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THE HIGH-VOLUME HORMONALLY ACTIVE CHEMICAL BISPHENOL A: HUMAN EXPOSURE, HEALTH HAZARDS AND NEED TO FIND ALTERNATIVES

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SOURCES AND ROUTES OF EXPOSURE AND METABOLIC FATE

The chemical bisphenol A (BPA) was first used as a component of Bakelite, a plastic from which billiard balls and some other products were made in the early to mid 20th century. Similar to many phenolic compounds, BPA was reported to be a synthetic estrogen in 1936, and BPA had the efficacy of estradiol (Dodds and Lawson 1936). In the 1950s polymer chemists discovered that these estrogenic BPA molecules could be polymerized to make polycarbonate, a hard, clear plastic. BPA is also used in the manufacture of the resin lining of food and beverage cans in the USA and many other countries. In addition to being the monomer that is used in the above products, BPA is also used as an additive (plasticizer) in other types of plastic, such as polyvinyl chloride (PVC). BPA is one of the highest production volume chemicals in commerce, with over 8-billion pounds produced in 2008 (Bailin et al. 2008). The range of products that contain BPA is not known due to product confidentiality laws that protect corporations from revealing the chemicals used in products. A question that is often asked is: How could chemists have used a chemical that had been reported to act like a sex hormone to make plastic products such as baby bottles? The “green chemistry” movement not only provides answers to this question (which is that they did not pay attention to biological effects), but most importantly, it provides solutions (Anastas and Kirchhoff 2002).

Food contact items (can lining, food packaging and food and beverage containers) were previously thought to be the major contributors to the mean values of about 3-4 ng/ml (parts per billion, ppb) of unconjugated (biologically active) BPA detected in adult and fetal serum (Vandenberg et al. 2007). However, recent evidence has shown that the amounts of BPA that leach out of food contact containers cannot account for these ppb levels of BPA in human serum (Vandenberg et al. 2007; Stahlhut et al. 2009). This has led to speculation that the use of BPA in products such as carbonless or thermal paper (used for receipts, in hospitals, etc.) results in dermal exposure that will lead to higher levels of BPA than occur via the oral route due to the absence of first-pass metabolism of chemical absorbed from the gut; ingested BPA is transported via the mesenteric portal vessels from the gut to the liver, where it is inactivated by the enzymes glucuronosyltransferase and sulfotransferase (Vandenberg et al. 2007).

Route of exposure (oral, dermal, inhalation) to BPA has become a highly controversial issue, because articles funded by chemical corporations that manufacture BPA have proposed that all experimental animal studies of BPA that have not involved oral administration of BPA are irrelevant to the assessment of the health risk posed to people by BPA. However, as noted above this view is now disputed by the findings by Stahlhut and colleagues based on the United States National Health and Nutrition Examination Survey (NHANES) of thousands of people (Stahlhut et al. 2009). In addition, we conducted an experiment with newborn mice that showed that in the

neonate, route of administration of BPA has no impact of the rate of clearance of unconjugated BPA from blood (Taylor et al. 2008). This finding was predicted by an extensive literature showing that fetuses and neonates have limited liver detoxifying capacity relative to adults (Vandenberg et al. 2007). This led the US National Toxicology Program (NTP) to determine in its review of BPA that due to limited ability to glucoronidate BPA during fetal and neonatal life, the more rapid metabolism after oral administration of BPA in the adult (when compared to non-oral routes) would not be expected to occur in fetuses or newborns (NTP 2008). In sharp contrast, the European Food Safety Authority (EFSA) made the determination that fetuses and newborns have the capacity to metabolize any BPA that they are exposed to (EFSA 2008), although this opinion, that went on to state that BPA posed no threat to humans regardless of life stage, has been challenged as directly contradicting the published literature by both the German and Danish Ministries of the Environment.

