

## Bisphenol A

### Introduction

Bisphenol A (BPA) is a synthetic chemical that was originally developed for use as a synthetic estrogen. It is now one of the highest-volume chemicals produced in the world, with over six billion pounds manufactured each year.<sup>1,2</sup> BPA is used as a monomer in the manufacture of polycarbonate plastics, in the resin lining of food and beverage cans, as a component of dental sealant, in digital media such as CDs and DVDs, and as an additive in other types of plastics.<sup>2,3</sup> The first reported synthesis of BPA was in 1905.<sup>4,5</sup> Bisphenol A was first used in epoxy resin in 1939 and in 1966 was incorporated into vinyl ester polymers.<sup>6</sup> Large-scale production of BPA began in the late 1950s, when commercial uses for polycarbonate plastics and epoxy resins were developed.

BPA is known to leach under normal conditions of use from the plastics and resins that contain it, but especially during heating and washing, which has led to widespread human exposure. An estimated 95 percent of Americans tested, including young girls, show detectable levels of BPA in their urine.<sup>7,8</sup> The ubiquity of human exposure to a chemical with reported estrogen-like characteristics has created considerable concern about BPA's potential role in breast cancer. In rodent studies, early-life exposure to BPA alters mammary gland development in ways that may alter the risk for breast cancer: changing mammary gland morphology, steroid receptor expression/responsivity, and pre-neoplastic lesions. BPA also increases the sensitivity of mammary tissue to endogenous estrogen.<sup>9,10</sup>

## Definitions and Sources of Exposure

### Environmental Exposures

BPA is a ubiquitous environmental contaminant.<sup>3,11</sup> It has been found in the waste water from factories that produce BPA<sup>3</sup> and has been identified as the compound responsible for the majority of estrogenic activity of landfill leachate.<sup>2</sup> In the U.S., the presence of BPA has been documented in surface water and drinking water,<sup>3,12,13</sup> ground water and private wells,<sup>14</sup> soil,<sup>3</sup> ambient air,<sup>3,15,16</sup> and residential dust samples.<sup>15</sup> A sampling of dust from 120 homes in Cape Cod, Massachusetts detected BPA in 86 percent of samples tested.<sup>15</sup>

Environmental degradation of BPA is thought to be fairly rapid and complete.<sup>11</sup> Atmospheric degradation occurs by reaction with hydroxyl radicals with a half-life of several hours.<sup>17</sup> In surface water, abiotic degradation is negligible, but degradation by bacteria is common, resulting in a half-life of a few days.<sup>3,11</sup> BPA released to ground or surface water can be absorbed to soil or sediments. Levels of BPA in sediments are generally higher than those in surface waters; the half-life of BPA in soil is estimated to be less than three days.<sup>3</sup> Thus, while environmental contamination is widespread, due to BPA's relatively fast degradation, levels of contamination appear to be generally low.<sup>3,11,12</sup> Consequently, environmental contamination is not considered a primary source of human exposure.<sup>2,3,11</sup>

### Occupational Exposures

The extent of human exposure to BPA through occupational sources is not known,<sup>2,11</sup> but

potentially could be considerable, given BPA's widespread industrial and commercial use. Occupations in which workers could be exposed include those involved in the manufacture of BPA, polycarbonate plastics, items made from polycarbonate plastics, epoxy resins, liquid epoxy paints, laquers, and powder coatings.<sup>11</sup> The only published data available on occupational exposures to BPA in the U.S. was collected over 20 years ago. In a National Institute of Occupational Safety and Health (NIOSH) occupational exposure survey of selected industries, the greatest number of female employees potentially exposed to BPA worked as electrical and electronic equipment assemblers; cementing and gluing machine operators; machine operators, not specified; welders and cutters; and assemblers.<sup>18</sup> The number and type of consumer products containing BPA has changed substantially over the last 20 years, with notable increases in the use of BPA in digital media and electronics. There clearly is a need for more current information on the prevalence of occupational exposures to BPA in today's workforce. Furthermore, the degree to which these occupational settings may result in biologically meaningful exposures has not been investigated.

