

**PARTNERS IN PERINATAL HEALTH CONFERENCE
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“The Case of Bisphenol A: Fetal Exposure and Human health Issues”

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Objectives:

Upon completion, participants will be able to:

- Identify products that contain BPA.
- Discuss amounts commonly found in the body.
- Understand the levels that are known to cause harmful effects.
- Gain greater understanding why pregnant women, fetuses and neonates should be protected from BPA, and how we can avoid exposure.

The Case of Bisphenol A: Fetal Exposure & Human Health

Background Information & Additional Reading Material

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Bisphenol A (BPA) was first synthesized by A.P. Dianin in 1891 and was later investigated in the 1930s during the search for synthetic estrogens. At that time, it was tested for its estrogenic properties but abandoned for pharmaceutical use when diethylstilbestrol (DES) was determined to be much more potent [1]. Thus, until recently, BPA was considered a weak environmental estrogen because of its relatively low affinity for estrogen receptors compared to estradiol [2, 3]. However, results from recent studies have revealed a variety of pathways through which BPA can stimulate cellular responses at very low concentrations, below the levels where BPA is expected to bind to estrogen receptors [4].

BPA is one of the highest volume chemicals produced worldwide with over 6 billion pounds produced each year and over 100 tons released into the atmosphere by yearly production. BPA is the building block of polycarbonate plastic. Numerous studies have found that BPA leaches from polycarbonate baby bottles [5] and re-usable water bottles [6]. Other polycarbonate containers intended to be used as reusable food containers, food-contact items such as polyvinyl chloride stretch films, and some papers and cardboards used as food containers have been shown to contain BPA [5]. Metallic food cans are protected from rusting and corrosion by the application of epoxy resins as inner coatings. Many of these resins are synthesized using BPA. Several studies have documented conditions such as heat, acidic foods, etc., that support or enhance BPA migration from the coating of cans [5]. BPA contamination has been found in a variety of canned foods including vegetables and fish as well as canned infant formula [5].

Human populations, including infants and children, are regularly exposed to BPA. Since 1999, more than a dozen studies using a variety of different analytical techniques have measured free, unconjugated BPA concentrations in human serum at levels ranging from 0.2–20 ppb (ng/ml) serum [5]. The relatively high levels of BPA in the serum of pregnant women, umbilical cord blood, and fetal plasma indicate that BPA crosses the maternal-fetal placental barrier. A 2008 study from the US Center for Disease Control and Prevention (CDC) examined urine from over 2500 Americans, with BPA detected in 92.6% of participants [7]. Measured urine

concentrations ranged from 0.4-149 ppb with a geometric mean of 2.6 ppb and were significantly higher in children and adolescents compared to adults.

BPA is suspected to affect human health. At this time, only one large and well-controlled study of the possible health effects of BPA exposure on humans has been conducted, revealing positive correlations between urinary BPA concentrations and the prevalence of diabetes, heart disease and liver toxicity [8]. This cross-sectional study was performed using samples and information collected for the CDC NHANES study and includes 1455 American adults. Several smaller studies have examined the effects of BPA exposure on other health outcomes. For instance, BPA levels in blood have been associated with a variety of conditions in women including obesity, endometrial hyperplasia, recurrent miscarriages, sterility, and polycystic ovarian syndrome (reviewed in [5]). High BPA exposure was also associated with chromosomal abnormalities measured in peripheral lymphocytes [9]. Higher maternal serum BPA was also found among women carrying fetuses with an abnormal karyotype [10].

Low doses cannot be deemed “safe”. For many years, when assessing the effects of possible endocrine disruptors, toxicologists have relied on the principle that “the dose makes the poison,” implying that higher doses were expected to cause greater harm. Thus, effects that were not seen at high doses were not expected at low doses. In contrast to this questionable and outdated toxicology dogma, many endocrinology studies have found that some responses to hormones defy the above-referred mistaken notion that “the dose makes the poison” [11-13]). These U- and inverted U-shaped dose response curves are called “non-monotonic” and are used as evidence that very low doses of natural and synthetic hormones can affect endpoints such as cell proliferation and organ size [12]. U- and inverted U-shaped curves have been observed following exposure of cultured cells to BPA, including pituitary, prostate, adipose and pancreatic cells [14-16].[17].