Whereas glucuronidation is the predominant pathway for inactivating BPA in adults, this enzyme is not expressed during the fetal period of sexual differentiation when manmade estrogenic chemicals are known to disrupt development, and, instead, what metabolism of BPA that does occur in fetuses is via sulfation (Richard et al. 2001). This is important because tissues in the fetus, as well as the placenta, express the enzyme sulfatase that cleaves the sulfate group resulting in biologically active BPA. The role of glucuronidase in the de-conjugation of BPA-glucuronide is less clear in the adult (Ginsberg and Rice 2009).

Regarding fetal exposure to BPA, sulfated metabolites of chemicals such as BPA can be de-sulfated to the parent compound by sulfatase activity in both the fetal liver and placenta (Collier et al. 2002). The cycling that occurs between sulfation and de-sulfation of chemicals such as BPA thus plays a critical role in determining exposure of fetuses and neonates to the bioactive compound. This shows the importance of a thorough study of the ontogeny of activities of sulfotransferases and glucuronosyltransferases, as well as the deconjugating enzymes, for understanding the risks posed by BPA exposure during prenatal and early postnatal life, when the levels of these enzymes are changing (Collier et al. 2002). There is a considerable exchange between the placenta, which expresses sulfatases that hydrolyze sulfated estrogens, and fetal tissues, which conjugate (via sulfatation) estrogens, providing a continuous cycling pool of unconjugated estrogens and estrogen sulfates. The sulfates may act as a "reserve" yielding active hormones following hydrolysis; the formation of estrogen sulfates may provide a protective mechanism, since sulfates are biologically inactive (Pasqualini 2005).

Exposure assessments

We have examined leaching of BPA from metal food and beverage cans and polycarbonate food-storage containers to determine the amount of BPA that people are be exposed to from the use of these products. BPA-free purified water was placed into cans that had contained different products as well as polycarbonate food storage container. The cans and containers were then heated to 95^{o}C for 24 h to simulate the food-sterilization process used after food is added to cans and to simulate the heating of polycarbonate food containers in the microwave, which manufacturers claim is "safe". BPA was analyzed after separation by HPLC with CoulArray detection (limit of detection ~10 parts per trillion). All cans and polycarbonate food containers leached detectable levels of BPA, although there were differences in the amount of leaching from different products and from different manufacturers. As expected, the cans that had contained acidic tomato sauce resulted in the highest BPA leaching rate. Specifically, one brand of canned tuna fish leached about 30 μg/L BPA, a brand of canned peas leached about 40 μg/L BPA, and a brand of tomato sauce leached

about 50 µg/L BPA. A polycarbonate food container leached 15 µg/L (J. Taylor, unpublished). It is a basic characteristic of the ester bond linking BPA molecules together in polycarbonate plastic and resins that the rate of breaking of the bond by hydrolysis increases with heat, releasing free BPA (Bae et al. 2002), and an increase in leaching also occurs as a result of either an increase or decrease in pH (Brotons et al. 1995; Vandenberg et al. 2007). When food or liquids (such as beer) are placed into a can, they are heated to a high temperature for sterilization. The consequence is that food and beverages in cans have variable levels of BPA based on whether the contents are lipophilic and/or acidic or alkaline, all of which increase leaching (see the Environmental Working Group web site for additional data on leaching of BPA from cans at www.EWG.org).

Another common use for BPA is as the monomer in dental sealants and composites used for fillings, from which BPA leaches in variable amounts and for different lengths of time depending on the product (Joskow et al. 2006). BPA has been reported to be present in PVC products such as stretch film and water pipes. BPA is used in printers ink and to coat paper used for receipts (referred to as "carbonless paper"); unpolymerized (free) BPA in carbonless paper interacts with a gel-encased dye to create a visible print when the dye is released from the gel by heat or pressure. BPA is also used in newspaper print and is thus a major contaminant in recycled paper products (Vandenberg et al. 2007). Polycarbonate food storage and beverage containers (the hard, clear containers, which may be tinted in the case of sport water bottles or baby bottles) cause concern for their potential to leach BPA because they are re-usable, and repeated use leads to an increase in leaching (Brede et al. 2003). Many of these containers are marketed for use in the microwave, despite the fact that heating is known to increase BPA leaching levels.

