ID HESI.04

In vivo genetic toxicity assessments for nitrosamines

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Some N-nitrosamines may be considered potent carcinogens in animals because metabolically activated N-nitrosamines may form stable DNA adducts that lead to mutations and initiation of cancer in animals. However, approximately 18% N-nitrosamines that have been tested in previous animal carcinogenicity studies show no indication of carcinogenic potential. Furthermore, the carcinogenic potencies for N-nitrosamines span about 4 orders of magnitude with TD50s overlapping non-nitrosamines that are not in the cohort of concern. The lifetime cancer bioassays in rodents are time- intensive and associated with high experimental costs. Assessment of in vivo genotoxicity in rodents to determine a robust point of departure is a practical surrogate for assessment of nitrosamines. Here we use NDEA as a case study to compare the sensitivities of three in vivo methodologies including the transgenic rodent assay (TGR), Duplex Sequencing (DS) and Comet assay in both Big Blue mice and rats. NDEA was administered to Big Blue® or wild type rodents at a wide range of doses to enable a robust dose-response analysis. Both comet and TGR assays detected significant increases in the genotoxicity of NDEA at doses of 1 and 3 mg/kg/day in the liver of rodents and the BMD ranges calculated from both assays are largely overlapping. The DS appears to be slightly more sensitive than TGR assay in detecting a statistically increase in MF in rat liver exposed to NDEA at dose of 0.1 mg/kg/day. However, none of the three in vivo assays detected a genotoxic effect caused by exposures to NDEA equal to or lower than 0.01 mg/kg/day, suggesting a no observed genotoxic effect level (NOGEL) could be observed for NDEA. Overall, this work shows that the results of both Comet and DS assays have a good agreement with the gold standard TGR assay in dose-response assessment of a well-studied N-nitrosamine and could be an excellent alternative for the assessment of nitrosamines *in vivo.*