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# Endocrine disruptors and reproductive health: The case of bisphenol-A

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**Abstract**

Epidemiological studies have reported that during the last 60 years the quantity and quality of human sperm has decreased and the incidence of male genital tract defects, testicular, prostate and breast cancer has increased. During the same time period, developmental, reproductive and endocrine effects have also been documented in wildlife species. The last six decades have witnessed a massive introduction of hormonally active synthetic chemicals into the environment leading some to postulate that the diverse outcomes documented in human and wildlife populations might be the result of extemporaneous exposure to xenoestrogens during development.

The estrogen-mimic bisphenol-A (BPA) is used as a model agent for endocrine disruption. BPA is used in the manufacture of polycarbonate plastics and epoxy resins from which food and beverage containers and dental materials are made. Perinatal exposure to environmentally relevant BPA doses results in morphological and functional alterations of the male and female genital tract and mammary glands that may predispose the tissue to earlier onset of disease, reduced fertility and mammary and prostate cancer.


*Keywords:* Xenoestrogens; Bisphenol-A; Estrous cycles; Mammary gland development; Breast cancer; Genital tract

In recent months, the issue of endocrine disruptors has attracted considerable public attention in the US. Large readership newspapers like *USA Today*, *The Wall Street Journal*, and *The New York Times* among others, published some of the latest results found in experimental animals and, more importantly, in humans regarding the deleterious effects of fetal exposure to endocrine disruptors. Although the weight of experimental data obtained from wildlife populations and from controlled studies in animal models has grown extensively during the last decade, the issue of its relevance to human health has continued to trigger controversy. For some, it is difficult to acknowledge that humans may be as vulnerable to endocrine disruption as alligators, bald eagles or mice. Understandably, because many of the chemicals found to be endocrine disruptors are important in the manufacturing industry, there has been controversy about whether low, environmentally relevant doses produce deleterious effects in humans.

## 1. The controversy about low dose effects

At the request of the US Environmental Protection Agency, the National Toxicology Program (NTP) convened a meeting in October 2000 on the low-dose issue. The final *NTP Endocrine Disruptors Low-Dose Peer Review* was published in 2001 (NTP, 2001). The report stated that there was "credible evidence for low-dose effects" and that "discrepancies in experimental outcome among studies showing positive and negative effects of BPA may have been due to different diets with differing background levels of phytoestrogens, differences in strains of animals that were used, differences in dosing regimen, and differences in housing of animals (singly versus group). Although some studies attempted to replicate previous findings, body weights and prostate weights of controls differed between these studies."

Although the low dose issue is applicable to all endocrine disruptors, the industry's reaction to this report focused on only one chemical, the ubiquitous BPA. A report funded by the American Plastics Council, written by a panel convened by the Harvard Center for Risk Analysis (HCRA), reviewed only a small number of studies, yet concluding that "the weight of the evidence for low-dose effects is very weak" (Gray et al., 2004). It is noteworthy that one of the panel members, Claude Hughes, in partnership with Fred vom Saal, published a separate, detailed and comprehensive analysis of all publications on BPA to date (vom Saal and Hughes, 2005). Readers are encouraged to consult this exhaustive article. Interestingly, Hughes and vom Saal found two predictors of negative results: animal strain and source of funding. First, Sprague–Dawley rats from Charles River are extremely insensitive to BPA. This strain was used in several

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studies that found no effect of BPA (Kato et al., 2005; Masutomi et al., 2004; Tyl et al., 2002). Second, 90% of the government-funded publications reported significant effects of low dose BPA while none of the industry-funded studies reported significant effects at similar doses. As succinctly put by vom Saal and Hughes: "It is thus reasonable to pose two questions: (a) Are government-funded scientists under real or perceived pressure to find or publish only data suggesting adverse outcomes? (b) Are industry-funded scientists under real or perceived pressure to find or publish only data suggesting negative outcomes?"

## 2. The human connection

An increase in the incidence of several cancers and reproductive system dysfunctions has been observed in the US and several European countries. During the period spanning 1973–1999, the US National Cancer Institute reported a cumulative increase in the incidence of breast cancer in all age and ethnic groups (34.8% among African–American and 27.9% among Caucasian women); an even higher increase was observed in prostate cancer incidence (82.5% among African–American and 74.4% among Caucasian men). Testicular cancer incidence has also been rising (49.4% among African–American and 51.8% among Caucasian men), and brain tumor incidence increased by 50.2% in children under the age of 14 years (Ries et al., 2002). A decline in the quantity and quality of sperm and an increase in the incidence of hypospadias and cryptorchidism has also been reported (Carlsen et al., 1992; Giwercman et al., 1993).

