Evaluation and comparison of bisphenol A analog activity using ToxCast data

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Bisphenol A (BPA) is used in consumer products and industrial applications, primarily in plastics, and has been detected in the environment, human urine, blood, and breast milk. Mainly studied as an endocrine disruptor, other toxicities, including obesity, metabolic conditions such as diabetes, and neurodevelopmental effects have also been associated with exposure to BPA, indicating that its effects may not be limited to estrogenicity. In addition, a number of BPA analogs are in use and may exhibit other additional toxicities. To address these unknowns, we examined the bioactivity of 21 BPA analogs across a selection of ToxCast/Tox21 assays grouped by 7 gene sets including estrogen receptor (ER), androgen receptor (AR), thyroid receptor (TR), peroxisome proliferator-activated receptor (PPAR), pregnane x receptor (PXR), aromatase (AROM), and aryl hydrocarbon receptor (AHR). The most active compounds were bisphenol AF (BPAF) (ER, AR, AROM, AHR), bisphenol A glycidyl methacrylate (TR), 3,3',5,5'-tetrabromobisphenol A (PPAR) and bisphenol B (BPB) (PXR). We used these data to produce toxicological prioritization index (ToxPi) scores and images to integrate and visually compare the toxicity profiles across all gene sets. The compounds with highest ToxPi scores were BPAF, BPA and BPB. We also mapped the intended gene targets for all ToxCast assays to their associated KEGG BRITE protein families in order to characterize their toxicity profiles on a broader spectrum. The compounds with the highest ToxPi scores were again BPAF, BPA and BPB, all of which were particularly enriched in the nuclear receptor, ion channel, transporter, and transcription factor protein families. Finally, we explored the structure-activity relationships of the analogs to the gene sets in order to determine how predicted models of their activity compares to our *in vitro* data. Using the OASIS Pipeline Profiler, we found good predictivity for ER and AR (17/21 and 13/21 correct) but not AHR or AR (3/21 and 8/21). These broad-based screening approaches allowed us to identify a wide spectrum of potential biological targets and build more comprehensive toxicity profiles of BPA and its analogs in order to better evaluate their potential health effects. *This abstract may not necessarily reflect official Agency policy*.

Keywords: Bisphenol A, ToxCast, alternative testing, analogs