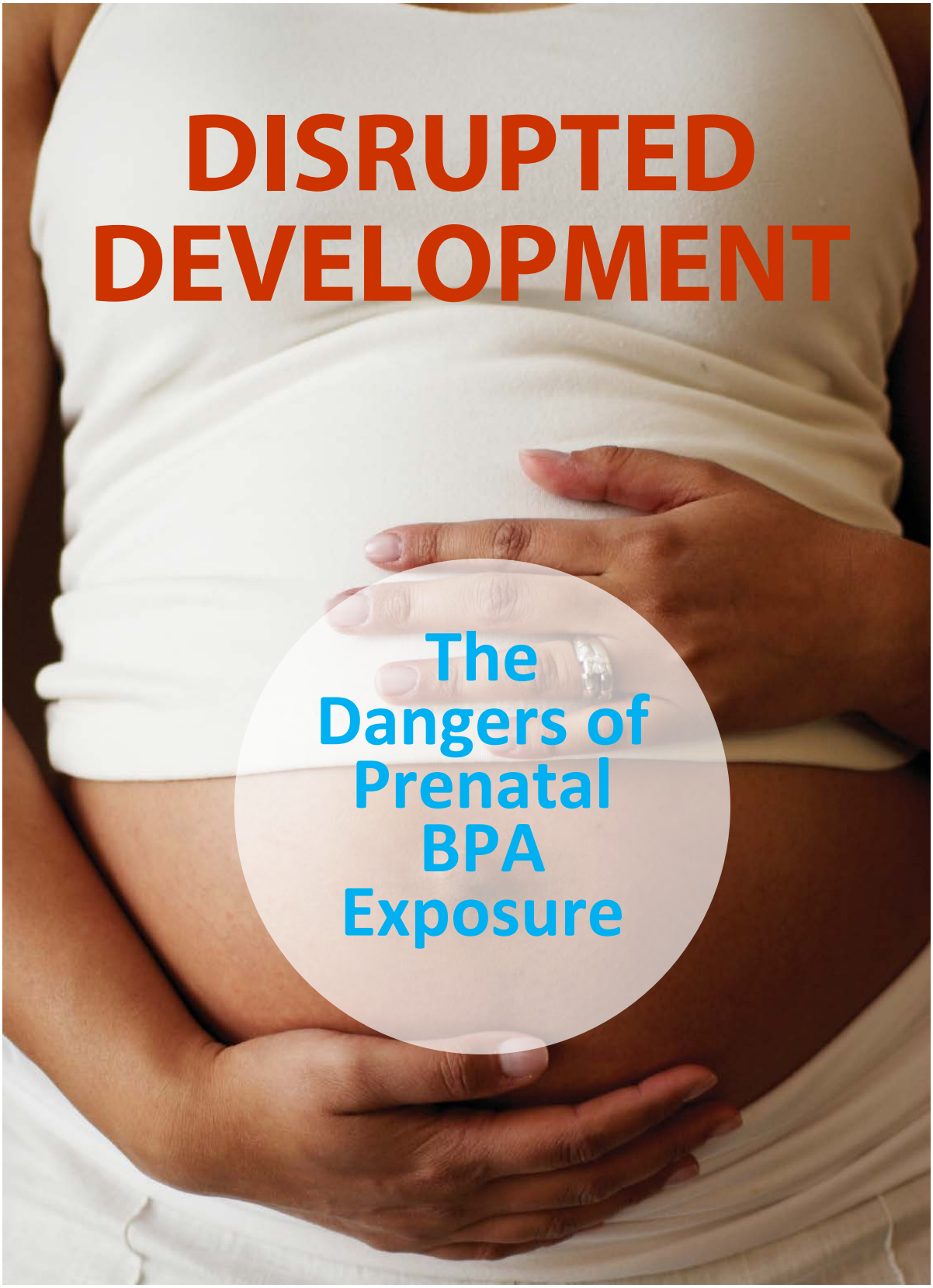

DISRUPTED DEVELOPMENT

The Dangers of Prenatal BPA Exposure

BREAST CANCER FUND

PREVENTION STARTS HERE.

A Report by the Breast Cancer Fund • 2013

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The Breast Cancer Fund is a national 501(c)(3) organization dedicated to preventing breast cancer by eliminating our exposure to toxic chemicals and radiation linked to the disease. The Breast Cancer Fund's Cans Not Cancer campaign is working to eliminate the toxic chemical bisphenol A (BPA) from food can linings and ensure that it is replaced with a safer alternative.

The Breast Cancer Fund thanks Sarah Clark, M.S, R.D., for her contributions to the research and writing of this report and Charlotte Brody, R.N.; Sarah Janssen, MD, Ph.D., MPH; Marisa Weiss, MD; and Sandy Worthington, MSN, WHNP-BC, CNM, for reviewing the report.

Protecting Us from BPA = Protecting the Next Generation

Bisphenol A, or BPA, is a ubiquitous chemical used to make food can linings, eye glasses, bike helmets, polycarbonate plastic, thermal receipt paper and many other everyday items. For more than a decade, scientific evidence has been mounting about the negative health effects associated with BPA exposure, including increased risk for breast cancer, prostate cancer, metabolic changes, decreased fertility, early puberty, neurological problems and immunological changes.

