Estrogenic effects of bisphenol A in mice following in utero and post-natal exposure

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Bisphenol A (BPA) is an estrogenic monomer that is used in the manufacture of a wide variety of products, including dental materials, food and beverage containers, and babies formula bottles. Investigations have revealed that BPA leaches from such products in concentrations that are sufficient to induce cell proliferation *in vitro.* The aim of this study was to explore the developmental and reproductive effects of BPA, administered during both postnatal life and *in utero* development. Immature female CD-1 mice were exposed to BPA in concentrations ranging from 0.1 to 100 mg/kg body weight for 3 days. Uterine wet weight and various indices of cell proliferation were measured. Results revealed a uterotropic response at a concentration of 100 mg/kg BPA only. In contrast, significant changes were seen in epithelial cell height at a concentration of 75 mg/kg BPA and, on the basis of preliminary work, in the expression of proliferating cell nuclear antigen (PCNA) at even lower doses. These data demonstrate that BPA induces estrogenic changes in the mouse uterus at the cellular level that are not accompanied by changes at the organ level, highlighting the need to re-evaluate the validity of the mouse uterotropic assay. In a different study, pregnant CD-1 mice were exposed to 25 and 250 μg/kg BPA from day 8 to 20 of gestation and the female offspring were assessed for reproductive tract abnormalities and changes in estrus cyclicity. The results presented here describe some aspects of this still continuing study. Histological assessment of the vagina at 3 months of age revealed marked interdigitation of the epithelial/stromal interface, a greater presence of euchromatic nuclei within the epithelial cells suggesting increased activity, and leukocytic and macrophage invasion of tissue. Assessment of estrus cyclicity over a 14 day period revealed persistent estrus in mice from both the 25 and 250 μg/kg BPA groups when this was not seen in the control group. These changes are strikingly similar to those described in the rodent vagina as a result of *in utero* exposure to estradiol and diethylstilbestrol (DES). It is evident that BPA induces alterations in the morphology and proliferative activity of the uterus at concentrations not detected using the classic mouse uterotropic assay. More importantly, this work reveals that *in utero* exposure to low, environmentally relevant doses of BPA induces marked vaginal pathology and changes in cyclicity.

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