

HEALTHCARE PROVIDER GUIDE:

Phthalates and Bisphenol A



Phthalates and bisphenol A (BPA) are man-made chemicals that are known endocrine disruptors. They can affect hormones such as estrogen and testosterone, and potentially disrupt normal growth and development. Historically, discussions of sources of phthalate and BPA exposure focused on plastics; but current research highlights several sources of exposure including food, personal care products, and dust.

Phthalates

Phthalates are man-made chemicals that give flexibility to soft plastics and polyvinyl chloride (PVC) products, and are used in a variety of personal care products (i.e. shampoos, lotions, makeup, perfume). They can be found in plastic medical devices (i.e. IV tubing, IV fluid/total parenteral nutrition bags, catheters) and in some time-released medications. They can also be present in the US food supply as contaminants (i.e. from plastics used in conveyer belts, jar lids, tubes storing food, gloves, packaging, storage). Processed

foods and high fat dairy and meats are particularly high in phthalates.

Bisphenol A (BPA)

Bisphenol A is a man-made chemical that gives rigidity to hard, polycarbonate plastics and is also used in food can linings (to prevent degradation of the metal) and in thermal /carbonless receipts (to stabilize ink). BPA can also come from dental sealants that are applied in the dentist's office.

-
- The majority of the US population is exposed to phthalates and BPAⁱ
 - The major sources of phthalates and BPA exposure for the general population are food (especially those high in animal fats, highly processed, or canned foods), personal care products, and dust.ⁱⁱ Phthalates and BPA leach out of plastics (food containers, packaging, can linings, kitchen accessories) and into food and dust. This is more likely to occur when the product is heated.
 - Children are exposed to phthalates and bisphenol A from ingestion (contaminated food and drink), inhalation (dust), and dermal absorption (personal care products). Main exposure sources can vary by age, developmental stage and individual behaviors.
 - Early childhood or fetal exposure to these chemicals, during important developmental windows, may have lasting effects throughout life. Infants and toddlers can have higher intakes of these chemicals compared to adults because of their increased food/water requirements per unit body mass, hand-to-mouth activity, and ventilation rate.
 - The Pediatric Environmental Health Specialty Units (PEHSU) recommend a precautionary approach. The information below will summarize health effects and help reduce exposures.

Possible Human Health Impacts:

Both phthalates and bisphenol A interfere with the production and function of hormones in animal studies and may increase the risk of a wide variety of adverse health effects. Current research is ongoing to determine definitive health impacts in humans.

Phthalates

These chemicals are anti-androgenic and can adversely impact androgen-sensitive tissues (ex. testicular function and genital development). They may also impact behavior, change pubertal development, and can increase the risk of allergies.

Animal Toxicologic Studies (all are high dose exposures in utero)

- Testicular toxicity in utero and in early development (testicular dysgenesis syndrome)ⁱⁱⁱ
- Male reproductive tract abnormalities in offspring of prenatally exposed rats including decreased anogenital distance, hypospadias, cryptorchidism, and testicular tumors^{iv}
- Decreased birth weight after prenatal exposure^v
- Malignant liver tumors (not thought to be relevant to human exposures)^{vi}

Human Epidemiologic Studies

- Prenatal exposure associated with a decreased anogenital distance (marker of androgenization)^{vii}
- Exposure through breast milk has been associated with increased LH, decreased free testosterone and increased serum human binding globulin in 3 month old male infants^{viii}
- Early childhood exposure may increase the risk of increased rhinitis, eczema, asthma and wheezing^{ix}
- Prenatal exposure may increase the risk of alterations in infant/toddler physical development as well as increased externalizing (hyperactivity and aggression) and autistic-like child behavior^x
- In adult males, concurrent exposure may increase the risk for abnormal sperm morphology/sperm DNA damage^{xi}

Bisphenol A

BPA acts as a weak estrogen. It has chemical properties similar to estradiol and can impact biological systems in **very low doses** potentially resulting in behavior, reproductive, and metabolic disorders.

