Dear Ms. Oshita:

We submit these comments to you for consideration by the Developmental and Reproductive Toxicant Identification Committee. Thank you for allowing us to participate in this important regulatory process.

The mission of the Breast Cancer Fund is to identify and advocate for the elimination of the environmental and other preventable causes of the disease. Our work to fulfill that mission brought bisphenol A (BPA) to our attention in 2001 during the development of the first edition of *State of the Evidence: The Connection Between the Environment and Breast Cancer*. Studies identified BPA as an endocrine disrupting compound that altered development of the mammary gland in animals, alterations that increased the risk of mammary cancers in later life. After nearly 10 years of collaborative work in environmental health, we recognize that BPA is linked not only to breast cancer but to alterations in the development of reproductive, metabolic, immune and neurobehavioral systems in humans and animals.

BPA is one of the most pervasive chemicals in modern life. More than 2 billion pounds are produced in the United States each year. It is a building block of polycarbonate plastic. Everyone in the industrialized world is exposed to BPA, primarily through food and food packaging, but also through dental sealants, plastic water pipes, air and dust.

BPA is also commonly found in the epoxy resin lining of metal food and beverage cans and in some types of plastic food containers, including some baby bottles, water bottles, microwave ovenware and eating utensils. Because BPA is an unstable, lipophilic polymer, it can leach into infant formula and other food products, especially when heated. Once in food, BPA moves quickly into people—a particular concern for women of childbearing age and for young children.

Over 200 scientific studies show that exposures to low doses of BPA, particularly during prenatal development and early infancy, are associated with a wide range of adverse health effects in later life. These effects mirror recent trends in human diseases and disorders such as:

- increased risk of genital abnormalities in male and female babies,
- decline in semen quality in men,
- early puberty in girls,
- metabolic disorders such as insulin resistant (Type 2) diabetes and obesity,
- neurobehavioral problems such as attention deficit hyperactivity disorder (ADHD).
Exposures that occur before birth are particularly troubling, as the effects on the developing fetus are irreversible and in some cases, transgenerational. As one researcher explains, “low-dose BPA exposure during pregnancy…increases the likelihood of chromosomally abnormal grandchildren.”

Much of the accumulated knowledge about the toxic effects of BPA exposure stems from animal studies. As a way to cast doubt on these studies, chemical industry lobbyists continue to question the applicability of animal research to human health effects, even though animal studies are an accepted model for preclinical testing of pharmaceuticals intended for human use. As Drs. Rosenthal and Brown write in their 2007 paper, “The laboratory mouse is widely considered the model organism of choice for studying the diseases of humans, with whom they share 99% of their genes.” Animal testing has been the basis for understanding how chemicals affect reproduction and development since the 1930s. Scientists can expose animals to known amounts and combinations of chemicals at specific times in the animals’ development. Small mammals such as rodents are the primary models used because they have short reproductive cycles and they bear multiple young, simplifying assessment of how prenatal exposures affect offspring.

Animal studies offer an early warning system for detecting chemicals that may prove hazardous to humans and other animals. Although humans are larger, more complex mammals who live longer than mice, rats, guinea pigs or rabbits, and who encounter multiple environmental exposures on a daily basis, toxicologists generally agree that laboratory animals and humans have more physiological, biochemical, and metabolic similarities than differences.

The scientific evidence documenting a spectrum of adverse effects linked to BPA is briefly summarized in the text that follows. Based on this evidence, the Breast Cancer Fund recommends that BPA be added to the Proposition 65 list of developmental and reproductive toxicants.

**Ubiquitous, chronic human exposure**
Human exposure to BPA is chronic and widespread among people of all ages. Levels in people are comparable to levels that have been shown to cause adverse effects in laboratory animals. CDC scientists found that concentrations of BPA were highest among non-Hispanic blacks and non-Hispanic whites. Concentrations also were higher in women than in men, and higher still in children. Using a computer model, scientists estimated that concentrations of BPA in the blood of 3- and 6-month-olds were 5 times higher than in adults. One study found that levels of BPA in the urine of premature infants in intensive care were an order of magnitude higher than in the general population.

Several studies have indicated that BPA is rapidly metabolized and cleared within about a day, suggesting that the pervasive presence of BPA in our bodies reflects its ubiquity in our food and our environment. A very recent study complicates this picture, with fasting for 9-24 h not leading to expected clearance of the chemical from adult human urine samples. This finding suggests that food and drink, may not be the only sources of exposure to BPA, and/or that because BPA is a fat-seeking (lipophilic) chemical, it accumulates in body tissue.

The presence of BPA in women of childbearing age is the most worrisome. Women are the first environment for their developing babies BPA crosses the placenta, enters the fetal bloodstream and is excreted by the fetus into the amniotic fluid. Scientists have detected BPA in human urine and blood (including the cord blood of newborns), in placental tissue and in breast milk.