More recently, studies have shown the extent of human exposure to endocrine disruptors. For instance BPA, one of the most ubiquitous endocrine disruptors, has been measured in the serum of adult men and women with mean concentration of $1.49 \pm 0.11$ and $0.64 \pm 0.10$ ng/ml, respectively (Takeuchi and Tsutsumi, 2002). Its presence was also reported in maternal and fetal plasma and in placental tissue in humans (Ikezuki et al., 2002; Schonfelder et al., 2002) and in the milk of nursing mothers (Sun et al., 2004). Remarkably, the concentration of BPA in amniotic fluid was approximately five-fold higher than levels measured in maternal plasma. The most recently published study, the first involving a reference human population (394 samples analyzed), reported that BPA was found in 95% of urine samples (Calafat et al., 2005). In a smaller study, Arakawa et al. (2004) reported a median daily urinary excretion of BPA of 1.2 μg/day and a maximum daily intake of BPA per body weight to be 0.23 μg/kg/day.

## 3. The importance of time of exposure

Several studies have reported the consequences of accidental exposures to endocrine disruptors. Men exposed to polychlorinated byphenyls (PCBs) under the age of 20 years were found to have a lower chance of fathering a male offspring compared to non-exposed age-matched men (del Rio Gomez et al., 2002). Few studies have examined the fate of the offspring of women who were pregnant at the time of exposure. One such study reported that the sperm of Taiwanese men born to those women exposed to polychlorinated byphenyls (PCBs) and their combustion products, the polychlorinated dibenzofurans, had abnormal morphology, reduced motility and strength (del Rio Gomez et al., 2002). Another study reported that breast-fed girls exposed *in utero* to high levels of polybrominated byphenyls (PBBs) due to an accidental contamination of the food chain in Michigan, experienced menarche at an earlier age compared to control population (Blank et al., 2000).

The true impact of endocrine disruptors on human health is difficult to assess because specific end points may be differentially affected at different ages (have different windows of vulnerability). For example, some studies found a direct correlation between the plasma levels of DDT metabolites and breast cancer risk, while other studies did not. Most of these studies were case–control studies; exposure was measured once the disease was diagnosed. Others were cohort studies that measured exposure during adult life, sometimes several years before diagnosis. Most of these studies measured dichlorodiphenyldichloroethene (DDE), a metabolite of DDT, as a surrogate, in specimens obtained long after DDT was banned.

A study by Cohn et al. used a different strategy. DDT was measured in samples taken before DDT was banned, and this study tested the hypothesis that DDT is a stronger breast cancer risk factor for women who were exposed during childhood and adolescence, when the mammary gland is undergoing prepubertal and/or pubertal development. They found that breast cancer risk increased with increasing concentrations of serum DDT for women exposed in childhood or adolescence. The association between high plasma levels of DDT and breast cancer was significantly stronger for women exposed to DDT before age 15 years than for women exposed after age 15 years (Cohn et al., 2002). This finding correlates with the observations that the mammary gland is most sensitive to developing cancer when irradiated at this age (Land et al., 2003). It may be concluded that there is no strong correlation between breast cancer and DDT exposure when DDT or DDE measurements are restricted to the time of onset or just before the onset of breast cancer. In contrast, breast cancer levels appear highly correlated with exposure to DDT prior to age 15 years.

Recently, Swan et al. (2005) showed for the first time a statistically significant link between prenatal exposure to phthalates and anogenital distance in infant boys. Anogenital distance is considered a sensitive marker of antiandrogen action during development in toxicologic studies in rodents. Anogenital distance is sexually dimorphic and androgen dependent, and in males is typically twice that of females (this holds true for humans and rodents). These investigators also observed that boys born to mothers with phthalate metabolites present in their urine are at higher risk of impaired testicular descent. A similar effect has been observed in experimental animals, and a "phthalates syndrome", which also includes testicular, epididymal and gubernacular cord agenesis, has been described by Gray and Foster (2003).

Another limitation inherent in epidemiological studies is that humans are not exposed exclusively to the chemical being investigated, but instead to a mixture of chemicals, some of them acting through common pathways. In addition, no single compound can act as a surrogate or marker for the others because the contaminant profile varies among individuals. Moreover, different