Animal Toxicologic Studies^{xii}

- Prenatal exposures lead to changes in behavior including hyperactivity, increased aggression, impaired learning^{xiii}
- Low dose prenatal exposure associated with early puberty and increased mammary tumors in offspring, increased risk of prostate hypertrophy^{xiv}
- Prenatal exposure associated with increased adipocytes and increased body weight in offspring^{xv}
- Adult and prenatal exposure associated with modulation of helper T1 and T2 cells which in turn adversely affects antibody production^{xvi}

Human Epidemiologic Studies

- Evidence that humans are exposed to concentrations similar or higher than doses used in several animal studies that document adverse health effects^{xvii}
- Prenatal BPA exposure has shown to have increased risk of externalizing (hyperactivity and aggression) in 2 year old female children^{xviii}
- Higher urinary BPA levels associated with delayed onset of breast development in girls^{xix}
- Associated with obesity and asthma^{xx}
- In adults, crosssectional studies found associations between higher BPA exposure and increased risk of cardiovascular diagnoses, abnormal liver enzymes, and diabetes diagnosis^{xxi}

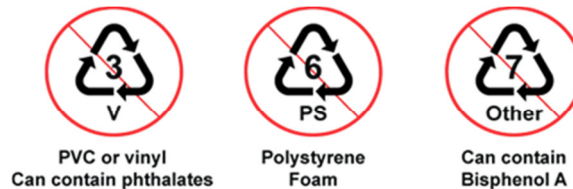
What's the Bottom Line?

Scientists and healthcare providers are concerned about phthalates and BPA because they are widely prevalent in everyday products, and universal exposures in the US population have been documented. The full extent of their potential health impacts is still unknown, but research supports a potential role in a wide range of health conditions. Until more is known, it is best to take a precautionary approach by preventing and reducing phthalate and BPA exposures.

Tips on Teaching Patients & Parents How to Reduce Exposure:

Disclaimer: Based upon interpretation of the current literature, the PEHSU program is providing this guidance for persons who wish to take a precautionary approach to personal decisions, and is not meant to substitute for personal medical consultation with your health care provider.

1. **Buy low fat dairy products such as skim milk and low fat cheeses.** Avoid high fat foods such as cream, whole milk, and fatty meats as much as possible.
2. **Buy fresh or frozen fruits and vegetables when possible. Avoid canned and processed foods.**
3. When possible, purchase items that are phthalate free or BPA free.
4. Minimize personal care product use. Keep it simple, less is more.
5. Use glass, stainless steel, ceramic, or wood to hold and store foods instead of plastics.
6. Do not microwave food/beverages in plastic.
7. If using hard polycarbonate plastics (found in some water bottles/baby bottles/sippy cups), do not use for warm/hot liquids.
8. If plastics cannot be avoided, use the following guide to avoid particularly dangerous plastics. Check the symbol on the bottom of plastics containers and try to avoid the plastics marked 3 (PVC or vinyl), 6 (polystyrene foam), or 7 (other, can contain BPA)¹:



9. Encourage frequent handwashing.
10. Minimize handling of receipts.
11. Take shoes off at home to avoid tracking in dust that may contain these chemicals.
12. Keep carpets/windowsills clean - vacuum and wet dust frequently to minimize dust that may contain these chemicals.

You or your patients may contact your local Pediatric Environmental Health Specialty Unit. Find our contact information at www.aoec.org/PEHSU.htm or call 1-888-347-2632.

Resources

American Academy of Pediatrics Council on Environmental Health. Etzel R, ed. *Pediatric Environmental Health*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012. (aka, AAP Green Book)

Braun JM, Hauser R. Bisphenol A and children's health. *Curr Opin Pediatr*. 2011; 23(2): 233-9. doi: 10.1097/MOP.0b013e3283445675.

Braun JM, Sathyanarayana S, Hauser R. Phthalate exposure and children's health. *Curr Opin Pediatr*. 2013; 25(2): 247-54. doi: 10.1097/MOP.0b013e32835e1eb6.

Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Environ Health Perspect*. 2008; 116(1): 39-44.

¹ Code #6: Styrene, a potentially toxic chemical, may be released from containers made from polystyrene foam (Styrofoam and related brands) when they are used to heat or store foods or liquids at temperatures exceeding 80°C (176°F). Code #7 covers "other" plastics, which includes polycarbonate. Therefore not all code #7 plastic bottles contain polycarbonate and leach BPA. Also, BPA can be given off from other products.

Centers for Disease Control and Prevention. Fourth Report on Human Exposure to Environmental Chemicals, 2009. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Available at: <http://www.cdc.gov/exposurereport/>.

Claudio L, Chace R. Quick Guide to Plastics. Staying Healthy in a Changing Environment #3. New York: Mount Sinai Community Health Bulletin; 2006.

Diamanti-Kandarakis E et al. Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews*. 2009.; 30(4): 293-342.

Gray LE, Jr., Wilson VS, Stoker T, Lambright C, Furr J, Noriega N, Howdeshell K, Ankley GT, Guillette L. Adverse effects of environmental antiandrogens and androgens on reproductive development in mammals. *Int J Androl*. 2006; 29(1): 96-104; discussion 5-8.

NIEHS. Since You Asked - Bisphenol A. NTP Brief; 2008.

Shea KM, American Academy of Pediatrics Committee on Environmental Health. Pediatric exposure and potential toxicity of phthalate plasticizers. *Pediatrics*. 2003; 111(6): 1467-1474.

World Health Organization. Bergman Å, Heindel J, Jobling S, Kidd K, Zoeller RT, eds. State of the Science of Endocrine Disrupting Chemicals – 2012. Geneva: United Nations Environment Programme and the World Health Organization; 2013.

Last updated 2/2014. Acknowledgment: A. Otter, DNP, ARNP, S. Sathyanarayana, MD, MPH, Northwest PEHSU. M. Galvez, MD, MPH, P.E. Sheffield, MD, Mount Sinai PEHSU. National PEHSU Education Committee.

This material was supported by the Association of Occupational and Environmental Clinics (AOEC) and funded under the cooperative agreement award number 1U61TS000118-03 from the Agency for Toxic Substances and Disease Registry (ATSDR).

Acknowledgement: The U.S. Environmental Protection Agency (EPA) supports the PEHSU by providing funds to ATSDR under Inter-Agency Agreement number DW-75-92301301-03. Neither EPA nor ATSDR endorse the purchase of any commercial products or services mentioned in PEHSU publications.

ⁱ Centers for Disease Control and Prevention. Fourth Report on Human Exposure to Environmental Chemicals, 2009. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. <http://www.cdc.gov/exposurereport/>

ⁱⁱ Fleisch AF, Sheffield PE, Chinn C, Edelstein BL, Landrigan PJ. Bisphenol A and related compounds in dental materials. *Pediatrics*. 2010 Oct;126(4):760-8. doi: 10.1542/peds.2009-2693. Epub 2010 Sep 6. Review. PubMed PMID: 20819896.; Martina CA, Weiss B, Swan SH. Lifestyle behaviors associated with exposures to endocrine disruptors. *Neurotoxicology*. 2012 Dec;33(6):1427-33. doi: 10.1016/j.neuro.2012.05.016. Epub 2012 Jun 26. PubMed PMID: 22739065; PubMed Central PMCID: PMC3641683.; Rudel RA, Gray JM, Engel CL, Rawsthorne TW, Dodson RE, Ackerman JM, Rizzo J, Nudelman JL, Brody JG. Food packaging and bisphenol A and bis(2-ethylhexyl) phthalate exposure: findings from a dietary intervention. *Environ Health Perspect*. 2011 Jul;119(7):914-20. doi: 10.1289/ehp.1003170. Epub 2011 Mar 22. PubMed PMID: 21450549; PubMed Central PMCID: PMC3223004.