Thanks to public outcry in response to this mounting scientific evidence of harm, BPA is no longer used in baby bottles or infant formula containers. But a closer look at the science reveals that this focus on babies may be missing a fundamental and urgent issue: Fetal exposure to BPA is of even greater concern than childhood exposure.

Eating food from cans—which are coated with a BPA polymer that leaches into food—is a major route of human exposure. While it is important to limit children's consumption of canned food, the science is telling us that we need to pay much more attention to protecting women who are pregnant or may become pregnant.

During the prenatal period, the foundation is set for how the body's systems develop. The ingredients that go into the complex and delicate development of breasts, organs and the endocrine system can determine their structure and functions even decades later. Thus, fetal exposures to chemicals—especially to endocrine disruptors like BPA—can set the stage for later-life diseases. Animal and human studies indicate that prenatal BPA exposure is linked to a variety of toxic health effects,1 including disruptions of reproductive-organ and mammary development, and negative behavioral changes.

If the science is revealing the harmful effects of prenatal exposure to BPA, then why is the chemical still widely in use? Because regulation and business practices have not caught up with the science. This report is a clarion call to legislators and manufacturers. We cannot place yet another burden on pregnant women by giving them the nearly impossible job of avoiding BPA. We must take action to eliminate the widespread use of BPA. And while the efforts to date to protect children from BPA exposures are important, until we get BPA out of food cans—and until we protect every woman who is or plans to be pregnant—the next generation is not safe from the toxic effects of BPA.

A Brief History of BPA

First synthesized in 1891, BPA re-emerged forty years later when Edward Charles Dodds, a London chemist and physician, was working to develop estrogenic pharmaceuticals. He discovered BPA's estrogenic properties, and the chemical was briefly considered as an estrogen-replacement therapy until Dodds synthesized a more potent estrogen, diethylstilbestrol (DES), in 1938.[2] (See the sidebar on p. 7 about the terrible legacy of DES, and the parallels to BPA.)

Soon chemists discovered that this estrogenic chemical was also extremely useful as a building block for plastics and epoxy resins, which rapidly led to BPA becoming one of the most ubiquitous chemicals in modern life.

Unfortunately, BPA has also become a mainstay of the American diet. That's largely because food cans are lined with epoxy resin made with BPA. The chemical is an unstable polymer and is lipophilic, or fat-seeking, so it leaches from the can lining and is drawn into the food. BPA has also been found in other food sources, although the most comprehensive review to date found most exposure is from canned foods.[3]

BPA's omnipresence in our food supply goes a long way toward explaining why more than 92 percent of Americans have BPA in our bodies.[4] It also accounts for why, despite the body's ability to rapidly eliminate BPA,[5] we maintain levels of the chemical in our bodies because we are constantly exposed through our food

and other sources, such as cash register receipts and plastics commonly used in household products.[6]

In 2010, the Breast Cancer Fund and Silent Spring Institute published a groundbreaking study that examined the effect of greatly reducing BPA from the diet. For three days, families were provided with catered food, carefully prepared to avoid BPA contamination. BPA urine levels were measured before, during and after this dietary intervention. On average, BPA levels dropped by 66 percent, and for one family they dropped by 75 percent.[7] Other studies have also found that food-based interventions can alter BPA levels;[8] one recent study found no change in BPA levels in response to dietary interventions, potentially because the study population was consuming very little canned food to begin with.[9] Overall, these studies show that canned food consumption is a major source of BPA exposure.

Why is it a problem that we have this chemical in our bodies? Remember: BPA is a synthetic estrogen that is recognized as an endocrine-disrupting compound. It interferes with the body's own hormonal system. An impressive and concerning body of research links exposure to BPA to an increased risk for breast cancer, prostate cancer, metabolic changes, decreased fertility, early puberty, neurological problems and immunological changes. The strongest evidence of negative health effects emerges from studies of prenatal exposures to the compound and its effects on fetal and childhood development.

What level of BPA in our bodies is safe? According to the U.S. Environmental Protection Agency, which last revised its standard in 1993, the reference dose, referred to as the "safe dose," for BPA exposure is 50 micrograms per kilogram of body weight each day (50 µg/kg/day). However, the EPA's evaluation did not include a full assessment for carcinogenicity, reproductive health outcomes, or neurological changes.[10] Additionally, the growing body of data since 1993 suggests that low doses of BPA (below the EPA safe dose) have different health impacts than the higher dose exposures used to calculate this safe dose. Currently, prenatal exposures to BPA at concentrations of up to 25 times lower than the EPA safe dose have been shown to cause negative health effects in the fetuses of animals. Evidence from human studies also documents an association between low levels of prenatal BPA exposure and adverse health effects in the fetus.

The first wave of BPA activism, led by the Breast Cancer Fund and our allies, resulted in landmark protections for infants. Many baby-bottle manufacturers voluntarily removed BPA from their products, and 11 states passed laws banning BPA from baby bottles before the U.S. Food and Drug Administration finally imposed a federal ban in 2012. Additionally, four states passed bans on BPA in infant formula before the FDA finally acted earlier this year to make the ban take effect nationwide. While there's still no ban on BPA in reusable water bottles, that industry saw the writing on the wall and moved away from use of the chemical in individual water bottles (though BPA is still used in some 5-gallon water-cooler bottles).

