

Investigation of the Application of Innovative Risk Assessment Approaches for Receptor-Mediated Endpoints: A Case Study with Di(2-ethylhexyl)phthalate (DEHP)

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The goal for this project is to apply advanced or novel risk assessment approaches to a toxicant that has an existing multi-endpoint animal toxicity database with no extensive studies of human endpoint effects. DEHP was selected as the demonstration compound for this project because the effects that result from exposure to this compound are well characterized, and the potential modes of action for some endpoints have been hypothesized, decreasing the uncertainty in these steps of the risk assessment process. In general, the database available for DEHP provides much of the information needed for conducting an innovative human health assessment, resulting in the determination of a non-cancer and cancer risk estimate. The proposed assessment plan has followed the standard steps for conducting a risk assessment. However, in each step advanced approaches have been considered in the quantification of internal dose, rather than relying solely upon external dose. In addition, investigations were conducted in the use of precursor endpoints in the dose-response assessment, both as endpoints and as potential dose-metrics. Multiple approaches were applied in the quantification of variability and uncertainty to demonstrate the potential bounds of the risk estimates, rather than relying upon standard default factors. Using the database for DEHP allowed for harmonization across cancer and non-cancer endpoints because available proposed modes of action support a common key event in the development of both reproductive toxicity and carcinogenicity in the rodent.

Implications: The results provided insights on how to conduct quantitative dose-response analyses and risk assessments for compounds that act indirectly by way of a common key event, such as receptor mediation. It also allowed for the application of innovative approaches in consideration of noncancer and cancer endpoints in combination. This included the integration of complex exposure protocols, such as those used in the assessment of reproductive/developmental endpoints that can cross multiple generations in the animal model. This result has also provided a framework for conducting risk assessments for compounds acting through modes of action suggesting a similar key event in the development of multiple endpoints.

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