ⁱⁱⁱ Hannas BR, Lambright CS, Furr J, et al. Dose-response assessment of fetal & testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, diisobutyl phthalate, diisooheptyl phthalate and diisononyl phthalate. *Toxicol Sci* 2011; 123:206 – 216.; Borch J, Metzdorff SB, Vinggaard AM, et al. Mechanisms underlying the antiandrogenic effects of diethylhexyl phthalate in fetal rat testis. *Toxicology*. 2006; 223:144 – 155.; Howdeshell KL, Furr J, Lambright CR, et al. Cumulative effects of dibutyl phthalate and diethylhexyl phthalate on male rat reproductive tract development: altered fetal steroid hormones and genes. *Toxicol Sci* 2007; 99:190– 202.; Macleod DJ, Sharpe RM, Welsh M, et al. Androgen action in the masculinization programming window and development of male reproductive organs. *Int J Androl* 2010; 33:279 – 287.

^{iv} Gray LE Jr, Ostby J, Furr J, Price M, Veeramachaneni DN, Parks L. Perinatal exposure to the phthalates DEHP, BBP, and

- DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. *Toxicol Sci.* 2000;58(2):350–365.; Carruthers CM, Foster PM. Critical window of male reproductive tract development in rats following gestational exposure to di-n-butyl phthalate. *Birth Defects Res B Dev Reprod Toxicol.* 2005; 74(3):277–285.
- ^v Tyl RW, Myers CB, Marr MC, Fail PA, Seely JC, Brine DR, et al. Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. *Reprod Toxicol.* 2004;18:241–264.
- ^{vi} Rusyn I, Corton JC. Mechanistic considerations for human relevance of cancer hazard of di(2-ethylhexyl) phthalate. *Mutat Res.* 2012 Apr-Jun;750(2):141-58. doi: 10.1016/j.mrrev.2011.12.004. Epub 2011 Dec 20.
- ^{vii} Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, Mao CS, Redmon JB, Ternand CL, Sullivan S, Teague JL. Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environ Health Perspect.* 2005 Aug;113(8):1056-61.
- ^{viii} Main KM, Mortensen GK, Kaleva MM, Boisen KA, Damgaard IN, Chellakooty M, Schmidt IM, Suomi AM, Virtanen HE, Petersen DV, Andersson AM, Toppari J, Skakkebaek NE. Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age. *Environ Health Perspect.* 2006 Feb; 114(2):270-6.
- ^{ix} Bornehag CG, Sundell J, Weschler CJ, Sigsgaard T, Lundgren B, Hasselgren M, Hagerhed-Engman L. The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study. *Environ Health Perspect.* 2004 Oct; 112(14):1393-7.
- ^x Engel SM, Miodovnik A, Canfield RL, Zhu C, Silva MJ, Calafat AM, Wolff MS. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environ Health Perspect.* 2010 Apr;118(4):565-71. doi: 10.1289/ehp.0901470.
- ^{xi} Hauser R, Meeker JD, Duty S, Silva MJ, Calafat AM. Altered semen quality in relation to urinary concentrations of phthalate monoester and oxidative metabolites. *Epidemiology.* 2006 Nov; 17(6):682-91.
- ^{xii} Wetherill YB, Akingbemi BT, Kanno J, McLachlan JA, Nadal A, Sonnenschein C, Watson CS, Zoeller RT, Belcher SM. In vitro molecular mechanisms of bisphenol A action. *Reprod Toxicol.* 2007 Aug-Sep; 24(2):178-98.
- ^{xiii} Patisaul HB, Bateman HL. Neonatal exposure to endocrine active compounds or an ERbeta agonist increases adult anxiety and aggression in gonadally intact male rats. *Horm Behav.* 2008 Apr;53(4):580-8. doi: 10.1016/j.yhbeh.2008.01.008. Epub 2008 Feb 8.; Jašarević E, Williams SA, Vandas GM, Eilersieck MR, Liao C, Kannan K, Roberts RM, Geary DC, Rosenfeld CS. Sex and dose-dependent effects of developmental exposure to bisphenol A on anxiety and spatial learning in deer mice (*Peromyscus maniculatus bairdii*) offspring. *Horm Behav.* 2013 Jan;63(1):180-9. doi: 10.1016/j.yhbeh.2012.09.009. Epub 2012 Oct 7.