The United States Centers for Disease Control and Prevention (CDC) has measured BPA in the urine of people in the USA as part of the 2003/2004 United States National Health and Nutrition Examination Survey (NHANES) (Calafat et al. 2008). The CDC reported that 93% of people had detectable levels of BPA in their urine. The median and mean levels of unconjugated (parent) BPA reported in blood, as well as the lower and upper range reported for women and their fetuses at the time of parturition in Germany (Schonfelder et al. 2002), were virtually identical to values reported for total BPA in urine by the CDC.

Currently a BPA dose of 50 µg/kg/day is considered "safe" for daily human consumption by the US EPA and FDA (IRIS 1988), although this safety standard was set in the 1980s and has at the time of preparation of this manuscript not been revised since then in spite of considerable pressure on the FDA by the US Congress, which has given the FDA a deadline of December 2009 to review its position on the safety of BPA (DailyGreen 2009). Findings reported by Vandenberg et al. (2007) led to a consensus conclusion by 38 scientists who attended a US National Institutes of Health (NIH) sponsored conference on BPA that current levels of human exposure to BPA already exceed the presumed "safe" daily exposure dose (vom Saal et al. 2007). We recently reported that daily oral administration of 400 µg/kg/day to adult female rhesus monkeys resulted in average blood levels of unconjugated BPA that were approximately 8-times lower than median/mean levels reported in women (VandeVoort et al. 2009). Since the rhesus monkey is considered a good model for human pharmacokinetics of chemicals such as BPA, these findings add to our concern that human exposure to BPA is currently much higher than has been estimated by government regulatory agencies, and is much higher than doses that cause a myriad of adverse health effects in a variety of animal species, such as rodents (rats, mice), farm animals (sheep) and primates (African green monkeys; Chlorocebus aethiops sabaeus).

ADVERSE HEALTH EFFECTS OF BPA IN LABORATORY ANIMALS

Experiments with laboratory animals are used to inform regulatory agencies about the safety of drugs and chemicals. As indicated previously, the "safe" dose of BPA was estimated to be 50 µg/kg/day based on a few studies conducted in the 1980s that only examined a few very high doses. These very high-dose studies have been challenged as invalid for accurately predicting the effects of low doses of chemicals that act through receptor systems for hormones, which are sensitive to very low doses (Myers et al. 2009). Examples of effects of acute exposure to low doses of BPA in adult animals are: a significant stimulation of insulin secretion followed by insulin resistance in mice (Ropero et al. 2008), a significant decrease in daily sperm production in rats (Sakaue et al. 2001), a decrease in maternal behavior in mice (Palanza et al. 2002), and disruption of hippocampal synapses, leading to the appearance of a brain in both rats and monkeys that is typical of that seen in senile humans (MacLusky et al. 2005; Leranth et al. 2008).

Related to the fact that type 2 diabetes is increasing in many regions of the world is the finding that exposure of adult mice to a low oral dose of BPA (10 µg/kg/day) resulted in stimulation of insulin secretion that was mediated by estrogen receptor ER alpha. The prolonged hyper-secretion of insulin was followed by insulin resistance and postprandial hyperinsulinaemia (Ropero et al. 2008). The low-dose studies of BPA effects on insulin secretion and insulin resistance in experimental animals have been confirmed in cell culture studies with human and animal tissues that have revealed molecular pathways that mediate effects of BPA in the low parts per trillion range, far below concentrations of BPA found in virtually all people who have been examined (Wetherill et al. 2007). Hugo et al. (2008) reported that human fat cells in primary culture showed a marked suppression of the critical regulatory cytokine adiponectin, with the maximum response occurring at 1 nM (0.23 ppb), at the low end of the range of human exposure to BPA. A decrease in adiponectin is related to insulin resistance and an increased risk for type 2 diabetes, cardiovascular disease and heart attack (Beltowski et al. 2008). It is thus of considerable interest that in an analysis of data from 1455 people examined for BPA levels in urine as part of the NHANES conducted in 2003/2004, there was a significant relationship between urine levels of BPA and cardiovascular disease, type 2 diabetes, and abnormalities in liver enzymes (Lang et al. 2008). The fact that these findings are related to studies that identify plausible mechanisms by which BPA at current levels of human exposure could result in these diseases greatly strengthens the importance of these findings (vom Saal and Myers 2008).

