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Adverse Health Effects of Bisphenol A (BPA): Implications for the Use of BPA in Hemodialyzers and Other Medical Equipment

Bisphenol A is a very high volume chemical with estrogenic activity that is used in a wide range of products, including medical equipment such as hemodialyzers. Virtually all people have measurable amounts of BPA, since this chemical readily leaches out of products that contain it. BPA is associated with a wide range of diseases because it alters programming of the expression of genes that are critical for the normal development and adult functioning of numerous organ systems. Hemodialysis patients have impaired kidney function and thus reduced capacity to eliminate BPA and other toxic chemicals. Exposing patients undergoing hemodialysis to BPA contained in hemodialysis equipment could contribute to an increase in other diseases.

Bisphenol A (BPA) is a very high volume chemical (Bailin et al. 2008) that was initially reported to have full efficacy as an estrogenic drug relative to endogenous estrogen in 1936 (Dodds and Lawson 1936). Chemists ignored these findings, and BPA was subsequently used in the 1950s as the monomer to produce polycarbonate plastic and as an additive (plasticizer) in polyvinylchloride (PVC) plastic, as well as eventually in many other products, such as the coating (developer) in receipt paper. BPA is a component of many medical products, including hemodialyzers (Haishima et al. 2001) and medical tubing (Kanno et al. 2007), and patients undergoing medical treatments can be exposed to high levels of BPA (Calafat et al. 2009).

One often hears BPA described as a "weak" estrogenic chemical, and in some in vitro assay systems BPA has a much lower potency than estradiol (Welshons et al. 2003). However, in other assay systems BPA and estradiol are equally potent and show effects at doses as low as 0.01 pM or 0.0023 pg/ml (Watson et al. 2010). These studies have thus revealed effects of BPA at concentrations millions of times lower than concentrations predicted to cause no effect by traditional toxicological testing methods (Welshons et al. 2006), which have typically focused on acute toxicity or mutagenesis as an outcome. Recent findings of adverse effects of BPA and other endocrine disrupting chemicals at doses far below those previously estimated to be "safe" have led the Endocrine Society, as well as other scientific and medical societies, to identify the need for a change in the assumptions used in traditional chemical risk assessments (Diamanti-Kandarakis et al. 2009; Hunt 2011). In particular, the Endocrine Society recommended that 21st century approaches and knowledge about endocrine active compounds be taken into consideration in assessing the hazards posed by endocrine disrupting chemicals such as BPA. The conclusion by endocrinologists is that a "safe" dose of BPA (or other endocrine active compounds) cannot be estimated based on outdated methods used in chemical risk assessments that were developed in the mid 20th century. In contrast, for endocrine active chemicals, such as BPA, that can alter critical cell signaling pathways at doses below one part per trillion, there is clearly no dose that does not pose some risk (Myers et al. 2009a; Myers et al. 2009b; vom Saal and Sheehan 1998).

There are now hundreds of studies that report a wide range of adverse effects due to exposure to very low doses of BPA (Table 1), primarily via oral or subcutaneous (sc) routes of administration. While a focus of many of these studies has been on exposure during early life when organogenesis is occurring, there are also many studies showing effects of exposure to BPA in adults (Richter et al. 2007). An important issue with regard to adult exposures is that BPA is an ubiquitous environmental contaminant, with the result that BPA is detected in 93% of adults in the USA based on the National Health and Nutrition Examination Survey conducted by the US Centers for Disease Control and Prevention (Calafat et al. 2008). However, a recent study reported that even short-term exposure to low doses of BPA in adult female mice leads to subsequent metabolic abnormalities relative to unexposed females, including increased body weight, higher plasma insulin, leptin, triglyceride, and glycerol levels and greater insulin resistance (Alonso-Magdalena et al. 2010).

