Published in final edited form as:

Curr Opin Pediatr. 2011 April ; 23(2): 233–239. doi:10.1097/MOP.0b013e3283445675.

Bisphenol A and Children's Health

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Abstract

Purpose of review—Bisphenol A (BPA) is a widely used chemical that has been shown to adversely affect health outcomes in experimental animal studies, particularly following fetal or early life exposure. Despite widespread human exposure in the United States and developed countries, there are limited epidemiologic studies on the association of BPA with adverse health outcomes. This review briefly summarizes the epidemiologic literature with special emphasis on childhood health outcomes.

Recent findings—Numerous studies have documented correlations between urinary BPA and serum sex steroid concentrations in adults. The clinical relevance of these associations and their applicability to children is uncertain. Two studies have documented potential associations between urinary BPA concentrations and delayed onset of breast development. Another study suggests a potential relationship between prenatal BPA exposure and increased hyperactivity and aggression in 2-year old female children.

Summary—Additional large prospective cohort studies are needed to confirm and validate findings from animal studies. Even in the absence of epidemiological studies, concern over the toxicity of BPA is warranted given the unique vulnerability of the developing fetus and child and potential health effects of early life BPA exposure. Health care providers are encouraged to practice primary prevention and counsel patients to reduce BPA exposures.

Keywords

Bisphenol A; Epidemiology; Pediatric; Children

Introduction

Bisphenol A (BPA) is a monomeric compound synthesized as a synthetic estrogen by Dodds and Lawson in the 1930s.(1) In the early 1950s, chemists discovered BPA had desirable chemical and physical properties that could be employed in making epoxy resins and polycarbonate plastics.(2) Since the 1950s, the global production of BPA has soared to 6 billion pounds a year.(3) BPA is used in a variety of consumer products including food can linings, thermal receipts, medical equipment, tableware, toys, food/beverage storage containers, and water supply pipes. Monomers of BPA can hydrolyze and leach from epoxy

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Conflict of Interest and Sponsorship Statements: The authors have no conflicts of interest. This work was funded by an NIEHS training grant (T32 ES007018) and NIEHS grant R01ES009718.

resins and polycarbonate plastics into food and liquids in contact with the container. The leaching is accelerated by high temperature, acidic, and basic conditions.(4–7) Over 90% of US persons have measureable concentrations of BPA in their urine and biomonitoring studies indicate a similar magnitude of exposure in other developed countries.(8, 9)

A large number of animal and limited number of human studies suggest that BPA exposure may be associated with adverse human health outcomes.(10, 11) Since BPA has endocrinologic activity, there is concern that BPA may act on hormonally mediated pathways to disrupt normal growth and development. Prenatal and childhood exposure to BPA may be associated with altered neurodevelopment, obesity, and precocious puberty.(11) Gestational exposure is of particular concern given the unique susceptibility of the fetus to environmental toxicant exposures.(12) It is imperative that clinicians have accurate information and an understanding of the health effects of BPA exposure so they can advise their patients to make informed decisions. Many parents are concerned about the impact of environmental toxicants on their children's health and frequently ask their health care provider for advice regarding exposures to chemicals. Since human exposure to BPA is so widespread, even small adverse effects of BPA could have large public health implications.(13) The purpose of this review is to summarize the existing human literature and provide clinicians with the resources to address patient's questions about BPA exposure and their children's health.

BPA Exposure among Humans

Exposure to BPA among persons in industrialized countries is widespread.(8, 9) BPA has been detected in the vast majority of urine samples from pregnant women in the US, Netherlands, and Norway.(14–17) BPA has also been detected in amniotic and follicular fluid and infant cord blood samples.(9) Young children have higher urinary BPA concentrations than adults, which likely reflect their higher food intake per pound of body mass.(8, 18) However, it is not known whether metabolic differences between adults and children partially account for the differences in urinary BPA levels. In addition, infants receiving care in the NICU may have higher BPA exposure than the general population due to intensive medical interventions and procedures.(19) BPA has a short biological half-life (5–6 hours) and is glucuronidated by Phase II metabolism and rapidly eliminated in the urine after ingestion.(20)

The primary source of BPA exposure in adults is oral intake from canned food.(21, 22) Breast milk and polycarbonate feeding bottles are the predominant source of BPA exposure among infants, while oral exposure from canned foods becomes the primary source of BPA exposure as children age.(21) Occupationally exposed persons, such as cashiers and persons employed in industries using BPA have additional non-dietary exposures.(23, 24) Secondhand and active tobacco smoke may be an additional source of BPA exposure since BPA is used as component of cigarette filters.(23, 25)