### **Exposures from Consumer Products**

By far the greatest sources of concern with respect to BPA are exposures from consumer products. Most of the BPA that is produced is used for the manufacture of polycarbonate plastics and epoxy resins, which are widely used in consumer products that come into contact with food and beverages.<sup>11, 19, 20</sup> Plastic water and milk jugs,

recyclable beverage containers, baby bottles, children's "sippy cups," and other food and beverage storage containers are commonly made from polycarbonate plastic. Epoxy resins are most commonly used as part of the protective linings in food and beverage cans. They are also used in resin-based adhesives, protective coatings, and printed circuit boards. Similar BPA-containing resins are used in some dental sealants.<sup>19, 20</sup>

While initially it was thought that human exposure to BPA from these consumer products would be minimal, given the stability of the BPA polymer, it is now well documented that BPA can leach out of these food and beverage containers under normal conditions of use. Migration of BPA into food and drink occurs when the polymer is hydrolyzed due to contact with acidic compounds or due to heating.<sup>3, 11</sup> BPA has been detected in myriad canned foodstuffs, including coffee, vegetables, fish, meat, beverages, dairy products, and infant formula.<sup>3</sup> The levels and presence of BPA in such items appear to be influenced by the duration of and temperatures used in the heating process during manufacture and may also be influenced by storage times.<sup>3</sup> Migration of BPA into food and beverages from polycarbonate plastic containers is also well documented.<sup>2, 3</sup> BPA leaching increases as the polymer degrades with use, and appears to be expedited by heating and repeated washing.<sup>21, 22</sup> This has created considerable concern over potential exposures to infants from baby bottles, which are typically heated and washed multiple times a day. Additional data has suggested that BPA can even leach from new polycarbonate plastic into water at room temperature.<sup>23, 24</sup>

### **Extent of Human Exposures**

The extent of human exposures from environmental, occupational, and consumer product sources has not been fully elucidated. Estimations of BPA levels in food and beverages stored in polycarbonate plastics and epoxy-resin-lined cans have been the primary focus, since these are believed to be the sources of the greatest potential for exposure. Initial estimates of human exposures to BPA were based on models predicated on assumptions of leaching rates observed in the laboratory, measurements of actual levels of BPA in canned goods, and/or average consumption rates of various foods and beverages.<sup>20</sup> Models generated on those assumptions generally predicted daily human consumption of BPA from food and beverage sources and through an oral route would be very low (<1 µg/kg body weight).<sup>3, 20</sup>

With the advent of laboratory techniques to detect BPA levels in a variety of biologic media, including sera, saliva, and urine, we are now able to measure BPA in humans at very low levels. Recent biomonitoring data from NHANES III reported 95 percent of participants had detectable levels of BPA in their urine, with a median concentration of 1.28 µg/L.<sup>7</sup> Measurements of BPA in biologic media from other studies conducted in the U.S., Europe, and Japan have yielded remarkably similar levels, with detection rates generally between 95 percent and 100 percent.<sup>2, 8, 25, 26</sup> In addition to urine, BPA also has been measured in plasma of adult men and women.<sup>25</sup> Furthermore, its presence in human fetal plasma, placental tissue, amniotic fluid, and breast milk<sup>11, 27-31</sup> has fueled considerable concern

with respect to potential breast cancer risks, as much attention has recently focused on the role of early-life estrogen exposures in breast cancer etiology.

Welshons and colleagues note that the nearly universal detection of BPA in human biologic media is not consistent with exposure prediction models predicated on low consumption and rapid metabolism/elimination, suggesting that BPA exposure must be virtually continuous, that there may be unidentified sources of BPA exposures, and/or that we may not fully understand the pharmacokinetics of this compound.<sup>2</sup>

In 1988, the U.S. Environmental Protection Agency set a maximum acceptable level (reference dose) for BPA at 0.05 mg/kg/day.<sup>32</sup> This level was based on toxicologic studies conducted in the 1980s that relied on the administration of high doses of BPA to rodents and recorded the lowest level at which adverse effects were observed, which was 50 mg/kg/day (the lowest dosage tested).<sup>33</sup> Then, as is common practice in risk assessment, this level was divided by a 1,000 (an "uncertainty factor") to account for potential differences in effects in humans. In 2002, the European Union, taking a more conservative approach, established a temporary tolerable daily intake of 10 µg/kg/day (0.01 mg/kg/day) based on the now well-documented liver, reproductive, developmental, and hormonal effects observed at relatively low doses of BPA.<sup>34</sup> However, several papers published in the last five years suggest effects at even lower levels.<sup>11, 35</sup>