Animal studies indicate that developmental exposure to environmentally relevant levels of BPA alters development of the brain, the male and female reproductive tracts, the mammary gland, and other organ systems. Natural estrogens bind estrogen receptors and they in turn bind to estrogen responsive elements and induce the expression of genes in their target cells. These cells include those in the reproductive organs (vagina, uterus, oviduct, ovary, cervix, testis and epididymis), the mammary gland, the brain and pituitary, the thyroid gland, and the skeletal and cardiovascular systems, among others [18]. As a synthetic estrogen

with the capability of binding to estrogen receptors, BPA also has the potential to alter development at various levels of organization. More than 100 peer-reviewed studies have found effects of developmental BPA exposure at doses below the EPA reference dose or “safe dose” of 50 µg/kg body weight/day, some finding effects after exposure to 1/2000th the safe dose [19]. Taken together, these data indicate that animals exposed to levels of BPA well below the established “safe dose” during gestation or the perinatal period show a wide variety of pathologies.

Differential hormone exposure is important for brain sexual differentiation. Perinatal exposure to estrogen-like chemicals, including BPA, has the potential to alter the development of sexually dimorphic pathways in the rodent brain. In a study performed in our laboratories, the expected sex difference in dopamine neuron number in a sexually dimorphic nucleus of the hypothalamus was obliterated in mice exposed perinatally to BPA; thus, BPA exposure led to the loss of a sexual dimorphism in this brain region [20]. Gonadal hormones are also known to influence sexually dimorphic behaviors. Studies of social and sexual behaviors in rodents have shown that exposure to low doses of BPA obliterated expected sex differences [20]. Perinatal BPA exposure has also been associated with aggressive behavior in adulthood [21, 22]. Behaviors shown to be affected by low-dose perinatal BPA exposure include timing of the copulatory sequence in male rats, play behaviors, and other socio-sexual behaviors [22-24]. Female rodents exposed to BPA during the perinatal period also displayed decreased maternal behaviors and loss of responsiveness to amphetamines [25, 26].

Low dose BPA exposure during perinatal development led to alterations of the organs of the male reproductive tract including changes in testis weight at puberty and in adulthood [21, 27]. BPA exposure during gestation also resulted in increased prostate size in adults [28], accompanied by histological changes and alterations in glandular cell function of this organ [29]. Increases in prostate size were detected in the fetus and correlated with increases in proliferation of basal epithelial cells located in the primary prostate ducts [30].

The female reproductive tract was affected by perinatal BPA exposure as well. Low doses of BPA induced both earlier vaginal opening, earlier first estrous and altered estrous cycles [31, 32]. In the ovaries of perinatally exposed females, a significant increase in antral follicles was observed at 3 months of age and an increase in the number of blood-filled ovarian bursae at 6 months of age, i.e., indications of premature/early reproductive aging [34]. Females

exposed to BPA *in utero* had a significant increase in the number of oocytes with gross aberrations; when these females were mated, there was a significant increase in the number of eggs and embryos with altered chromosome number [33]. Low dose BPA exposure altered the weight of the vagina and the volume of the uterine lamina propria; it also increased expression of estrogen and progesterone receptor and cell proliferation in multiple compartments of the uterus [31, 34].

In our laboratories we examined extensively the effects of perinatal exposure to low doses of BPA on the mouse mammary gland and found altered patterns of tissue organization at several stages including embryonic development, peripuberty, and adulthood [31, 35-37]. At puberty, we observed an increased sensitivity to estradiol [38]. We also detected intraductal hyperplasias, manifested as ducts with a “beaded” appearance, in adult females that were perinatally exposed to BPA [37]. Others observed that the immune system was affected in exposed male offspring [39]. Finally, cell culture studies have shown that BPA enhances the differentiation of fat cells and lipid accumulation and influences hormone secretion by fat tissue. Data from animal studies indicate that early exposure to BPA can have lasting effects on body weight [reviewed in [19]].