While several small organic food companies have eliminated BPA from their cans, the major canned food manufacturers still largely rely on BPA, and there are currently no laws in the United States restricting BPA in food cans. Although pressure from the Breast Cancer Fund's Cans Not Cancer campaign led Campbell Soup Company to announce it will stop using BPA-containing resins, and although other major manufacturers have signaled their intention to move away from BPA, no major company has given a timeline, and most companies have not disclosed what alternatives they are or will be using. Several organic food companies have stated they have eliminated BPA from their cans.

It is critical that this chemical be removed immediately from all canned food so that we can protect the population that is the most vulnerable to BPA exposure: pregnant women.

Prenatal Exposure to BPA: Exploring the Science

Background

When we consume BPA it enters the body in an *active* form that can weakly bind to estrogen receptors and mimic the effects of estrogen in the body. Although much BPA consumed through food is metabolized rapidly into an *inactive* form without estrogenic effects, some active BPA persists in the bloodstream after digestion. In addition, active BPA can also directly enter the bloodstream via the mouth,[11] prior to digestion. The health effects of BPA largely result from exposure to the active form of BPA, and researchers are just beginning to routinely measure both forms of BPA.

Human biomonitoring studies have reported measurable BPA levels in pregnant women and fetuses (see Appendix 1 on p. 13), raising concerns about fetal exposures to both active and inactive BPA.

Metabolism of BPA appears to differ across species. A complex and rapidly evolving literature is just beginning to clarify the extent of human exposures to the active form of BPA. These issues are examined in more detail in Appendix 3, p. 15.

Early Exposures and Health Effects

Research in the growing field of study known as the Developmental Origins of Adult Disease (DoHAD),[12,13] raises concerns that exposure to BPA and other chemicals early in life can increase the risk of later-life disease.

In the first 11 weeks of gestation, a time during which many pregnant women are not yet aware they are pregnant, the fetus's organs and internal communication systems develop rapidly and can be exquisitely sensitive to external factors. Some organs, such as the mammary gland[14] and the brain, develop throughout gestation, and therefore have a longer window of vulnerability. Fetal development of these and other organ systems is sensitive to fluctuations of estrogen, and to compounds that act like estrogen, such as BPA. While the mother's body and the placenta offer protection from many things, some chemicals and radiation can reach the fetus. The developing fetus modifies its development to "adapt" to these environmental cues. This adaptive ability is important for survival, but the permanent changes that result have also been linked to adult disease.[15,16,17,18,19,20] As one example, imbalances in maternal diet have been linked to low birth weight, increased blood pressure and impaired glucose tolerance in the offspring. As another example, recent studies, which will be discussed here, look at how prenatal BPA exposure can affect the development of mammary glands, the brain and other organ systems, increasing risk for later-life disease.[21]

Prenatal BPA Exposure

The weight of the human and animal evidence suggests the fetus is exposed to biologically active BPA as a result of maternal exposure. Animal research suggests that a fetus exposed to active BPA can metabolize it into inactive BPA within a matter of hours; however, under real-world conditions of constant re-exposure in people, it is a legitimate concern that fetuses are constantly exposed to active BPA.

BPA reaches the fetus through the mother's bloodstream. While the mother's body partially metabolizes BPA before it reaches the fetus, strong evidence indicates that the fetus is exposed to the active, estrogenic form of BPA. The placental barrier does not protect the fetus from exposure to the more potent, active form of BPA. Relevant animal[22,23,24,25,26] studies document the transfer of BPA across the placenta, and human studies document the presence

of BPA in various maternal and fetal fluids and tissues.[27,28,29,30,31,32,33,34] Both human and animal studies have detected the active form of BPA in these tissues; a 2013 study in rats found fetal serum levels of active BPA were about 50 percent of those found in the mothers.[35]

A study of radioactive BPA (which allows researchers to ensure the results are not due to contamination) found higher levels of active BPA in the placenta and the fetus than in maternal plasma.[36] This may be explained by the reactivation of inactive BPA in the fetus,[37,38] although not all studies have found evidence of reactivation.[39,40]

A study of rat fetal metabolism of BPA demonstrated that fetal tissue had levels of active BPA similar to that of the placenta. This study found that gestational age was a factor in fetal metabolism of BPA, and that more developed fetuses were better able detoxify active BPA themselves than younger fetuses.[41] This is important because it suggests that, even within the gestational period, age may be a factor that affects BPA metabolism.

Because BPA metabolism may vary in different mammals, it has also been explored in non-rodent species. A small 2012 study looking at five late-stage rhesus monkey fetuses (gestation days 121-139 out of a normal 165-day term) showed that as much as 45 percent of the levels of active BPA in the mother's serum reached the fetus very rapidly. In addition, nearly one-third of the BPA in the placenta was the active form. These fetuses then metabolized the active BPA over time, but it took 8 hours to achieve a 99 percent drop in active BPA levels. Therefore, these fetuses were exposed to active BPA through the course of this 8-hour time period. Furthermore, since this was a one-time exposure, the study could not address fetal metabolism of BPA under the real-world scenario of constant re-exposure.[42]

A 2013 study in late-gestation sheep fetuses[43] reported that BPA crossed the placenta into the fetus and, per kilogram of body weight, the doses were nearly equal in the mother and fetus. Researchers exposed the mothers continuously for 24 hours, and active BPA levels in the mother and the fetus reached a steady state during the 24-hour dosing period. Once BPA exposure was stopped, the active BPA that reached the fetus was rapidly conjugated. However, high, sustained, inactive BPA levels remained in the fetal compartment (fetal plasma, amniotic fluid). These results suggest that sustained re-exposure to BPA in the environment can lead to a continuous state of low-dose active BPA exposure in the fetus.

