ToxStrategies

Assessment of Relative Potency Factors for Six Phthalates

S. Fitch, D. Wikoff, J. Foreman, A. Buerger, L. Haws, and C. Palermo

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Abstract:

Background and Purpose: The U.S. EPA has proposed to conduct a cumulative risk assessment (CRA) using a relative potency factor (RPF) approach for six phthalates. Though RPFs have been discussed by various entities, no consensus RPF values have been established; proposed RPFs have been limited to selected studies rather than being representative of a systematic evaluation of the underlying evidence base. Expert reviews by the National Academies and Science Advisory Committees have consistently recommended that if such an approach is applied for phthalates, fundamental aspects underlying relative potency - including a common mode of action, clear index chemical, and parallelism in dose response curves - are to be addressed. As such, the objective of this research is to systematically assess key issues for phthalate syndrome as a first step in developing RPFs for phthalates to be used in cumulative assessments.

Methods: A protocol was developed for the systematic identification and evaluation of data suitable for developing RPFs for diethylhexyl phthalate (DEHP), di-n-butyl phthalate (DBP), butyl benzyl phthalate (BBP), diisononyl phthalate (DINP), dicyclohexyl phthalate (DCHP), and diisobutyl phthalate (DIBP) based on fetal testosterone and anogenital distance (AGD). An initial database was established based on the Phthalates Human Health and Environmental Hazards Evidence Map developed by EPA TSCA; titles and abstracts were screened using specific inclusion criteria (e.g., ≥3 treatment groups; statistically significant responses). Study information, including dose-response data, were extracted. RPFs were developed for individual datasets using multiple dose-response methods to assess variability in values around two key issues: index chemical selection (DEHP or DBP) and dose-response parallelism.

Results: From the ~400 studies in HAWC (or identified with hand-searching) categorized as reporting at least two phthalates, 6 studies were carried forward to assess key issues (only 2 studies met all inclusion criteria). Many studies were excluded from the evaluation due to lack of statistically significant response, indicating general inconsistency within and across the evidence base for fetal testosterone and AGD measurements. Across the 6 studies evaluated, the candidate index phthalates DBP and DEHP were not consistently the most potent and in several cases were less potent than other phthalates assessed. Benchmark values varied by response level (e.g., ED_5, ED_{10}, and ED_{50}) within datasets; resulting RPF values were also variable (e.g., ranging from 0.403-1.14 for the 50% and 5% effect levels in one study, respectively). RFP values also varied by index phthalate within and across datasets (e.g., BBP RPF values ranged from 0.09-0.86 across index chemicals in one study).

Conclusions: RPF estimates varied substantially for individual datasets as well as across datasets, demonstrating the importance of addressing key issues previously raised by experts in developing RPFs for phthalates. Combined data approaches that standardize dose-response curves and accommodated heterogeneity in underlying data could be used to address variability in response and lack of parallelism.

Collectively, these findings demonstrate the importance of addressing key issues when developing RPFs as well as quantitatively evaluating uncertainty and variability both at risk assessment and risk management stages in a cumulative assessment.