BPA exposure increases the incidence of prostate and mammary cancers in rodents. A recent study examined the effects of neonatal BPA exposure on prostate cancer in male rats [40] and noticed that when treated with hormones in adulthood, these animals showed a significant increase in the incidence and severity of prostatic intraepithelial neoplasias (PIN). The connection between perinatal BPA exposure and mammary cancer in rodents is currently strengthening. First, the results described above in mice indicate that BPA caused changes in the organization of the mammary gland at puberty and in adulthood. Some of these changes are similar to known risk factors for breast cancer in humans. For instance, at puberty, alterations in cell death leads to an increase in the number of terminal end buds that persist in the mammary gland and an increase in terminal ducts, the structures where cancers are thought to arise [35, 41]. An increase in the number of epithelial cells expressing progesterone receptor leads to an increase in ductal branching and eventually to increased ductal density [35, 36], which may be equivalent to the human breast cancer risk factor of increased mammographic density [42].

Using a rat model, we have observed that at puberty, rats exposed to BPA during the prenatal period had a 3-4 fold increase in the number of hyperplastic ducts when compared to

controls [43]. These lesions were both estrogen sensitive and proliferating. Additionally, cribriform-like structures, identified as carcinomas *in situ*, were observed in both puberty and adulthood in animals exposed perinatally to BPA. Further, maternal exposure to BPA during lactation increased mammary carcinogenesis in their offspring [44].

Turning to BPA effects in humans, results of a recent study revealed that BPA antagonizes the cytotoxicity of several chemotherapy drugs [45]. While this study was conducted *in vitro*, it highlights the possibility that exposure of human patients to BPA during cancer treatments may decrease the efficacy of chemotherapeutic drugs. And finally, as demonstrated by the increased risk associated with early age of menarche and late age of menopause, estrogen exposure throughout a woman's life is a major risk factor for the development of breast cancer [46]. It is still unknown whether exposure to environmental estrogens could have the same impact on breast cancer risk, though a recent epidemiological study supports this notion [47]. The multitude of environmental chemicals with hormonal activities to which we are all exposed involuntarily and unknowingly, in addition to prescribed hormones (hormonal contraceptives or hormone replacement therapy), might contribute to the increased breast cancer incidence that has been observed during the last 50 years in the industrialized world.

Mice and rats are likely to be excellent predictors of the effects of BPA exposure on humans. The potent synthetic estrogen DES was administered to pregnant women from 1948-71; it produced striking effects in exposed offspring, but much less serious effects in exposed mothers [48]. For instance, daughters who were exposed *in utero* (so-called DES daughters) had significantly increased rates of uterine, cervical and vaginal malformations including clear cell adenocarcinoma of the vagina [49]. Breast cancer incidence in DES daughters older than 40 years of age is significantly increased when compared to unexposed women of the same age [50]. Rodents became excellent surrogate models to understand the sad episode of the human DES syndrome and to predict a correlation between gestational estrogen exposure and breast cancer two decades before epidemiological data became available.

BPA experts support a ban of this endocrine disrupting chemical. Because of the societal impact of exposure to endocrine disruptors, and of BPA in particular due to the widespread exposure to this compound, controversies over legislation and regulation abound.

In the fall of 2006, 38 experts in the field of BPA research signed a document called the Chapel Hill Consensus Statement [51] at a meeting organized by the National Institutes of Environmental Health Sciences (NIEHS). It stated in part “The published scientific literature... reveals that human exposure to BPA is within the range that is predicted to be biologically active in over 95% of people sampled. The wide range of adverse effects of low doses of BPA in laboratory animals exposed both during development and in adulthood is a great cause for concern with regard to the potential for similar adverse effects in humans... There is extensive evidence that outcomes may not become apparent until long after BPA exposure during development has occurred... These developmental effects are irreversible and can occur due to low dose exposure during brief sensitive periods in development, even though no BPA may be detected when the damage or disease is expressed.” Additionally, the National Toxicology Program released a statement agreeing that there is some concern for neural and behavioral effects and the prostate gland in fetuses, infants and children at current human exposures [52]. While the FDA has taken the position that products currently on the market containing BPA are safe, the report from the FDA Science Board Subcommittee on Bisphenol A read: “Coupling together the available qualitative and quantitative information (including application of uncertainty factors) provides a sufficient scientific basis to conclude that the Margins of Safety defined by FDA as “adequate” are, in fact, inadequate [53]”.

