Two excellent review articles pertinent to breast cancer risk were just published in the current issue of Endocrine Reviews. One provides a thorough review of the issues regarding BPA exposure (Soto, A et al. Endocrine Reviews 2009; 30: 75-95) and the other reviews the role of IGF-I in normal mammary development and in pre-neoplastic mammary lesions (Kleinberg D, et al. Endocrine Reviews 2009; 30: 51-74). For those who are interested, these articles can be found at: http://edrv.endojournals.org/current.shtml. Taken together, these articles lend further support to the proposition that BPA and cow milk may be the most problematic of all environmental hormonal exposures.

In the article by Soto et al., the estimated range of exposure in young children to the synthetic estrogen, BPA, is given as 43-74 ng/kg BW per day, numerous physiological effects in animal models from low dose exposure are reviewed and controversial issues regarding experimental design and non-monotonic dose response curves are addressed. I estimate that the comparable exposure in young children to the more potent, natural estrogens in commercial cow milk is 19 ng/kg BW per day. This estimate is based on: (1) the estrogen concentration in commercial skim milk (a total of 11 different estrogens and estrogen metabolites were recently measured by LC/MS-MS by Tim Veenstra et al. of the Proteomics Lab at NCI, the manuscript for which has just been accepted for publication in the Journal of Chromatography B), (2) the USDA recommended dietary guidelines of 16 ounces of milk/day (473 ml) for 2 to 8 year olds, (3) the WHO weight standard (50th percentile) for 2 year-old girls of 11.5 kg (25.3 lbs), and (4) the American Academy of Pediatrics dietary recommendation of nonfat milk for all Americans 2 years of age and older.

The recent and dramatic drop in use of hormone replacement therapy (HRT) has been shown to be the principal factor in the recent and unprecedented decline in post menopausal breast cancer incidence. Prempro, the most frequently prescribed HRT, contains the synthetic progestin, medroxyprogesterone acetate (2.5 mg) plus conjugated equine estrogens (0.625 mg) extracted from the urine of pregnant mares. Commercially pooled milk contains natural progesterone and conjugated bovine estrogens originating from the milk of pregnant cows. Pharmacokinetic studies of the estrogens in HRT indicate that conjugated estrogens are more readily absorbed into the bloodstream and hence are the more bioavailable form of orally ingested exogenous estrogen. Ninety eight percent of the estrogens in skim milk were found to be conjugated (per Veenstra et al. study to be published in J Chromatography B). Although the estrogen and progesterone concentrations in cow milk are a small fraction of that in HRT, as with BPA, decades of chronic low dose exposure to the hormones in milk, particularly during sensitive periods of breast development should not be ignored. Although no direct investigations of the effect of milk consumption on circulating conjugated estrogen levels have been published, as noted by Qin et al. several studies suggest indirectly that dairy consumption increases circulating levels of estrogen in both men and women. With respect to the effects of endocrine disruptors, Soto et al argue that the existence of non-monotonic dose response (NMDR) curves can no longer be denied. Cow milk fits the definition of an endocrine disruptor and by extension NMDR curves should also apply to studies on the hormonal effects of milk.
In the second article, Kleinberg et al. describe the requirement for the presence of insulin-like growth factor-I (IGF-I) in order for breast tissue to be responsive to estrogen and progesterone stimuli and that together these hormones act synergistically to promote breast cell proliferation that can lead to the preneoplastic lesions from which breast carcinomas are thought to arise. They also suggest that the protective effect of parity on breast cancer risk may be related to the lower serum IGF-I levels found in multiparous women. In the Nurses Health Study, multiparous women were found to have 14% lower plasma IGF-I levels than nulliparous women. By contrast, in a three month randomized intervention trial in older adults, daily intake of 3 cups of milk (the current USDA dietary recommendation for all Americans 9 years of age and older), resulted in a 10% increase in serum IGF-I levels in comparison to controls.

High milk consumption has consistently been shown to increase circulating IGF-I levels in children and adults, with one exception. Several of these studies found that the ratio of IGF-I to its main binding protein, IGFBP-3 (which generally inhibits IGF-I activity), also rises with milk consumption, indicating an increase in bioavailable IGF-I. Milk, but not meat intake was associated with higher IGF-I levels among British men and women and U.S. adult male and female health professionals. In 50,000 pairs of Danish women and their offspring the effect of diet during pregnancy on higher offspring birth weight was isolated to the protein component of milk and was milk-specific; non-dairy protein had no effect. Three intervention studies that rigidly controlled for energy balance including physical expenditure, found statistically significant increases in serum IGF-I only in isocaloric groups fed milk protein. The same was also observed in an intervention study among 8 year-old Danish boys, although energy intake was less rigidly controlled in this study.

Cow milk is the only environmental exposure that contains IGF-I, estrogen and progesterone in addition to other growth promoting peptide and steroid hormones as well as BPA and other persistent organic pollutants. In addition to these chronic low dose exposures, the effect of cow milk consumption on human serum IGF-I levels suggests that, with respect to breast cancer risk, cow milk may be the most problematic of all environmental hormonal exposures.