- ^{xiv} Nah WH, Park MJ, Gye MC. Effects of early prepubertal exposure to bisphenol A on the onset of puberty, ovarian weights, and estrous cycle in female mice. *Clin Exp Reprod Med.* 2011 Jun;38(2):75-81. doi: 10.5653/cerm.2011.38.2.75.; Betancourt AM, Eltoum IA, Desmond RA, Russo J, Lamartiniere CA. In utero exposure to bisphenol A shifts the window of susceptibility for mammary carcinogenesis in the rat. *Environ Health Perspect.* 2010 Nov;118(11):1614-9. doi: 10.1289/ehp.1002148.; Richter CA, Birnbaum LS, Farabolini F, Newbold RR, Rubin BS, Talsness CE, Vandenberg JG, Walser-Kuntz DR, von Saal FS. In vivo effects of bisphenol A in laboratory rodent studies. *Reproductive Toxicology.* [Review]. 2007; 24(2):199-224.
- ^{xv} Rubin BS, Soto AM. Bisphenol A: Perinatal exposure and body weight. *Mol Cell Endocrinol.* 2009 May 25;304(1-2):55-62. doi: 10.1016/j.mce.2009.02.023. Epub 2009 Mar 9.
- ^{xvi} Yoshino S, Yamaki K, Li X, Sai T, Yanagisawa R, Takano H, Taneda S, Hayashi H, Mori Y. Prenatal exposure to bisphenol A up-regulates immune responses, including T helper 1 and T helper 2 responses, in mice. *Immunology.* 2004 Jul;112(3):489-95.; Rogers JA, Metz L, Yong VW. Review: Endocrine disrupting chemicals and immune responses: a focus on bisphenol-A and its potential mechanisms. *Mol Immunol.* 2013 Apr;53(4):421-30. doi: 10.1016/j.molimm.2012.09.013.
- ^{xvii} Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV. Human exposure to bisphenol A (BPA). *Reprod Toxicol.* 2007 Aug-Sep; 24(2):139-77.
- ^{xviii} Braun JM, Yolton K, Dietrich KN, Hornung R, Ye X, Calafat AM, Lanphear BP. Prenatal bisphenol A exposure and early childhood behavior. *Environ Health Perspect.* 2009 Dec;117(12):1945-52. doi: 10.1289/ehp.0900979.
- ^{xix} Wolff MS, Teitelbaum SL, Pinney SM, et al. Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols and pubertal stages in girls. *Environ Health Perspect* 2010; 118:1039–1046; Wolff MS, Britton JA, Boguski L, et al. Environmental exposures and puberty in inner-city girls. *Environ Res* 2008; 107:393–400.
- ^{xx} Trasande L, Attina TM, Blustein J. Association between urinary bisphenol A concentration and obesity prevalence in children and adolescents. *JAMA.* 2012 Sep 19;308(11):1113-21.; Spanier AJ, Kahn RS, Kunselman AR, Hornung R, Xu Y, Calafat AM, Lanphear BP. Prenatal exposure to bisphenol A and child wheeze from birth to 3 years of age. *Environ Health Perspect.* 2012 Jun;120(6):916-20. doi: 10.1289/ehp.1104175. ; Vaidya SV, Kulkarni H. Association of urinary bisphenol A concentration with allergic asthma: results from the National Health and Nutrition Examination Survey 2005–2006. *J Asthma.* 2012 Oct;49(8):800-6. doi: 10.3109/02770903.2012.721041.
- ^{xxi} Lang IA, Galloway TS, Scarlett A, et al. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. *JAMA* 2008; 300:1303–1310; Melzer D, Rice NE, Lewis C, et al. Association of urinary bisphenol A concentration with heart disease: evidence from NHANES 2003/06. *PLoS One* 2010; 5:e8673.