Dear Mike:

We were pleased to learn that the Chronic Hazard Advisory Panel (CHAP) for phthalates is aware of our recent paper titled “The human relevant potency threshold: reducing uncertainty by human calibration of cumulative risk assessments” published in *Regulatory Toxicology and Pharmacology* and recognize that it has implications for cumulative assessment of phthalates. In order to aid the CHAP discussions related to the content of our paper, I thought it would be useful to summarize its key points.

The Human-Relevant-Potency-Threshold (HRPT) approach we recommend explicitly assumes the Dose Addition - Common Adverse Outcomes (DA-CAOS) approach, proposed by the National Research Council (2008) and Kortenkamp & Faust (2010), as a screening-level assessment. The HRPT approach then builds upon this work to produce a second-tier analysis that calibrates application of the DA-CAOS approach based on potency and effect data for relevant human pharmaceuticals. In doing so, it combines the tenable assumptions of the DA-CAOS approach and empirical data utilized by Kortenkamp & Faust with the biologically based inclusion criteria of the Toxic Equivalency (TEQ) approach, and calibrates these using empirical data on chemical potency from relevant human pharmaceuticals.

Based on the comparisons of human versus test-species sensitivity, potency differences between chemicals, and concentrations at which DA adverse effects are demonstrable in test species, we estimated the potency threshold at which DA would be a conservative, but tenable, as-
sumption for humans. Section 4 of our paper describes application of the HRPT approach to phthalates and other chemicals with anti-androgenic potential in humans. Based on the steps described therein, we propose applying DA to chemicals capable of producing CAOS whenever humans are exposed to concentrations of those chemicals greater than one-fifth the rat NOAEL for effects on the developing male reproductive tract.

The analysis presented in Section 2 of Borgert et al. show that calibrating the application of DA in this manner imparts at least an order of magnitude conservatism to the human risk assessment of chemicals with anti-androgenic potential. From those analyses, we conclude that independent action (IA) should be applied as the most appropriate mixture model for human exposures to mixtures of potential anti-androgenic chemicals at concentrations lower than the derived HRPTs.

As we state in the publication, the HRPT approach accommodates both the DA-CAOS concept, where tenable, and the well-established TEQ concept, but improves upon each by providing a means for calibrating the assumption of DA with human data. Using the refined HRPT approach, we conclude that under current exposure conditions, the anti-androgenic potential of the phthalates under review by the CHAP should be assessed by IA rather than by DA.

Please feel free to contact me if you have any questions on the publication.

Sincerely yours,

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President & Principal Scientist