Ten studies have found BPA in human fetal tissues, including cord blood and plasma.[44,45,46,47,48,49,50,51,52,53] (See Appendix 2 on p. 14.) The largest of these studies detected total BPA in the blood of 40 percent of fetal samples collected. Researchers have only recently begun to routinely measure active BPA. The studies that have done so detected active BPA in 47 percent[54] to 100 percent of cord blood samples tested.[55,56]

BPA has also been detected in other human pregnancy fluids and tissues, including amniotic fluid collected both early and late in pregnancy,[57,58,59]umbilical cord tissue[60] and placental tissue samples collected at delivery.[61] (See Appendix 2 on p. 14.) The studies assessing BPA in amniotic fluid support the theory that fetuses are exposed to active BPA since fetuses routinely and repeatedly ingest and eliminate amniotic fluid. One study found 8-times-higher total BPA levels in early- versus late-pregnancy amniotic fluid and a higher percentage of active BPA in early amniotic fluid compared to other biological fluids tested (maternal and fetal serum and late-pregnancy amniotic fluid).[62] These results raise concerns because they indicate that the highest levels of exposure to BPA may occur early on in fetal growth when some of the most important and delicate developmental processes are taking place.

DES: A Cautionary Tale

The drug diethylstilbestrol (DES) provides a striking and tragic example of the effects of prenatal exposures to chemicals that disrupt our hormones. DES was initially synthesized by a research team in London[63] that had been searching for compounds that could be used for estrogen replacement during menopause, then referred to as "deficiency disease."[64] DES was approved by the FDA in 1941 to prevent miscarriages. It was prescribed to pregnant women for this purpose until 1971.

Early systematic studies failed to find evidence that DES was effective at preventing miscarriages,[65] but it continued to be prescribed to pregnant women. The wide use of DES created an accidental experiment that led to 5 to 10 million pregnant women —and the children born from those pregnancies — being exposed to this synthetic estrogen.[66]

From 1966 to 1969, doctors at the Vincent Memorial Hospital in Boston noted a pattern of rare vaginal cancers in young women.[67] These cancers were rare even in women over 50, and the hospital had never seen a single case of that specific type of cancer in younger women prior to 1966. The doctors conducted a study to determine similarities among the women, and found that the common thread was their mothers' use of DES during their pregnancies. The doctors published a paper reporting their findings in the New England Journal of Medicine in 1971, after which DES prescriptions were halted.

Since 1971, further research has linked prenatal DES exposure to a nearly two-fold increase in breast cancer among women over 40, and even higher rates among women over 50.[68,69] Women who were presumed to have the highest exposures to DES (estimated based upon how much their vaginal cells were altered) had a higher risk of breast cancer.[70]

The story of DES provides a cautionary tale about prenatal exposures to chemicals that can mimic the body's own hormones. BPA is one such compound —In fact, BPA was even considered as an estrogen replacement by the same London laboratory that first created DES. As the DES story underscores, it can take decades to recognize the long-term health effects of early exposures to hormone-disrupting compounds in the general population, making it even more critical that we act on early warnings of harm.

Health Effects of Prenatal BPA Exposure

There is mounting evidence linking BPA exposure in the womb and soon after birth to health effects including breast cancer, prostate cancer, metabolic changes, decreased fertility, early puberty, neurological problems and immunological changes.

Significantly, many of these studies document negative health effects from low-dose BPA exposure, with most documenting effects at doses much lower than the EPA's safe dose for BPA (50 µg/kg body weight/day).[71] For the purposes of this report we will only discuss the evidence for prenatal BPA exposure.

Animals

At least 48 relevant animal-model experiments document the link between prenatal BPA exposure and later-life health problems. Sixteen of those studies administered BPA orally to the mother at doses significantly lower than the EPA's safe dose (see Table 1 on p. 8), and most of these reported adverse health effects in the fetus. The main outcomes included negative effects on mammary gland development in females and on prostate and other reproductive organ development in males, and changes to brain physiology and behavior in both males and females.

A subset of these studies specifically focus on the effects of BPA exposure on the development of the mammary gland. They indicate that the timing of exposure may fundamentally affect susceptibility to later-life mammary tumors. Early-life exposures—particularly prenatal exposures—to BPA may alter mammary gland development in ways that predispose animals to later-life tumors, particularly when exposed to carcinogens.[72] Prenatal exposure to oral doses in the range estimated to mimic that of human serum levels resulted in altered ovary formation[73] and mammary gland formation[74] in the fetuses of rhesus monkeys.