While exposure to BPA as a result of its use in food packaging is considered a significant source of human exposure (Muncke 2011), other non-food sources also contribute to BPA in the general population (Stahlhut et al. 2009). Route of exposure has a significant impact on pharmacokinetics of environmental chemicals as well as drugs. Intravenous (IV) exposure to BPA, such as during hemodialysis,

BPA effects in mice and rats	*Human health trends*
Cancer	
Prostate hyperplasia and cancer	Prostate cancer increase
Mammary hyperplasia and cancer	Breast cancer increase
Male and female reproductive system	
Abnormal urethra / Obstruction	Hypospadias increase
Sperm count decrease	Sperm count decrease
Early puberty in females	Early sexual maturation increase
Ovarian cysts / Uterine fibroids	PCOS / Uterine fibroids increase
Abnormal oocyte chromosomes	Miscarriage increase
Metabolic disease	
Body weight increase	Obesity increase
Insulin and glucose increase	Type 2 diabetes increase
Brain and behavior	
Hyperactivity / Impaired learning	ADHD increase
Abnormal play and social behavior	Autism increase

Tab. 1
Effects caused by exposure during development to low doses of BPA in experiments with laboratory animals in relation to disease trends in humans.

is not subject to the first pass metabolism that occurs for a substantial portion of BPA consumed in food. Exposure via an IV route results in higher serum levels of bioactive (unconjugated) BPA during the first few hours after administration relative to oral exposure (Pottenger et al. 2000).

Of particular concern for physicians is the potential for patients to experience an increase in exposure to BPA as a result of its use in medical equipment. BPA leaches from these devices, as do other plasticizers, such as phthalates (another class of endocrine disrupting chemicals used in PVC). Leaching of plasticizers from plastic products occurs because they are not bonded to the polymer backbone and can thus freely migrate out of plastic products, particularly at elevated temperatures. In addition to leaching from plastic products such as PVC plastic in which BPA is used as a plasticizer, polycarbonate plastic, in which BPA is polymerized and thus is not a plasticizer, is also a source of BPA exposure from medical products containing polycarbonate plastic. Leaching of BPA from polycarbonate plastic is due to the fact that BPA molecules are linked by ester bonds. The ester bonds linking BPA molecules in polycarbonate are subject to hydrolysis, which increases as a function of increased heat, increased alkalinity or increased acidity (Fig. 1).

The level of BPA detected in urine (as part of the NHANES 2003/2004 study) was related to serum glucose, insulin, insulin resistance and type 2 diabetes (Lang et al. 2008). There is extensive evidence from experimental animal studies relating acute BPA exposure to elevated serum insulin, elevated serum glucose and glucose resistance (Alonso-Magdalena et al. 2011). The significance of a cross-sectional study, such as the report by Lang et al. (2008), is strengthened by mechanistic findings identifying the molecular pathways by which BPA stimulates an increase in pancreatic beta cell insulin secretion as well as an increase in insulin resistance (Hugo et al. 2008). The relationship of elevated BPA to dysregulation of insulin and glucose homeostasis is not unexpected, given that BPA and estradiol are equally potent in terms of causing these effects in experimental animals and in vitro studies with human cells. It is well known that elevated estradiol during that latter part of human pregnancy is related to pregnancy-induced transient insulin resistance, which is required for sufficient glucose to be transported across the placenta to the fetus (as opposed to being taken up into maternal tissues) during the period of rapid fetal growth in the last trimester of pregnancy (Alonso-Magdalena et al. 2011). The problem is that the effects of BPA on insulin and glucose homeostasis in experimental animals occur at serum concentrations that fall within the range of unconjugated serum BPA detected in multiple human studies (Taylor et al. 2011a; Vandenberg et al. 2010). The available data thus suggest that any factor that results in an increase in exposure to BPA contributes to the elevated concentrations of BPA that are associated with type 2 diabetes (Lang et al. 2008).