Epidemiological Studies

While hundreds of experimental studies on animals have assessed the biological response to and toxicity of pre- and early postnatal bisphenol A (BPA) exposure, a limited number of human studies have been conducted.(10) After conducting a literature search, we located 22 peer-reviewed epidemiological studies (26) (14, 15, 24, 27–44) that examined relationships between BPA exposure and human health outcomes (Table 1). The majority (n=16) of these studies were cross-sectional or case-control studies. Only 6 epidemiological studies have examined health outcomes in children. Few of the 22 studies examined the same health outcomes. However, outcomes could be grouped and reviewed as categories of cancer (34), reproductive (24, 26–29, 31, 33, 35, 39, 41–44), metabolic (30, 36), pubertal development (32, 38), infant and childhood growth (15, 37, 40), and neurodevelopment outcomes (14). Given that there is relatively little literature on the health effects of BPA exposure in children, we summarize the known literature to date, with special emphasis on findings related to the fetus and child.

Cancer

One case-control study examined the association between BPA exposure and breast cancer (70 cases and 82 controls).(34) No information was provided on the type, stage, or grade of the tumors. The authors concluded there was no difference in mean serum BPA concentrations among cases and controls. However, women with breast cancer had higher median serum BPA concentrations than women without breast cancer. Because BPA has a short half-life, concurrent serum BPA concentrations may not reflect the etiologically relevant window of exposure for the development of breast cancer, which is years to decades before clinical recognition.

Reproductive outcomes

Because BPA is a suspected endocrine disrupting compound, several studies examined sex steroids, sexual function, and ovarian response as a target of BPA exposure. Epidemiological studies among adults have observed associations between urinary BPA concentrations and serum reproductive hormones.(27, 29, 31, 44) The findings of these studies provide some evidence that BPA exposure may be associated with increased serum FSH, LH, SHBG, and testosterone concentrations in men. Two additional studies reported sexual dysfunction in occupationally exposed men in China and suggest that high BPA exposure may be associated with sexual dysfunction.(24, 28) Mok-Lin and colleagues reported that urinary BPA concentrations were associated with decreased serum estradiol concentrations and number of oocytes among women undergoing IVF.(35) While these findings suggest potential associations between BPA exposure and reproductive health endpoints, they may not be relevant to pediatric populations, their clinical impact is uncertain, and the range of exposure in some of these studies exceeds that observed in typical pediatric populations.

Metabolic outcomes

Two studies examined the correlation between urinary BPA concentrations and metabolic disorders in two nationally representative cross-sectional samples of 2,948 US adults participating in the National Health and Nutrition Examination Survey (NHANES) in

2003/2004 and 2005/2006.(30, 36) The authors observed positive correlations between urinary BPA concentrations and odds of self-reported CVD (OR: 1.3; 95% CI: 1.1, 1.4) and diabetes (OR: 1.3; 95% CI: 1.1, 1.4); however associations between BPA and CVD and diabetes were stronger in the 2003/2004 cycle, when geometric mean BPA concentrations were higher (2.5 vs. 1.8 μg/L). Positive correlations between urinary BPA and serum liver enzyme concentrations were also observed. These cross-sectional studies are limited by their design. CVD and metabolic disorders have long latency periods and contemporaneous urinary BPA concentrations may not reflect the relevant etiologic window for the development of cardiovascular and metabolic diseases, which is known to be years or decades earlier. It is also important to note that animal studies show that prenatal BPA exposure may influence the development of metabolic disorders.(45) Thus, fetal exposure to BPA may be more important to the development of metabolic disorders than later life exposure.

Pubertal Development Outcomes

Since BPA is an endocrine disrupting compound, early life exposure may increase the risk for altered pubertal development, which in turn is a risk factor for breast cancer.(46, 47) Some rodent studies suggest that early life BPA exposure may accelerate pubertal development and increase breast cancer risk.(48, 49) However, the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) had minimal concern for BPA to accelerate pubertal development.(10) To date, two epidemiological studies have examined the relationship between BPA exposure and pubertal development.(32, 38)

A cross-sectional study in New York City, NY examined the correlation between concurrent BPA exposure and pubertal development in 192 9-year old girls.(38) The authors examined associations between urinary BPA concentrations, breast development, and pubic hair development. Higher urinary BPA concentrations were not associated with advanced (stage 2+) breast (OR: 0.96; 95% CI: 0.92, 1.01) or pubic hair (OR: 0.98; 95% CI: 0.89, 1.08) development. However, BMI modified the associations between BPA and breast development, where higher urinary BPA concentrations were more strongly associated with delayed breast development among girls below the median BMI (OR: 0.6; 95% CI: 0.38, 0.96) compared to girls above the median BMI with low BPA concentrations.