The greatest concern with exposure to BPA is during development: fetuses, neonates, infants, children and adolescents. There are two important issues driving this concern: 1. Exposure to BPA has been found to be significantly greater as age decreases (Calafat et al. 2008), and recent findings indicate that premature infants in a neonatal intensive care unit have approximately 10-fold higher BPA levels relative to adults (Calafat et al. 2009). 2. Fetuses and neonates are particularly vulnerable to the "programming" effects that endogenous hormones and chemicals that act like hormones such as BPA have on genes in cells undergoing differentiation. These programming events are referred to as "epigenetic" modifications of genes because they do not involve classical mutations, but instead, involve addition and removal of methyl and acetyl groups from bases that make up genes as well as the associated proteins that form part of the chromosomes. The result of exposure during development to hormonally active chemicals is thus permanent abnormal programming of genes that can lead to diseases later in life (Dolinoy et al. 2007).

The laboratory animal research on BPA is unique in that there are now hundreds of studies that have examined doses of BPA within the range of human exposure rather than the more typical approach

in regulatory toxicology of only testing a few doses that are thousands of times higher than human exposure levels (vom Saal et al. 2007). There was surprise associated with the first "low dose" publications on the effects of BPA in laboratory mice (Nagel et al. 1997; vom Saal et al. 1998), which showed that feeding pregnant mice 2 or 20 μg/kg/day BPA caused abnormalities of the entire reproductive system in male offspring when they were examined in adulthood. The 2 μg/kg/day dose was a daily oral dose to pregnant mice that was 25,000-times lower than had ever been examined, and 25-times below the current "safe" daily exposure dose according to the US FDA and US EPA, as well as EFSA. Numerous reviews have since been published challenging as invalid the assumptions used by these regulatory agencies to estimate "safe" exposure levels for endocrine disrupting chemicals such as BPA (Welshons et al. 2003; Myers et al. 2009; Myers et al. 2009).

One of the main concerns with the adverse effects reported in response to developmental exposure to low doses of BPA (that produce blood levels in animals below those in humans) is that they all relate to disease trends in humans. For example, there is an obesity epidemic in many regions of the world, and developmental exposure to BPA increases body weight later in life (Heindel and vom Saal 2009). The incidence of prostate and breast cancer is increasing, and BPA exposure during early life causes these cancers in rodents; most animal carcinogens are human carcinogens (Richter et al. 2007).

The largest literature on the adverse effects of BPA exposure during development concerns adverse effects on brain structure, chemistry and behavior (Richter et al. 2007). One of the most interesting aspects of this literature is that there is a consistent finding of a loss of sex differences in brain structure, chemistry and behavior due to fetal/neonatal exposure to low doses of BPA. BPA thus appears to interfere with the normal processes that govern sexual differentiation, with brain changes reported in both males and females, depending on the outcome measured (Palanza et al. 2008). The implications at the population level for disruption of normal socio-sexual behaviors has not been extensively studied, although there are reports of changes in play behavior (Dessi-Fulgheri et al. 2002) as well as other socio-sexual behaviors (Farabollini et al. 2002) that could impact population dynamics.