Based on the large body of scientific evidence, we believe that the time has come for strong regulatory measures on BPA. We support a ban of BPA from consumer products, particularly those products used by pregnant women, infants and children. The National Toxicology Program’s report, the most recent statement by the FDA’s commissioner [54], and a report from Health Canada classifying BPA as a human and environmental toxin all suggest a potential change in the perception of the regulatory community towards recognizing the risk posed by BPA exposure. Some states (CT, IL, HI, MD, MN, MS, MO, MT, NM, NJ, NY, OR, PA, RI, TX, VT, WA) are currently evaluating the possibility to ban BPA, and some manufacturers have voluntarily eliminated BPA from some of their products. We hope that the Massachusetts Department of Public Health will take action at this time. We are happy to discuss with you in person any questions you may have about the studies we have summarized here, or answer any other questions you or your staff may have about BPA and its potential impact in public health.

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High Time for a Ban on Bisphenol A

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We live in a chemical stew. So pervasive are the chemicals in the food we eat, in the products we use to keep our bodies, clothes and houses clean, and in keeping our lawns manicured that it has become impossible to avoid them, no matter how hard we try. Americans are surrounded by chemicals. Over 80,000 are in use and an additional 1000-2000 are introduced each year; however, only about 2% are tested by regulatory agencies for safety.

One chemical that has received a lot of attention lately is Bisphenol A, or BPA, an ingredient in plastics used to make reusable food and beverage containers (including baby bottles) and that also coats the insides of food and beverage cans. Although ingestion is its main route of exposure, inhalation and absorption through the skin has not been ruled out. Human populations, including infants and children, are regularly exposed to BPA as shown by its presence in blood, amniotic fluid, umbilical cords and breast milk. Additionally, the US Center for Disease Control and Prevention detected BPA in the urine of 92.6 percent of the more than 2500 Americans examined; levels were higher in children and adolescents compared to adults.

While BPA has its benefits by “improving our living standards,” like preventing interactions between food items and metal cans, it has the biological actions of the female hormone estrogen. Why should we worry about that? Exposure to estrogenic chemicals during the time when our organs are developing, specifically during the fetal and neonatal periods and puberty, is a risk factor for breast and prostate cancers, malformations of the male and female reproductive organs, infertility, and alterations in brain development.

BPA was originally synthesized in 1891; in the 1930's it was considered for pharmaceutical use because of its estrogenic properties but was abandoned when diethylstilbestrol (DES) was found to be a more potent synthetic estrogen. DES was prescribed to at least 2 million women to prevent miscarriage under the assumption that during pregnancy “some estrogen is good, so more must be better.” By 1971, girls exposed to DES in the womb were presenting with an extremely rare vaginal cancer typically found in elderly women, causing the Food and Drug Administration to ban its use by pregnant women.

We often hear: “But we're all exposed to BPA and we've turned out fine...” Unfortunately this isn't true. Since the chemical revolution when BPA and hundreds of other common chemicals containing hormonal activity were added to our lives, the incidence of diseases and disorders has been on the rise, including early puberty, obesity, reduced sperm count, hyperactivity, genital malformations, breast and prostate cancer. BPA can cause all of these in exposed laboratory animals. Last year, a study of 1455 American adults, published in *The Journal of the American Medical Association*, showed a positive correlation between urinary BPA levels and diabetes and heart disease.

BPA is regulated by the US Environmental Protection Agency which considers 50 parts per million of BPA per day to be a safe dose. However, over 100 animal studies have found effects below this dose, some after exposure to 2000-times less than the “safe” dose. In fact, scientists have yet to find a harmless dose of BPA. Why hasn't BPA been banned, at least from use in food-contact applications? Mostly because BPA exposure cannot be associated with a single disease; the effects can be subtle and complications may appear many years later. Animal studies revealed that BPA exposure during gestation contributed to behavioral disorders, obesity, diabetes, early puberty, breast and prostate cancer and infertility. In 2007, 38

international experts on BPA signed the Chapel Hill Consensus Statement at a meeting organized by the National Institutes of Environmental Health Sciences. It concluded that such a wide range of adverse effects, though found in laboratory animals, provided “great cause for concern” for “the potential for similar adverse effects in humans.” Experts at the National Toxicology Program agreed. It is now up to federal and state regulatory agencies, including the Massachusetts Department of Public Health, to stop ignoring the hundreds of government-funded studies showing that BPA exposure can contribute to a variety of chronic diseases. A new set of policies should eliminate BPA from products that expose our most vulnerable populations: fetuses, infants and children.

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