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The interpretation of in vitro dose-response data for risk assessment and regulatory decision-making

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Chemical risk assessments are routinely performed using data derived from rodent toxicity tests; however, there is increasing awareness that non-animal alternatives are more ethical and potentially more relevant for evaluating human risk. Indeed, global efforts are establishing new guidelines to reduce or replace the use of animals in toxicity testing. Given these international pressures, there is an urgent need to build scientific confidence in the effective use of non-animal alternatives for quantitative risk assessments. An Expert Working Group (EWG) of the 8th International Workshop on Genotoxicity Testing (IWGT) was convened to initiate discussions towards the standardization of testing strategies and data interpretation for quantitative in vitro genotoxicity concentration-response data for risk assessment. The EWG first reviewed the in vitro mammalian cell assays used currently for genotoxicity assessment. The variability and maximal response of in vitro tests were examined to estimate biologically relevant critical effect sizes for use in point-of-departure (POD) determination. Next, the EWG reviewed the results of computational models employed to determine human-relevant PODs from in vitro concentration-response data. Lastly, the EWG evaluated risk assessment applications for which in vitro data are ready for routine use, and applications where further validation efforts are required. The EWG concluded that in vitro genotoxicity concentration-response data can be interpreted in a risk assessment context; however, additional research will be required to address remaining uncertainties and limitations before broadly applying an in-vitro-only strategy in regulatory decision making.

Keywords:
new approach methodologies, risk assessment, genotoxicity.