In summary, there is well-documented evidence of widespread human exposures to BPA. The most likely exposure route is ingestion through food and

beverage containers made from products containing BPA, although we have not yet fully elucidated the primary determinants of levels in humans. It appears pre- and peri-natal exposures are also likely through transplacental transport of BPA and ingestion of BPA-contaminated breast milk. Detectable levels of BPA in humans, while extremely prevalent, are generally low. Until recently, most monitoring of BPA has been in urine.<sup>36</sup> A large body of literature from studies in rodents, however, mostly published within the last few years, has suggested that adverse health effects can be caused even at these very low levels. The interpretation of these findings and their pertinence to breast cancer risk in humans remains a source of considerable debate (see discussions below).

### **Biologic Plausibility**

BPA is not currently classified as a carcinogen by any large health regulatory agency. This is largely based on the results from carcinogenic bioassays conducted in the 1970s-80s in which mice were administered large doses of BPA and no increase in the incidence of malignant tumors was observed.<sup>11,33</sup> These assays, however, are designed to capture direct genotoxic effects and may fail to detect the promotional and other potential indirect routes by which endocrine disruptors may affect carcinogenesis. While it has been argued that a lack of carcinogenic effect at high doses makes carcinogenicity at lower doses implausible, others have noted that endocrinology boasts numerous examples of compounds that at low doses can stimulate a response, while they can inhibit the same response at much higher doses.<sup>37</sup> As breast cancer research has begun to focus more

attention on the potential role of endocrine disruptors, BPA has received intense scrutiny due to its well-documented estrogenic properties. Within the last few years, many studies have been published documenting estrogenic effects of BPA at levels currently observed in human populations (see Critical Review of the Literature, below). Whether these estrogenic effects result in an elevated breast cancer risk has not yet been determined, but two recent studies suggest that prenatal exposure to very low levels of BPA can induce mammary gland neoplasias in the absence of further insults.<sup>9,10</sup>

In addition to estrogenic activity, it has been suggested that low doses of BPA may act to increase breast cancer risk by a number of other mechanistic pathways. There is some evidence, both in vitro<sup>11</sup> and in vivo,<sup>38</sup> of BPA disrupting microtubule formation, and increasing the risk of aneuploidy. There also is evidence emerging that BPA may disrupt thyroid function<sup>2,39</sup> and may stimulate prolactin release.<sup>11</sup> Furthermore, very low levels of BPA may act via non-genomic receptors to activate cell signaling pathways and promote proliferation.<sup>2</sup> The lines of evidence supporting these various mechanisms are discussed in the next section. Nearly the entire body of literature to date has focused on the estrogenic mechanisms of BPA, with very little devoted to these other potential modes of action.

### **Critical Review of the Literature**

The majority of findings to date have been from in vitro or in vivo studies, with almost no human health data available. As discussed previously, while results from these kinds of studies can be informative, they are fraught with limitations.

Nearly all studies have focused on documenting BPA's estrogenic properties. In this regard, most studies have examined the effects of BPA on intermediate endpoints (such as timing of pubertal development and mammary gland morphology), rather than mammary tumor susceptibility or incidence. Recently-published evidence suggests that BPA affects the fetal mammary gland in a significant and persistent manner, leading to increased mammary epithelial cell proliferation in adult animals.<sup>9, 10, 40</sup> With nearly ubiquitous exposures occurring in a complex milieu of endogenous and exogenous hormones, the study of BPA and breast cancer is highly challenging and will require creative multi-disciplinary thinking.

#### *In Vitro Studies*

BPA consistently has been shown to bind to estrogen receptors with an affinity approximately 2-4 orders of magnitude lower than that for estrogen,<sup>41-46</sup> and it was noted by Nagel and colleagues that in MCF-7 breast epithelial cells, the presence of human serum increased the binding affinity of BPA.<sup>47</sup> Recently, Welshons and colleagues followed up on this finding with a novel in vitro assay that considers the effects of plasma-binding proteins on the uptake of estrogenic chemicals into cells. They found that BPA bound only weakly to albumin in blood, and therefore was delivered to cells with a physiologic advantage compared to estradiol.<sup>2, 37</sup> This suggests that the estrogenic potential of BPA may be greater than what is suggested by most of the in vitro studies conducted to date.