Table 1. Prenatal BPA Exposure and Biological Effects in Animals

Reference (year, first author)	Animal	BPA dose administered (µg/kg BW/day)*	Biological effect
2012, Hunt[75]	Rhesus Monkey	400**	Disrupted egg development, chromosomal damage
2012, Tharp[76]	Rhesus Monkey	400**	Increased density of mammary buds; more advanced mammary development at birth
2013, Angle[77]	Mouse	5	Increased gonadal fat cells during prenatal development in male mice; increased insulin levels; decreased insulin sensitivity and glucose tolerance. Effects of other exposures were also assessed, and non-linear dose effects were found for aspects of metabolic syndrome***
2013, Kundakovic[78]	Mouse	2 and 20	Epigenetic changes in estrogen receptors in the brain; sex-specific differences in social and anxiety-like behavior; disrupted sexually dimorphic behavior
2011, Weber Lozada[79]	Mouse	25	Increased susceptibility to mammary tumor development when exposed to BPA followed by later exposure to a known mammary carcinogen
2007, Kawai[80]	Mouse	2	Increased estrogen-receptor activity in the brains of young mice
2005, Laviola[81]	Mouse	10	Altered brain organization in females (dopamine); reduced response to classical conditioning
2005, Nishizawa[82]	Mouse	2	Disruption of hormone-receptor signaling (arylhydrocarbon receptor)
2005, Timms[83]	Mouse	10	Increased size and number of prostate ducts; constriction of the urethra where it enters the bladder
2004, Yoshino[84]	Mouse	3	Increased immune-response-related cells in spleen
2003, Imanishi[85]	Mouse	2	Altered gene expression in the placenta
2003, Kawai[86]	Mouse	2 and 20	Increased aggressive behavior; lower testis weight
2002, Palanza[87]	Mouse	10	Decreased time nursing pups among mother rats
1999, Howdeshell[88]	Mouse	2.4	Faster weight gain after birth; early onset of puberty
1998, Vom Saal[89]	Mouse	2 and 20	Altered male reproductive organ development; decreased sperm production
1997, Nagel[90]	Mouse	2 and 20	Increased prostate weight in adulthood
2013, Acevedo[91]	Rat	.25, 2.5, 25 and 250 via osmotic pump; fetal serum levels, .63 ± .39 ng/ml	Development of precancerous lesions in prenatally exposed rats at age 50 days; development of mammary gland adenocarcinomas at age 90 days
2010, Betancourt[92]	Rat	25	Alterations in protein expression in mammary gland cells
2008, Moral[93]	Rat	25	Epigenetic changes in mammary gland; changes in genes that regulate (1) cell proliferation and differentiation, (2) cell communication, (3) signal transduction, (4) immunity, protein metabolism and modification, and (5) apoptosis

**Unless otherwise noted, doses were administered to animals through food or water and were measured by concentration relative to body weight. BPA concentrations in biological fluids (such as blood or urine) are measured by concentration in volume.*

***Although not generally considered "low dose," this oral BPA dose replicated active BPA levels observed in human serum.*

****The maximum response for metabolic disruption was found in doses between 5 and 500 µg/kg/day, while high doses of 50,000 µg/kg/day had no effect on metabolic outcomes.*

Humans

Thirteen studies have looked at BPA exposures in human fetuses (measuring BPA levels in maternal urine or maternal or fetal cord blood samples) and have correlated those levels to later behavioral and health outcomes as the children develop (Table 2). Seven of those studies reported negative physical health effects, while four studies associated prenatal BPA exposure with negative behavioral changes in both females and males. One study reported low-birth-weight babies in mothers exposed to BPA in the workplace, with increasing maternal exposure associated with a greater magnitude of decreased birth weight.

Table 2. Prenatal BPA Exposure and Health Associations in Humans

Reference (year, first author)	*Sample size*	*Sample type*	*BPA level (ng/mL)*	*Health association*
2013, Chevrier[94]	335	Maternal urine	GM, 1.3 µg/g creatinine	Reduced thyroid-stimulating hormone in male newborns
2013, Donohue[95]	375	Maternal urine	Range, 1-3.5	Inversely associated with wheeze (respiratory) at age 5
2013b, Harley[96]	292	Maternal urine	GM, 1.1	Increased conduct problems in girls at age 7; increased internalizing behaviors and inattention and hyperactivity behaviors in boys and girls at age 7
2013, Lee[97]	757	Maternal urine	GM, 1.29	Increased birth weight in males; increased weight-to-length ratio in females
2013a, Harley[98]	402	Maternal urine	GM, 1.1	Decreased body mass index; decreased body fat; decreased likelihood of being overweight or obese in female 9-year olds
2012, Spanier[99]	365	Maternal urine	GM, 2.4 ug/g creatinine	Increased odds of wheezing from 6 months to 3 years
2012, Fenichel[100]*	152	Fetal cord blood	Mean 1.12, SD, 0.86	Increased testosterone levels among newborn boys with descended testicles; BPA did not correlate with cryptorchidism (undescended testes)
2012, Perera[101]	198	Maternal urine	GM, 1.96	Increased aggression and emotional reactivity in boys; decreased depression, anxiety and aggression in girls ages 3 to 5
2011, Braun[102]	244	Maternal urine	Median, 2.0	Increased anxiety, depression; decreased emotional control in girls at age 3. No association for boys
2011, Chou[103]	97	Maternal blood Fetal cord blood	GM, 2.5 GM, 0.5	Low birth weight; small for gestational age; altered metabolism and appetite-regulation markers among newborn boys
2011, Miao[104]	143	Maternal urine** Maternal urine***	GM, 15.98 GM 2.2µg/g creatinine	Decreased birthweight among children born to mothers or fathers with workplace exposures
2009, Braun[105]	249	Maternal urine	Range, ND-421	Increased externalizing behavior in 2-year-olds
2008, Padmanabhan[106]	40	Maternal blood	Mean, 5.9; SD, 0.94	No association with gestational length or birth weight

BPA levels reflect measured active BPA; **mothers exposed at work; * fathers exposed at work (indirect maternal exposure); GM=geometric mean, a measure that reflects both the average and the variability; SD=standard deviation, a measure of variability; ND= non-detectable*

Solutions: Getting BPA out of Food Packaging

If we're serious about protecting the next generation from BPA's negative health effects and about not placing the impossible burden on pregnant women to avoid exposure, we must enact laws that restrict BPA.

