The Xenoestrogen Bisphenol-A Alters Development of the Fetal Mouse Mammary Gland

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A recent study observed that Bisphenol-A (BPA), a chemical found in food and beverage containers, can be detected in the urine of 95% of Americans, indicating that exposure is widespread. Laboratory experiments have shown that BPA has estrogenic activity *in vitro* and *in vivo*. Our previous studies showed that perinatal exposure to environmentally relevant doses of BPA leads to alterations in the mammary gland (MG) observed at puberty and adulthood, long after BPA exposure ended. Some of these alterations are equivalent to human risk factors for breast cancer.

We hypothesized that BPA acts via the estrogen receptors present in the fetal MG altering normal morphogenesis. To explore this hypothesis, we exposed litters to either vehicle or 250ng BPA/kg/day from embryonic day (E)8 until E18, when fetuses were delivered by C-section and their MG removed. We observed that in unexposed fetuses, the relative position of the fetus with respect to its siblings in the uterus influenced growth of the ductal tree, which was more developed in females positioned between two males than in females positioned between two females. BPA exposure significantly increased ductal area and extension, and obliterated these positional differences. Because positional effects are thought to be hormone-related, we suspect that the estrogenic properties of BPA are interfering with the normal hormonal milieu of the fetus.

The alterations of the ductal architecture observed in whole mounts may be attributed to changes in both the stromal and epithelial compartments of the fetal MG. In the stroma, BPA exposure promoted maturation of the fat pad and altered the localization of collagen. Within the epithelium, BPA led to a decrease in cell size and delayed lumen formation. Because MG development is dependent on reciprocal interactions between these compartments, the advanced maturation of the fat pad and changes in the extracellular matrix may be responsible for the altered growth, cell size and lumen formation observed in the epithelium. Together, these results suggest that the altered MG phenotypes observed at puberty and adulthood in perinatally exposed mice have their origins in fetal development.

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