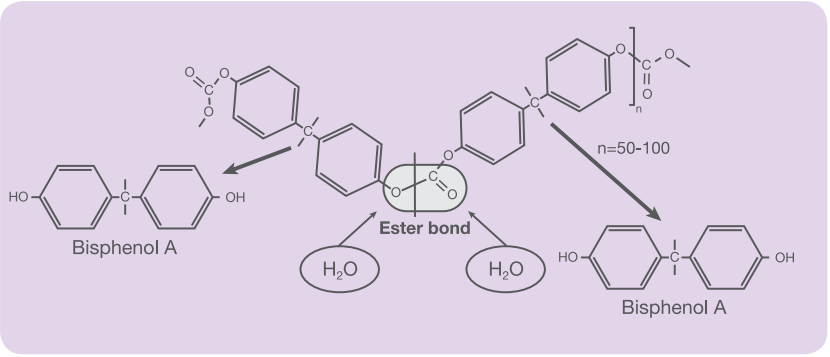

Fig. 1
Polycarbonate is composed of molecules of bisphenol A linked by ester bonds. The ester bonds are susceptible to hydrolysis that increases as a function of temperature as well as an increase or decrease in pH relative to a pH of 7. Hydrolyzed BPA molecules are released into the surrounding medium.

Effects of BPA on the urogenital system

We discovered that the development of the embryonic urogenital sinus, which differentiates into the bladder neck, prostate and urethra, is exquisitely sensitive to small changes in estradiol. Specifically, we experimentally increased free serum estradiol in male mouse fetuses by 0.1 pg/ml, which resulted in a reduction in urethral diameter, an increase in the number of primary prostatic ducts and prostatic duct volume, and a permanent increase in prostatic androgen receptors, rendering the prostate hypersensitive to androgen throughout the remainder of life (vom Saal et al. 1997). Subsequently, we fed pregnant mice of a 10-µg/kg/day dose of BPA, which is 500-fold lower than the dose that the European Food Safety Authority (EFSA) and the US Food and Drug Administration (FDA) still consider the "no effect dose" for BPA. This very low daily dose of BPA fed to pregnant female mice during the last part of pregnancy resulted in a significant increase in the number of primary prostatic glandular ducts, hyperplasia of basal epithelial cells (the progenitor cells implicated in prostate cancer) in the primary prostatic ducts, and a gross malformation resulting in a marked constriction in the bladder neck of male fetuses; these effects were all detected within 2 days of the initiation of prostate differentiation (Timms et al. 2005). In the mouse prostate differentiation is initiated on gestation day 17 (parturition occurs on day 19), while in humans prostate differentiation begins during gestation week 10.

The molecular mechanisms by which endogenous estrogen and estrogenic chemicals alter development of the urogenital system are beginning to be understood (Taylor et al. 2011b). Of particular concern are the disease consequences of developmental exposure to factors (including environmental chemicals and other stressors) that program gene expression patterns for the remainder of life via epigenetic mechanisms. Evidence is accumulating that is consistent with the developmental origins of health and disease (DOHaD) hypothesis. Regarding BPA and the urogenital system, the hypothesis is that developmental exposure to estrogenic chemicals is implicated in the development of prostate cancer later in life via effects on prostate stem/progenitor cells (Hu et al. 2011; Timms et al. 2005), as well as kidney disease and other co-morbidities associated with metabolic disease (Alonso-Magdalena et al. 2010); Dotsch et al. 2011; Zandi-Nejad et al. 2006). Recently, we found that developmental exposure to doses of BPA that are far below levels considered "safe" for daily human exposure by US and European regulatory agencies leads to obstructive voiding disorder (OVD), which then results in hydronephrosis in adulthood in male mice (unpublished observation).

As indicated above, some medical equipment used in hemodialysis and other hospital procedures contains BPA and phthalates, which leach into the blood during dialysis (Sugimura et al. 2001; Vandentorren et al. 2011; Yamasaki et al. 2001). Impaired renal function is associated with an inability to clear BPA or other toxins from the blood (Murakami et al. 2007). In a study using data from NHANES 2003/2006, glomerular filtration rate was estimated by the Modification of Diet in Renal Disease (MDRD) Study equation. For study participants without known renal disease, there was evidence that even mildly decreased renal function was associated with a decrease in urinary BPA excretion (You et al. 2011). Thus, the use of BPA-containing plastic in hymodialysis equipment can lead to an increase in the levels of this endocrine disrupting chemical in the blood of patients, who are then not able to eliminate BPA due to renal disease.