There is strong evidence that BPA can elicit a proliferative response in MCF-7 cell strains with an order of magnitude approximately three to five

times less potent than 17  $\beta$ -estradiol.<sup>11, 48</sup> In vitro studies also have suggested the ability of free BPA to stimulate prolactin release,<sup>49</sup> progesterone activity,<sup>11</sup> and anti-androgenic activity,<sup>11</sup> and to disrupt microtubule formation and increase the risk of aneuploidy,<sup>11</sup> although these findings are not as well documented as BPA's estrogenic properties.

#### *In Vivo*

For the most part, in vivo studies of BPA have focused on the developmental toxicity of BPA in rats and mice. In a recent review of this literature, Vom Saal noted that through the end of 2004, 115 in vivo studies had been conducted to investigate low-dose effects of BPA, 94 of which reported significant findings.<sup>37</sup> Thirty-one of these studies reported effects at doses below the current standard of 5.0 mg/kg/day.<sup>37</sup> In fact, within the last year, a committee of experts on BPA convened to review the literature on the low-dose health effects of this compound and made several sound conclusions on low-dose effects of BPA, existing below the current NOAEL (no observed adverse effect level).<sup>35</sup> A number of these effects, including morphologic changes in the mammary glands, and alterations in the onset and cyclicity of estrus, could have potential impacts on breast cancer risk.

Perhaps most worrisome is the growing body of evidence that low doses of BPA administered prenatally can result in a variety of changes in the mammary glands of female rodent offspring.<sup>2, 8-10, 35, 40, 50</sup> Such morphologic changes are likely to be irreversible and permanent. It has been noted that the mammary glands of the female offspring of exposed animals also demonstrate precocious

development, often resembling the gland in early pregnancy.<sup>51</sup> Morphologic changes of the mammary gland associated with low doses of in-utero exposures in rats and mice include: an increase in terminal end buds;<sup>10, 50-53</sup> a decrease in apoptotic activity (programmed cell death) in the terminal end buds;<sup>50</sup> an increase in ductal density;<sup>10, 40, 51</sup> and an increase in progesterone receptor-responsive ductal epithelial cells.<sup>50</sup> These morphologic changes could potentially be linked to increased mammary tumor risk, because the tumors are known to arise from the cells of the terminal end buds. Perhaps the most convincing evidence of a direct association between low doses of BPA and breast cancer in vivo comes from a recently-published report in which rats exposed prenatally to very low doses of BPA were significantly more likely to develop pre-neoplastic lesions and carcinoma in situ of the breast.<sup>54</sup> To our knowledge, this is the first report to directly link prenatal exposure to very low levels of BPA to subsequent breast cancer in laboratory animals.

Other effects of prenatal BPA exposures that could potentially increase breast cancer risk include: larger size of offspring and an increase in postnatal growth,<sup>51, 55</sup> earlier onset of sexual maturation,<sup>37, 51</sup> alterations in estrus cyclicity,<sup>51, 56</sup> earlier mammary gland development in female offspring,<sup>37, 51</sup> and altered immune function.<sup>37</sup> Furthermore, it has been reported that animals exposed in utero to BPA have significantly-increased sensitivity to estradiol throughout their life<sup>10, 50</sup> and greater susceptibility to known breast carcinogens when exposed subsequent to prenatal exposures to BPA.<sup>9</sup> Replication of these findings is a clear priority.

However, results from in vivo studies have not been entirely consistent across studies and replication of some of the key findings has proven problematic.<sup>11, 19, 35, 57</sup> A great deal of discussion has ensued concerning the sources of the disparate findings. This highlights a number of key issues in studying the effects of endocrine disruptors in rodents, including the wide variation in effects by species, and even within strains of a single species. For example, the Charles-River Sprague Dawley strain of rat was commonly used in many of the studies that failed to find any effects of low-dose BPA. This strain, however, is well known for its low sensitivity to estrogens.<sup>35, 58</sup>