**Human Health Studies**
One of the few human studies on health effects of BPA showed that women who experienced recurrent miscarriage (three or more consecutive first-trimester miscarriages) had higher exposure levels of BPA than women with no history of live birth and infertility.
In a study of nearly 1,500 U.S. adults, scientists found that higher concentrations of BPA in urine were associated with cardiovascular problems, diabetes and abnormalities in liver enzymes. These findings suggest that higher levels of BPA may contribute to chronic health problems in adults. This is the first human study with results similar to findings in laboratory animals described later in this document.16

**Reproductive system effects**
BPA is classified as an endocrine-disrupting compound, which is not surprising because the chemical was developed in the 1930s as one of the first synthetic estrogens. BPA was soon shunted aside as a pharmacological estrogen in favor of diethylstilbestrol (DES), now known to cause cancer and reproductive abnormalities in both males and females.17 In 1941, the Food & Drug Administration (FDA) ignored the animal evidence of DES reproductive toxicity and approved DES for medical use in humans, and in subsequent years for use during pregnancy and for use in cattle and poultry. When male agricultural workers exposed to DES suffered sterility and breast cancer, FDA banned the use of DES in poultry, but not in cattle or women. Between 1941 and 1971, an estimated 5 to 10 million women in the U.S. were prescribed DES.18 Their daughters and granddaughters paid the price—reproductive anomalies and a rare vaginal cancer that led to infertility and sometimes loss of life. DES is recognized as a reproductive toxicant and a transgenerational carcinogen, whose damaging effects continue today.

A number of studies in rodents have shown DES-like effects from prenatal exposure to BPA.19 20 For example, one study showed that neonatal exposure to low levels of BPA causes uterine fibroids and cystic ovaries in female middle-aged mice. In women, such effects are major contributors to infertility and the most common reasons for hysterectomy.21

**Metabolic effects**
Low-dose BPA exposure in female mice has been associated with early puberty and increased body weight.22 Other studies show that exposure to BPA caused insulin resistance, hyperlipidemia, hypertension, and increased body weight in adult mice and in their offspring.23 24 25 Two studies found that BPA exposure alters normal glucose metabolism in fat cells and increases the number of fat cells in the body.26 27 Both of these effects increase the risk of Type II diabetes and obesity.

**Immune system effects**
Research indicates that exposure to BPA modulates the immune system in mice. Effects on the immune response vary according to timing of exposure and sex of the animal exposed.28 29 30 31 In humans, altered immune system response can affect the development and progression of allergy and autoimmune diseases such as lupus, rheumatoid arthritis, scleroderma and multiple sclerosis.

**Neurobehavioral effects**
A growing body of evidence suggests that BPA exposure during critical windows of development—the perinatal period and puberty—can affect brain and behavior in later life.

Estrogen is one of the most important hormones in brain development in both men and women. It normally promotes the growth and health of developing neurons in the brain. As an artificial estrogen, BPA both mimics the action of estrogen (primarily estradiol) in neurons and at low doses—in the parts per trillion (PPT) range—totally inhibits the action of estrogen, and may result in permanent harm to developing brain cells.

A study in non-human primates showed that BPA exposure can inhibit the action of estrogen on the developing brain, particularly the hippocampus and prefrontal cortex. These two structures play a critical role in cognition, memory and mood. The dose of BPA used in this study was equal to what the U.S. Environmental Protection Agency says is safe.32
Scientists concluded from a study of female rats that environmental BPA exposure may inhibit the formation of estrogen-dependent hippocampal synapses, and may also exacerbate the impairment of hippocampal function seen during normal aging, as endogenous estrogen production declines. Imaging studies of patients with Alzheimer’s disease reveal continuing atrophy of the hippocampus as erosion of memory progresses.

In reviewing a series of studies on how maternal BPA exposure affected behavior of the mouse offspring, researchers identified the most consistent finding: Lack of sexual differences in behavior between males and females. In contrast, there were marked sexual differences in behavior among animals in the unexposed (control) group. In addition, female mice exposed to BPA during fetal life or during adulthood spent less time nursing and more time out of the nest than the unexposed females.

Other brain and behavioral effects of BPA exposure included hyperactivity, impaired spatial learning, memory and cognitive function; increased aggressive behavior in males even without increased testosterone production, and masculinization of female behavior. One study also suggested that BPA exposure affects thyroid function, which can also interfere with normal brain development and lead to behavioral and cognitive deficits.

In summary
Given the evidence of the multisystem, trangenerational hazards of bisphenol A, it is essential that this chemical be legally identified as a developmental and reproductive toxicant. Failing to do so would knowingly put the public’s health at risk. The Breast Cancer Fund urges this committee to act on the evidence and list this dangerous chemical.

Sincerely,

Jeanne Rizzo, R.N.
President and CEO
8 Edginton AN and Ritter L. “Predicting Plasma Concentrations of Bisphenol A in Young Children (< Two Years) Following Typical Feeding Schedules using a Physiologically-based Toxicokinetic Model.” Environmental Health Perspectives, doi:10.1289/ehp.0800073 [Online 14 November 2008].
21 Newbold RR, Jeffrey WN, Padilla-Banks E. “Prenatal Exposure to Bisphenol A at Environmentally-Relevant Doses Adversely Affects the Murine Female Reproductive Tract Later In Life.” Environmental Health Perspectives, doi: 10.1289/ehp.0800045 [Online 15 January 2009].


