Our Stolen Future: Bisphenol A affects mammary tissue growth


Markey *et al.* raise the stakes in the debate over human health risks of bisphenol A by demonstrating, in laboratory mice, that low level exposure in the womb to the contaminant causes changes in mammary tissue that are associated with carcinogenesis in both rodents and humans.

Their findings are consistent with three facts: that the level of intrauterine estrogens is associated with increased risk of breast cancer in daughters (see Ekbom *et al.* 1997; Weiss *et al.* 1997; Braun *et al.* 1995); that bisphenol A is estrogenic (e.g., Brotons *et al.* 1995); that bisphenol A in the pregnant rat quickly reaches the fetus, where it is more bioavailable than in the mother's serum (Miyakoda *et al.* 1999, Takahashi and Oishi 2000).

**Human exposure to bisphenol A is now widespread** because of its use in the manufacture of polycarbonate plastics and epoxy resins. Many consumer products are made from these materials, including large drinking water containers, baby bottles, and reusable milk and food containers. The resins are also used to coat the interior of food cans and to create dental sealants. Leaching is known to occur from several of these products but the amount of leaching has not been assessed for many of the current uses of bisphenol A. **Hence it is impossible to assess cumulative exposure experienced by people based on current data.**

Nonetheless, the exposure levels that have been established *already* are within the range shown by Markey *et al.* to have adverse effects on mice. Moreover, bisphenol A is but one of a host of environmental estrogens, whose activities at the molecular level most likely will be additive because of their common mechanism of...
action, binding with the estrogen receptor.

**What did they do?** Markey et al. exposed fetal female mice *in utero* to bisphenol A via implanted osmotic pumps. Two doses were used, 25 µg/kg body weight of the mother and 250 µg/kg. Bisphenol A was delivered from day 9 of pregnancy onward through delivery (day 20). Different subsets of the treated female offspring were examined at 10 days, 1 month (puberty) and 6 months after birth, using a series of histological, immunochemical and morphometric measurements, comparing treated animals with controls.

**What did they find?** Significant differences emerged by 1 month of age:

The 25 µg/kg treated animals showed "a greater ductal elongation beyond the edge of the lymph node" whereas the 250 µg/kg showed retarded growth. The difference between the two treatment groups was statistically significant, suggesting a nonmonotonic dose-response curve. Neither group of treated animals, however, was statistically separable from the control group at this age.

While morphological differences between treated and control animals were not noted at this age, biochemical differences were already apparent at 10 days old. Within the epithelium of the mammary gland, DNA synthesis was suppressed. Both treatment groups had lower rates of DNA synthesis compared to controls. In the mammary gland stroma, however, DNA synthesis rates decreased compared to controls at age 10 days but increased compared to controls at 6 months age.

Morphological differences accumulated between 1 month and 6 months age. Typically, untreated mice experience significant development of the mammary gland during this period, with growth of a "ductal tree that comprises terminal ducts, terminal endbuds...
and very few alveolar buds." Markey et al. discovered that bisphenol A exposure produces a significant increase of the ductal and alveolar structures compared to controls:

Their quantitative analysis of mammary gland structure revealed significant increases in the relative area occupied by ducts (upper left), terminal ducts (upper right), terminal endbuds (lower left) and alveolar buds (lower right).

**What does it mean?** At this stage of the study of BPA in relation to breast cancer, it is impossible to reach any conclusions. Two aspects of their results raise concerns, however, because they reveal patterns in the impact of BPA that resemble the initiation of breast cancer:

"In the present study, two findings may suggest a predisposition of the BPA-exposed mammary gland to neoplastic change. The altered relationship in DNA synthesis between the epithelium and the stroma that was observed at all stages of development is striking, because disruption of the communication between these two tissue compartments is acknowledged as being critical to the development of neoplasia within both human breast and rodent mammary..."
gland. In addition, the significant increase in terminal ducts and terminal end buds in the 6-mo-old mice is also remarkable, because an increase in these structures in rats and humans correlates positively with the incidence of carcinomas that arise specifically from such sites."

"In summary, in utero exposure to low, presumably environmentally relevant doses of BPA changes the timing of DNA synthesis in the epithelium and stroma of the mammary gland, resulting in an histoarchitecture that is atypical for a virgin mouse. **These changes, which are apparent long after the period of exposure is over,** strengthen the hypothesis that in utero exposure to environmental estrogens may predispose the developing fetus to mammary gland carcinogenesis in adulthood." (emphasis added)

Two practical notes:

- The strain of mice used by Markey *et al.* is known for its insensitivity to estradiol. This suggests that other inbred strains, as well as wild-type mice, are likely to be more sensitive to BPA than is reported here.
- Secondly, their analysis of mammary gland changes reveals BPA effects at a level 4000 times lower than the level of BPA found to be biologically active by the standard assay for estrogen activity in live rodents, the uterotropism assay. **This suggests that the uterotropism assay is insufficiently sensitive to be used for establishing regulatory standards.**