The variation in sensitivity to estrogenic effects within and between species underscores the importance of using positive controls in these types of studies, something that was inconsistently done for this body of literature. When positive controls were used, DES (a well-documented estrogenic compound and developmental toxicant) was the most common choice and in those studies, BPA effects essentially mirrored those of DES. The inconsistency in findings across laboratory studies may also be due to the wide variability in the phytoestrogen content of the animal feed used in various laboratories.<sup>2, 57-59</sup> Finally, it has been noted that the source of research funding appears to be correlated with study results. Vom Saal and Hughes recently pointed out that while no industry-funded studies have reported effects of BPA at low doses, 90 percent of government-funded studies have reported significant findings.<sup>58</sup> They further note that industry-funded studies often use inappropriate animal models (such as the Charles-River Sprague Dawley rat)

and fail to use (or fail to report that they used) positive controls.<sup>58</sup>

While industry continues to debate the estrogenic effects of BPA, during the last few years, solid evidence for low-dose estrogenic effects in rodents has emerged.<sup>35</sup> Development of *in vivo* studies to extend these findings to more directly investigate BPA exposures and breast cancer, such as the ones recently published by Murray and Durando and colleagues<sup>10, 54</sup> is a necessary next step.

### **Studies in Humans**

The wide variation in sensitivity to estrogenic effects in different species/strains of animals highlights the limitations in making inferences about BPA's effects in humans based on observed effects in rodents. Another complication of inferring effects from rodents to humans for this compound is that the major pathway for metabolizing ingested BPA in rats involves glucuronide conjugation. The glucuronide form is absorbed by the gut and demonstrates less estrogenicity than the free form of BPA. Humans do not glucuronidate BPA as efficiently as rodents, thus we may underestimate the potency of this compound in humans if directly translating dose to effect from rodent data.<sup>9, 11</sup> Furthermore, the large variation due to feedstuffs in rat studies is slight compared to the enormous variation in the daily diets of U.S. children and adolescents.

To our knowledge, no epidemiologic studies of breast cancer risk and BPA exposures have been published. There are, however, some very limited human data on other endocrine-related effects in humans that may have some relevance to breast cancer risk. Results from a small study recently

conducted in Japan found a significant relationship between serum levels of BPA in women and obesity, ovarian dysfunction, and blood androgen concentrations.<sup>25</sup> It also has been reported that BPA levels are positively correlated with repeated miscarriage<sup>60</sup> and inversely correlated with endometrial hyperplasia.<sup>61</sup> Another recent study measuring BPA in the adipose tissue of women may help us understand the amount of this compound that actually reaches the breast.<sup>36</sup>

### **Future Directions**

Given the well-documented and widespread human exposures to BPA, in conjunction with some clear evidence of estrogenic effects at low levels, more study of effects in humans is warranted. Unfortunately, the study of a non-persistent—but nearly continuous and ubiquitous—exposure at relatively low levels for a disease, such as breast cancer, with a long latency period is fraught with difficulty. There is, however, a rapidly emerging literature on exposure assessment issues surrounding this compound. For example, recent data suggests fair-to-excellent intrapersonal variability for BPA urinary metabolites, despite BPA's short half-life.<sup>62</sup> New biomonitoring methods and data from NHANES may help establish better reference ranges.

The potential of BPA to hasten the onset of breast development in girls needs to be explored. Clearly, a multi-disciplinary approach is needed, requiring creative thinking from a team including endocrinologists, toxicologists, epidemiologists, and geneticists.

Some first steps might include:

- Conduct occupational studies to identify groups at high risk for exposures, paying special attention to women of childbearing age.
- Document the degree to which body-burden levels change over time, i.e., how representative of lifetime exposures are a single or a few body-burden measurements?
- Conduct a body-burden study to examine age of puberty and amount of BPA in umbilical cord blood at birth, or BPA in urine of young children (a current aim of epidemiological studies by the Breast Cancer and Environment Research Centers, jointly funded by the National Institute of Environmental Health Sciences and the National Cancer Institute).
- Elucidate major factors that determine body-burden levels in humans. While it is assumed that oral ingestion from contaminated food and drink is the main route of exposure in humans, this is mostly based on models and speculation, not real data. Welshons and colleagues have emphasized the importance of considering inhalation and transdermal exposures through bathing with contaminated water.
- Further investigate BPA pharmacokinetics in humans, especially in infants and children.

- Consider BPA effects in context of mixtures.

BPA exposures may be curtailed by regulatory action before we figure out if there is a breast cancer connection.<sup>63</sup> If so, documenting past and persistent exposures may become critically important to studying and understanding BPA's health effects.

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## *Identifying Gaps in Breast Cancer Research*

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