That's why the Breast Cancer Fund is calling for a federal ban on BPA in food packaging—arguably the largest single route of BPA exposure—and for reform of the regulatory system that allowed BPA to be used as a food-contact chemical in the first place.

The Food and Drug Administration's current system for managing food-contact substances is so broken that it allows the use of polyvinyl chloride (which can leach vinyl chloride), perfluorinated compounds and formaldehyde—all known or suspected carcinogens—as well as endocrine-disrupting compounds like phthalates, alkylphenols and, of course, BPA to be used in food packaging. The FDA does not have a process for re-assessing approved chemicals based on emerging scientific evidence of toxicity, and requires only minimal safety data on new food-contact chemicals. We need to reform this broken system to require the FDA to re-review approved chemicals based on new scientific data and to enable the agency to require manufacturers to prove that new food-contact chemicals are safe. This reformed system would mean not only that BPA would be banned, but also that any replacement substances would be safe for the public.

To date, it has been the states, not the federal government, leading the way in regulating BPA. Thirteen states have laws on the books restricting BPA in infant feeding devices and food packaging. The passage of these laws forced these industries out of BPA, leading the FDA to officially ban the chemical from baby bottles and formula based on market abandonment. In 2013, an additional 13 states introduced legislation to restrict or label BPA. Most bills focused on products marketed to children; six bills mandated either the labeling of or full ban of BPA in all food packaging.

As the public becomes more aware of the risks of prenatal exposure, state campaigns to restrict BPA should focus not just on children's exposure but on all food packaging so that we are protecting everyone.

Policy efforts in other countries to restrict BPA include France's recently announced ban on BPA in all food packaging by 2015.

The federal government should not just follow the lead of the states and other countries. It should take decisive and immediate action to ban BPA from food packaging and reform the system that allowed the chemical to be used as a food-contact substance in the first place.

Alternatives to BPA

A number of potential alternative can linings are in development,[107] but we do not know which of these are actually being used in food cans. The alternatives currently registered with the FDA for use on metal coatings include a number of complex polymer mixtures that contain styrene and acrylics, chemicals closely related to BPA, vinyls, plant-derived compounds, and additives for use with polypropylene and polyethylene terephthalate.

Many older chemicals were approved as food-contact substances decades ago, and the FDA has no authority to require these substances be re-reviewed for safety. If a manufacturer wants to use one of these chemicals, it does not need to inform the FDA. Moreover, if any manufacturer wants to use a new substance as a replacement for BPA, it merely needs to notify the FDA and provide minimal evidence of safety. The FDA currently does not require tests to be completed to evaluate a chemical for endocrine disruption or for low-dose effects, both of which are concerns for chemicals like BPA.

While many canned food companies have indicated their intention to move away from BPA in food cans, they are not being transparent about their timelines to phase out BPA, nor about what alternatives they are using or plan to use. This lack of transparency leaves consumers with no way of knowing if a company has replaced BPA in a given can of food or whether the replacement can lining is safe.

The combination of weak FDA policies governing the registration of food-contact materials, trade secret claims, and significant data gaps about the safety of some of the BPA alternatives we do know about underscores the need more transparency on the part of manufacturers and more stringent regulatory guidelines governing the safety testing and disclosure of BPA alternatives.

Demand Change from Food Companies

While we push for legislative change, we must also continue to demand that industries still using BPA protect the public from exposure to the chemical by voluntarily replacing BPA with safer alternatives. And because fetal exposure is particularly problematic, companies must move away from use of the chemical in all food packaging—not just those products consumed by or marketed to children. That is why the Breast Cancer Fund founded the Cans Not Cancer campaign and has been pushing canned food manufacturers to begin using safer alternatives to BPA immediately.

Most food cans on supermarket shelves today are lined with BPA. While many canned-food manufacturers have committed to eliminating BPA, no company is labeling products to warn consumers about the presence of the chemical in cans, few are revealing the identity of alternatives, and no manufacturer has demonstrated the safety of those alternatives. For more information about individual manufacturer's policies regarding BPA, please see the Cans Not Cancer page on our website:
www.breastcancerfund.org/cansnotcancer

In order to protect public health for this generation and the next, the Breast Cancer Fund and its Cans Not Cancer campaign call on canned food manufacturers to do the following:

1. Eliminate BPA from all canned food by 2015.
2. Label food cans containing BPA so that consumers can make educated purchasing decisions.
3. Publicly disclose the identity of any alternatives used to replace BPA.
4. Demonstrate the safety of those alternatives by making safety studies publicly available.