There are also numerous studies of the effects of low doses of BPA on development of the female (Soto et al. 2008). Findings include chromosomal abnormalities in oocytes in female (Susiarjo et al. 2007), and long-term effects on reproductive organs that are not observed until mid-life, such as uterine fibroids and para-ovarian cysts (Newbold et al. 2007). Other studies have shown that very low doses of BPA during prenatal or neonatal development can result in permanent effects in male rats and mice. For example, fetal exposure to a low dose of BPA causes a permanent decrease in testicular sperm production in mice (vom Saal et al. 1998).

THE NEED FOR ALTERNATIVES TO BPA

Over the last decade there have been approximately 1000 published articles concerning the endocrine disrupting effects of BPA. Many of these studies link BPA to diseases that have been increasing in incidence over the last part of the 20th century and beginning of the 21st century (Talsness et al. 2009). As a result of numerous studies documenting products that leach BPA into the environment after disposal, typically into landfill or into the oceans (Thompson et al. 2009), and also leach out of products used to store food and beverages, out of medical devices, and other products such as carbonless paper and water pipes, there has been public pressure in developed countries to find alternatives to BPA that can be used to make these products (EnvironmentCanada 2008). For example, in the late 1990s the three major Japanese can manufacturers voluntarily

replaced BPA-based resin as the surface coating of cans and replaced BPA-based resin with polyethylene terephthalate (PET), although BPA is still present as an adhesive undercoat that serves to bind the PET to the metal can. We have found that Japanese cans leach less than 5% of the amount of BPA relative cans containing similar products made in the USA (J. Taylor, unpublished), which is certainly a step in the right direction. At the same time carbonless and thermal paper containing BPA completely disappeared from the Japanese market, since there have always been other chemicals available for use to react with the dye in these products, so no product development was required. These actions in Japan occurred due to public concern and did not require changes in laws by legislators or regulatory agencies in Japan. Similarly, there are plastic alternatives that already exist to the PVC-based products used in hospitals (such as dialysis and IV tubing), and some hospitals (notably those owned by Kaiser Permanente) have stated their intention to only buy non-PVC-based products, due to clear evidence that these products leach high levels of BPA as well as another class of endocrine disrupting chemicals called phthalates (Calafat et al. 2009). Finally, the product that has received the most public attention is baby bottles and reusable sport water bottles. BPA-free plastic bottles (and glass bottles) are now replacing BPA-based polycarbonate bottles, since Canada has banned the sale of polycarbonate bottles (EnvironmentCanada 2008), a few states in the USA have taken similar action, and similar legislation is pending in the US Congress (DailyGreen 2009).

A variety of other chemicals are now entering the market place to replace BPA-based polycarbonate in bottles and food containers, such as a polyester in Eastman's Tritan (chemical composition unknown) and polyethersulfone (PES). One of the major goals of the green chemistry movement is to establish a paradigm (the 12 principles of green chemistry) that can be followed for introducing chemicals for new products into the marketplace as well as replacements for bad chemicals such as BPA (Anastas and Kirchhoff 2002). It is clear that the public wants products, particularly those targeted at babies, to not contain dangerous chemicals. However, without the cooperation of chemical corporations, which was demonstrated by Japanese corporations, this will not be an easy goal to achieve. So far, corporations in the USA and Europe have taken the opposite approach to the Japanese and have continued to deny that BPA or other endocrine disrupting chemicals have any adverse effect. The denial of science was a successful strategy for the tobacco industry for decades, and US and European chemical corporations have so far chosen that approach. An important argument from "green chemists" is that replacing bad chemicals with safe chemicals is not just important for survival of the planet, it will increase profits over the long run. It appears that unlike the situation in Japan, this may require legislation in the USA, which the current Congress appears willing to tackle (DailyGreen 2009). The Europeans have moved forward with a new approach called Registration, Evaluation and Authorization of Chemicals (REACH), which is a step in the right direction for stimulating corporations to find alternatives for chemicals to ensure a sustainable planet.

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