Individual and mixture endocrine activity of BPS and BPC using in vitro estrogenic/anti-androgenic transcriptional activation assays and the in vivo uterotrophic assay

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Bisphenol A (BPA) is gradually being phased out of many consumer products and processes leading to potential increases in human and environmental exposures to relatively understudied replacement compounds, including Bisphenol S (BPS) and Bisphenol C (BPC). Research from our lab has shown that BPA and Bisphenol AF (BPAF) display nearly identical anti-androgenicity and similar estrogenicity (BPAF ~10-fold more potent) in vitro, whereas BPAF stimulated uterine weight gain with oral administration in vivo (≥50 mg $kg^{-1} d^{-1}$) but BPA had virtually no effect. Here we asked, do BPS and BPC behave similarly to either BPA or BPAF in vitro and/or in vivo estrogenicity/anti-androgenicity assays? We conducted estrogen receptor (ER) transactivation assays utilizing T47D-KBluc cells and androgen receptor (AR) antagonism assays utilizing transient transduction of CV-1 cells with chimp AR. We found that BPS was less potent than BPA at both inducing ER gene expression (~6-fold greater EC_{50}) and AR antagonism (~100-fold greater EC_{50}) in vitro. In contrast, BPC was remarkably potent at both inducing ER activation and AR antagonism as compared to BPA (~100-fold lower EC_{50} for both). Since BPA and BPS are currently in use, exposures to mixtures of BPA, BPS, BPC, other replacement compounds, and associated metabolites are possible. In order to determine if a mixture of BPA and BPS acts in an additive, antagonistic or synergistic manner, we conducted ER transactivation assays with binary mixtures of BPA and BPS (8x8 factorial design) and found that these compounds conformed to dose addition model predictions for ER agonism in vitro. In addition, we are examining the effects of BPS, BPC, and mixtures with other chemicals in vivo using oral exposures to determine the estrogenicity of these chemicals when administered via a relevant route of exposure. Abstract does not reflect U.S. EPA policy.