The major goal of the workshop was to identify in vitro genotoxicity testing advancements, including IVIVE approaches, and the risk assessment applications that could be enhanced by quantitative interpretation strategies. Additional goals included analyses to determine the critical effect size (CES) that is suitable for analysis and interpretation of in vitro concentration-response data, i.e., response levels above background that could be considered as adverse or unacceptable. The results suggest that the CES need to be endpoint-specific, and that it should be scaled to response variability or the maximum response for the endpoint. The EWG summarised limitations and uncertainties related to the use of in vitro concentration data for PoD determination and risk assessment; the workshop outcome will provide a direction for future work that ultimately supports routine use of in vitro-dominant testing strategies in regulatory settings.