

Effects of Prenatal Exposure to Bisphenol A (BPA), n-benzyl butyl phthalate (BBP), and 2,3,7,8 Tetrachlorodibenzo-p-dioxin (TCDD), on the Genomic Profile of the Rat Mammary Gland

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Environmental xenoestrogens, such as bisphenol A (BPA), a plastic monomer commonly found in dental sealants and food cans, n-benzyl butyl phthalate (BBP), which is used as a plasticizer, and 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD), a highly toxic dioxin produced as an impurity during the manufacture of certain herbicides and by incineration of industrial waste, are endocrine disruptors that mimic the effects of endogenous hormones. This work was designed with the purpose of determining whether prenatal exposure to these xenoestrogens has a lifetime effect on the development of the rat mammary gland that could predispose this organ to cancer development. BPA and BBP were administered intragastrically to pregnant rats from the 10th to the 21st day post-conception (date of delivery), at a low and a high dose: 25ug or 250ug BPA/kg body weight (kgbw) and 120mg or 500mg BBP/kgbw. TCDD was administered as a single dose of 3ug/kgbw on day 15 post-conception. Equivalent doses of sesame oil were administered to control groups. After delivery the female offspring was transferred to foster mothers and separated in groups of twenty each. On days 21, 35, 50 and 100 of post-natal life, ten female offspring from each group were euthanized and mammary glands were rapidly frozen in liquid nitrogen for RNA extraction and gene expression analysis using an Agilent platform of 60-mer oligo-microarrays containing 22,000 features. The most representative genes were validated using Real time PCR. BPA exposure upregulated immune system-related genes, such as Cd3d that mediates T-cell transduction signal at both doses. BBP treatment induced changes in the expression of genes related to cell proliferation, differentiation and immunosurveillance, with upregulation of Ptprc, Cd5, and Cd3d at all the ages tested. GAD1 expression was consistently downregulated at 50 and 100 days of age. The most significant genomic changes were observed at 100 days, with significant modification of proliferation and differentiation related genes, such Notch, and Cry61. These data clearly indicate that BBP induces long lasting changes in the genomic profile without affecting the pattern of gland development and morphological architecture. TCDD treatment induced an asynchrony between the morphological changes observed and the expression of a genomic profile that was significantly different to the control group at 100 days of age. (This work was supported by NIEHS Grant UO1 ES012771).