Warn Pregnant Women

Until we see decisive governmental action to protect women from BPA exposure, reproductive health practitioners should integrate information about the risks and how to avoid the chemical (as well as other toxic exposures that may be harmful to reproduction and fetal development) into their routine patient education and interaction,[108,109] including:

- Ask questions about BPA and other chemical exposures on patient intake forms, including occupational exposures (e.g., solvents in manufacturing, pesticides) and consumer products, such as cleaning products, home-use pesticides and personal care products.
- Ask questions specifically focused on BPA exposure, including how much and the type of canned food a patient consumes in a typical week and if they handle receipts regularly.
- Provide guidance on reducing exposure to BPA. As demonstrated via a dietary intervention study, simple changes in food preparation can reduce BPA exposure.[110] Recommendations include:
    - Use glass, ceramic and stainless steel food storage containers and water bottles.
    - Use glass and ceramic in the microwave.
    - Avoid canned foods (choose fresh and frozen instead).
- Personalize recommendations based on a patient's education and income level, and the availability of fresh food in their community.

Reproductive and environmental health groups can serve as a resource on the issue for health practitioners who may be unfamiliar with the science linking chemical exposure to reproductive and developmental problems.[111]

Change Your Shopping List

While we work for policy and market solutions, you can take the following actions to avoid BPA in your diet.

1. Avoid canned food, especially during the first trimester of pregnancy. Women who are trying to get pregnant should also avoid canned food to reduce exposure very early in pregnancy.
2. Look for fresh or frozen fruits and vegetables. Not only will you avoid BPA, you will also avoid the sugar and salt that often accompany canned produce.
3. Look for soups and sauces in aseptic cardboard containers, which are BPA-free.
4. Buy food in glass jars, which are BPA-free. Glass jars are easy to clean and can be reused for serving, drinking, storing, freezing and heating foods.
5. Skip the can and soak your beans overnight and cook them the next day, or use a pressure cooker for dried beans that are recipe-ready in an hour or so. Another tip: double the amount of beans you're cooking, and freeze half – that way you'll always have some on hand.
6. Avoid canned food when eating out. Many restaurants use canned food as part of their recipes. Ask your server if anything on the menu contains canned food and try to order items that don't.
7. While you're skipping the can, also skip the receipt. Many thermal cash register receipts contain BPA or related chemicals of concern. If you do handle a receipt, remember to wash your hands before handling food.

APPENDIX 1

Maternal BPA Levels in Humans

Reference	Sample size	Sample type	Total BPA level (ng/mL)
2013, Hoepner[112]	375	Maternal urine	GM 1.8
2013, Chevrier[28]	335	Maternal urine	GM, 1.3 ug/g creatinine
2013, Harley[27,96]	402	Maternal urine	GM, 1.1
2012, Spanier[99]	365	Maternal urine	GM 2.4 ug/g creatinine
2012, Perera[29]	198	Maternal urine	GM, 1.96
2011, Braun[30]	244	Maternal urine	Median, 2.0
2011, Woodruff[1]	72	Maternal urine	GM, 1.63
2009, Braun[31]	249	Maternal urine	Range, ND-421
2009, Ye[113]	110 (10 pools)	Maternal urine	GM, 4.5
	110	Maternal urine	GM, 2.52
	87	Maternal urine	GM, 3.93
2008, Wolff[114]	404	Maternal urine	Range, ND-35.2
2008, Ye[115]	100	Maternal urine	GM, 1.1
2011, Chou[33]	97	Maternal blood	GM, 2.5
2008, Lee[49]	300	Maternal blood	GM, 3.10
2008, Padmanabhan[106]	40	Maternal blood	Mean, 5.9; SD, 0.94
2003, Kuroda[50]	9	Maternal serum	Mean, 0.46; SD, 0.46
2002, Ikezuki[52]	37	Maternal serum (early)	Mean, 1.5; SD, 0.8
	37	Maternal serum (late)	Mean, 1.4; SD, 0.9
2002, Schonfelder[53]*	37	Maternal serum	Mean, 4.4; SD, 3.9
2002, Yamada[58]	200	Maternal serum	Median, 2.24

**BPA levels reflect measured active BPA; GM=geometric mean, a measure that reflects both the average and the variability; SD=standard deviation, a measure of variability; ND=non-detectable*

APPENDIX 2

Prenatal BPA Levels in Humans

Reference	Sample size	Sample type	BPA level (ng/mL or ng/g, mean)
2013, Gerona*[116]	85	Fetal cord blood	GM, .16
2013, Zhang[117]	30	Fetal cord blood	GM, .08
2012, Fenichel[32]*	106	Fetal cord blood	Mean, 1.12, SD, 0.86
2012, Kosarac[118]	12	Fetal cord blood	Median, 1.82
2011, Chou[33]	97	Fetal cord blood	GM, 0.5
2008, Lee[49]	300	Fetal blood	GM, .65
2006, Engel[59]	21	Amniotic fluid (early)	Median, 0.55
2003, Kuroda[119]	9	Fetal cord serum	Mean, 0.62; SD, .19
2003, Tan[120]	180	Fetal cord plasma	Range, ND-4.05
2002, Ikezuki[121]	32	Fetal cord serum	Mean, 2.2; SD, 1.8
	32	Amniotic fluid (early)	Mean, 8.3; SD, 8.9
	38	Amniotic fluid (late)	Mean, 1.1; SD, 1.0
2002, Schonfelder[53]*	37	Fetal cord serum	Mean, 2.9; SD, 2.5
	37	Placenta	Mean, 11.2; SD, 9.1
2002, Todaka[60]	NR	Umbilical cord tissue	Mean, 4.4; SD, 5.0
2002, Yamada[58]	200	Amniotic fluid (early)	Median, 0.26