Summary

The likelihood of developing a disease due to exposure to elevated levels of BPA appears to involve an interaction with the genetic background of an individual as well as an interaction with the other thousands of manmade chemicals to which humans are exposed, since the additive impact of chemicals with similar modes of action is well documented (Kortenkamp 2008). Patients with reduced kidney function have elevated levels of BPA and other toxins due to reduced elimination from blood. An increase in exposure to BPA and other endocrine disrupting chemicals used in the manufacture of hemodialysis equipment can contribute to an increase in diseases due to leaching of these chemicals into blood during dialysis.

Literature

Alonso-Magdalena P, Quesada I, Nadal A. 2011. Endocrine disruptors in the etiology of type 2 diabetes mellitus. Nat Rev Endocrinol 7(6): 346-353.
Bailin PD, Byrne M, Lewis S, Liroff R. 2008. Public awareness drives market for safer alternatives: bisphenol A market analysis report. http://www.iehn.org/publications.reports.bpa.php. Access date: Octover 1, 2011.
Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. 2008. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. Environ Health Perspect 116(1): 39-44.
Calafat AM, Weuve J, Ye X, Jia LT, Hu H, Ringer S, et al. 2009. Exposure to bisphenol A and other phenols in neonatal intensive care unit premature infants. Environ Health Perspect 117(4): 639-644.
Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, et al. 2009. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 30(4): 293-342.
Dodds EC, Lawson W. 1936. Synthetic oestrogenic agents without the phenanthrene nucleus. Nature 137: 996.
Dotsch J, Plank C, Amann K. 2011. Fetal programming of renal function. Pediatr Nephrol. Online February 7, 2011.
Haishima Y, Hayashi Y, Yagami T, Nakamura A. 2001. Elution of bisphenol-A from hemodialyzers consisting of polycarbonate and polysulfone resins. J Biomed Mater Res 58(2): 209-215.
Hu WY, Shi GB, Hu DP, Nelles JL, Prins GS. 2011. Actions of estrogens and endocrine disrupting chemicals on human prostate stem/progenitor cells and prostate cancer risk. Mol Cell Endocrinol. Online September 5, 2011.
Hugo ER, Borcherding DC, Gersin KS, Loftus J, Ben-Jonathan N. 2008. Prolactin release by adipose explants, primary adipocytes, and LS14 adipocytes. J Clin Endocrinol Metab 93(10): 4006-4012.
Hunt PA. 2011. Assessing chemical risk: Societies offer expertise. Science 331: 1136.
Kanno Y, Okada H, Kobayashi T, Takenaka T, Suzuki H. 2007. Effects of endocrine disrupting substance on estrogen receptor gene transcription in dialysis patients. Ther Apher Dial 11(4): 262-265.
Kortenkamp A. 2008. Low dose mixture effects of endocrine disrupters: implications for risk assessment and epidemiology. Int J Andrology 31(2): 233-240.
Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, Wallace RB, et al. 2008. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. JAMA 300(11): 1303-1310.
Muncke J. 2011. Endocrine disrupting chemicals and other substances of concern in food contact materials: An updated review of exposure, effect and risk assessment. J Steroid Biochem Mol Biol. Online November 10, 2010.
Murakami K, Ohashi A, Hori H, Hibiya M, Shoji Y, Kunisaki M, et al. 2007. Accumulation of bisphenol A in hemodialysis patients. Blood Purif 25(3): 290-294.
Myers JP, Zoeller TJ, vom Saal FS. 2009a. A clash of old and new scientific concepts in toxicity, with important implications for public health. Environ Health Perspect 117: 1652–1655.