**BPA levels reflect measured active BPA; GM=geometric mean, a measure that reflects both the average and the variability; SD=standard deviation, a measure of variability; ND=non-detectable; NR=not recorded*

APPENDIX 3

Research Methods: Making Sense of Animal and Human Studies

Researchers are investigating what happens to BPA after adult oral consumption in order to better estimate how much of the active form of BPA[1] is available to exert adverse physiological changes. The research is complex and evolving, and requires scrutiny of both animal and human studies.

Despite recent studies suggesting that adult mammals efficiently detoxify and eliminate BPA,[122] total BPA levels (active and inactive BPA combined) have been associated with physiological changes in several human biomonitoring studies. This highlights the need for further research on BPA metabolism and its mechanisms of action. Since association studies cannot demonstrate a causal relationship, it is necessary to employ an animal-to-human[123] research model, in part because the widespread exposure to BPA today makes it impossible to identify an unexposed control population.

Several aspects of study design need to be considered when evaluating both animal and human research on BPA exposure and metabolism: (1) animal studies should mimic the active dose of BPA found in human blood or serum; (2) prenatal studies in animals should look at both early- and later-stage pregnancy; and (3) metabolic studies should consider the real-life scenario of continuous re-exposure to BPA found in humans.

Animal studies should mimic the active dose of BPA found in human blood or serum

Since BPA metabolism varies across species, the capacity to apply animal research to human health outcomes relies on efforts to mimic the dose of active BPA found in human serum. Recent studies using both non-pregnant and pregnant rhesus monkeys have shown that oral BPA doses of approximately 400 µg/kg body weight (roughly 10 times higher than the EPA safe dose) were necessary to replicate active BPA levels observed in human blood.[124,125,126]

[1] The active form is referred to as unconjugated, aglycone or free BPA. The inactive form of BPA is referred to as conjugated, glucoronidated or glycone BPA.

Metabolism is suspected of being comparable across primate species, so it is unclear why such high doses were needed to match the active levels of BPA found in biomonitoring studies of humans whose oral doses are considerably lower than 400 µg/kg body weight. It could be that human exposure from sources other than food and beverages is higher than estimated (for instance, from air, water and dermal contact). Another possible explanation is that metabolism of BPA in the gastrointestinal tract and liver may not be as rapid or complete as currently thought.[127] It is also possible that BPA may be rapidly absorbed in the mouth by the sublingual route (under the tongue) directly to the bloodstream, as found in a 2013 study of dogs.[128] This would lead to higher internal active BPA exposures than those currently estimated from studies of BPA absorption through the gastrointestinal tract.

A 2013 study of mice found that active BPA levels in the fetus were approximately 200-fold lower than oral doses administered to the mother during pregnancy. Thus, oral doses of 5 µg/kd/day resulted in active BPA levels of 2 pg/ml (or two parts per trillion). Despite these very low doses (below the levels of active BPA found in human biomonitoring studies), they led to significant metabolic changes in the mice including weight increases and decreased glucose tolerance.[129]

Prenatal studies in animals should study both early- and later-stage pregnancy

Studies in sheep and rhesus monkeys have looked at metabolism in fetuses that were the equivalent of third trimester in humans,[130,131,132] after most critical organ development has occurred. It is crucial that we better understand whether earlier-stage fetuses (equivalent to first- or second-trimester human fetuses) have a lower metabolic capacity (as has been found in rats[133]) and may therefore be exposed to higher levels of active BPA over a longer time period.

Metabolic studies should consider the real-life scenario of continuous re-exposure to BPA found in humans

Biomonitoring studies indicate that the general population receives a steady daily dose of BPA[134,135] despite BPA being absorbed, metabolized and eliminated quite rapidly by human adults.[136,137] Metabolic studies that examine one-time exposure to BPA isolate that single exposure and allow for observation of BPA metabolism over time. However,

this may not offer clues to what happens with the continuous re-exposure that occurs in humans. More research is needed to consider whether under a scenario of continuous re-exposure to BPA fetuses are being exposed to even higher levels of active BPA than these experiments have found.

The Science Indicates the Need for a Precautionary Approach

The combination of human-association studies and experimental studies in animals provide compelling evidence that low-dose, prenatal exposures to BPA can lead to a wide range of later-life health concerns. These health effects encompass a wide range of adverse outcomes, including altered brain development, behavior changes, metabolic changes, adverse reproductive outcomes, and changes in breast and prostate development linked to later-life cancer risk in these organs. This collection of health effects is biologically plausible,[138] given BPA's capacity to mimic estrogen, and to therefore disrupt the delicate process of fetal development that is orchestrated by hormones. While inter-species differences may exist in the absorption and metabolism of BPA, the weight of the compiled evidence suggests that viable routes of exposure to active BPA exist for humans. This indicates a compelling need for a precautionary approach to avoid human exposure to BPA during prenatal development.

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