Myers JP, vom Saal FS, Akingbemi BT, Arizono K, Belcher S, Colborn T, et al. 2009b. Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A. Environ Health Perspect 117(3): 309-315.
Pottenger LH, Domoradzki JY, Markham DA, Hansen SC, Cagen SZ, Waechter JM. 2000. The relative bioavailability and metabolism of bisphenol A in rats is dependent upon the route of administration. Toxicol Sci 54(1): 3-18.
Richter CA, Birnbaum LS, Farabollini F, Newbold RR, Rubin BS, Talsness CE, et al. 2007. In vivo effects of bisphenol A in laboratory rodent studies. Reprod Toxicol 24(2): 199-224.
Stahlhut RW, Welshons WV, Swan SH. 2009. Bisphenol A data in NHANES suggest longer than expected half-life, substantial nonfood exposure, or both. Environ Health Perspect 117(5): 784-789.
Sugimura K, Naganuma T, Kakiya Y, Okada C, Sugimura T, Kishimoto T. 2001. Endocrine-disrupting chemicals in CAPD dialysate and effluent. Blood Purif 19(1): 21-23.
Taylor JA, vom Saal FS, Welshons WV, Drury B, Rottinghaus G, Hunt PA, et al. 2011a. Similarity of bisphenol A pharmacokinetics in rhesus monkeys and mice: relevance for human exposure. Environ Health Perspect 119(4): 422-430.
Taylor JA, Richter CA, Ruhlen RL, vom Saal FS. 2011b. Estrogenic environmental chemicals and drugs: Mechanisms for effects on the developing male urogenital system. J Steroid Biochem Mol Biol. Online July 30, 2011.
Timms BG, Howdeshell KL, Barton L, Bradley S, Richter CA, vom Saal FS. 2005. Estrogenic chemicals in plastic and oral contraceptives disrupt development of the mouse prostate and urethra. Proc Natl Acad Sci 102: 7014-7019.
Vandenberg LN, Chahoud I, Heindel JJ, Padmanabhan V, Paumgartten FJ, Schoenfelder G. 2010. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. Environ Health Perspect 118(8): 1055-1070.
Vandentorren S, Zeman F, Morin L, Sarter H, Bidondo ML, Oleko A, et al. 2011. Bisphenol-A and phthalates contamination of urine samples by catheters in the Elfe pilot study: implications for large-scale biomonitoring studies. Environ Res 111(6): 761-764.
vom Saal FS, Timms BG, Montano MM, Palanza P, Thayer KA, Nagel SC, et al. 1997. Prostate enlargement in mice due to fetal exposure to low doses of estradiol or diethylstilbestrol and opposite effects at high doses. Proc Natl Acad Sci 94(5): 2056-2061.
vom Saal FS, Sheehan DM. 1998. Challenging risk assessment. Forum Applied Res Public Policy 13: 11-18.
Watson CS, Jeng YJ, Kochukov MY. 2010. Nongenomic signaling pathways of estrogen toxicity. Toxicol Sci 115(1): 1-11.
Welshons WV, Thayer KA, Judy BM, Taylor JA, Curran EM, vom Saal FS. 2003. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environ Health Perspect 111(8): 994-1006.
Welshons WV, Nagel SC, vom Saal FS. 2006. Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. Endocrinol 147(6 Suppl): S56-S69.
Yamasaki H, Nagake Y, Makino H. 2001. Determination of bisphenol A in effluents of hemodialyzers. Nephron 88(4): 376-378.
You L, Zhu X, Shrubsole MJ, Fan H, Chen J, Dong J, et al. 2011. Renal Function, Bisphenol A, and Alkylphenols: Results from the National Health and Nutrition Examination Survey (NHANES 2003-2006). Environ Health Perspect 119(4): 527-533.
Zandi-Nejad K, Luyckx VA, Brenner BM. 2006. Adult hypertension and kidney disease: the role of fetal programming. Hypertension 47(3): 502-508Alonso-Magdalena P, Vieira E, Soriano S, Menes L, Burks D, Quesada I, et al. 2010. Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. Environ Health Perspect 118(9): 1243-1250.