A large multi-center prospective cohort of 1,151 6 to 8 year old female children from Cincinnati, OH, San Francisco, CA, and New York City, NY prospectively collected urine samples to assess BPA exposure and examined the relationship between urinary BPA concentrations and pubertal development 1 year later.(32) Compared to the lowest quintile of urinary BPA concentrations, the odds of advanced breast development (stage 2+) were similar but slightly below the null (ORs between 0.95 and 0.97) for the top four quintiles, with no discernible dose-response pattern. Compared to the first quintile of urinary BPA concentrations, the odds of advanced pubic hair development (stage 2+) were slightly increased in the second (OR: 1.03; 95% CI: 0.96, 1.09) and third (OR: 1.06; 0.99, 1.13) quintiles of urinary BPA concentrations and null in the fourth and fifth quintiles. The authors did not report whether BMI modified the association between urinary BPA concentrations and pubertal development.

Both of these studies observed ORs with similar direction and magnitude between urinary BPA concentrations and stage 2+ breast development, indicating that BPA exposure was associated with slightly later breast development. However, findings from the prospective cohort indicate accelerated pubic hair development only among girls in the 2nd and 3rd quintiles of urinary BPA concentrations compared to girls in the first quintile. The presence of non-monotonic dose-response curves has been previously reported in the BPA toxicology literature and the expectation of linear dose-response functions may not be appropriate when studying endocrine disrupting compounds.(50)

These two studies suggest that childhood BPA exposure may have modest effects on pubertal timing in girls. However given the relatively small effect sizes, there are several important limitations including residual confounding by measured and unmeasured confounders, and the potential for differential pharmacokinetics among pre-pubertal and pubertal girls accounting for differences in urinary BPA concentrations. The role of childhood BPA exposure in pubertal development requires further study. Given the short half-life of BPA and temporal variability of urinary BPA concentrations, a single spot urine sample may not correctly classify exposures that occurred prenatally or much earlier in childhood, which may be more strongly related to pubertal development. Studies examining the association between BPA exposure and pubertal development in males are also needed.

Fetal and childhood growth outcomes

Three studies examined associations between BPA exposure and infant/childhood growth.(15, 37, 40) A cross-sectional study examined associations between maternal serum BPA concentrations and birth outcomes in 40 mother-infant pairs in Ann Arbor, MI.(37) The authors concluded there was no association between serum BPA concentrations and birth weight or gestational age; however, numerical results were not presented. Their figure suggests lower birth weight among infants born to mothers with serum BPA concentrations > 5 μg/L. A prospective birth cohort of 367 women in New York City NY examined the association between multiple non-persistent toxicant exposures, including BPA, in the 3rd trimester (25–40 weeks) of pregnancy and infant birth weight, length, head circumference, and gestational age.(15) Prenatal urinary BPA concentrations were associated with increases in birth weight (38 grams; 95% CI: -6, 82 grams), length (0.1 cm; 95% CI: -0.1, 0.4 cm), head circumference (0.1 cm; 95% CI: -0.1, 0.3 cm), and no change in gestational age (0 weeks; 95% CI: -0.2, 0.2 weeks). While these findings were non-significant, the association between urinary BPA concentrations and birth weight was the largest, but one of the least precise estimates, of all the toxicant exposures examined. The direction of observed effects was discrepant in these two studies. This could be due to different methods (urine vs. serum) and timing (3rd trimester vs. birth) of BPA exposure.

A cross-sectional pilot study of 6- to 8-year old female children (n=90) from Cincinnati OH, San Francisco CA, and New York NY found a suggestive correlation between urinary BPA concentrations and Body Mass Index (BMI).(40) Urinary BPA concentrations were lower (2.2 vs. 3.7 μg/g) among children with BMI ≥ 85th percentile, which is typically used to define overweight status during childhood. These findings are surprising given that BPA may partition into fat compartments.(51)

Neurodevelopmental outcomes

A single prospective birth cohort of 249 mothers and infants from Cincinnati OH examined the association between prenatal BPA exposure and childhood behavior at 2 years of age.(14) The authors measured urinary BPA concentrations twice during pregnancy (16 and 26 weeks gestation) and at birth. Mean gestational BPA concentrations and those from samples take at 16 weeks gestation were positively associated with externalizing behaviors (aggression and hyperactivity) in children, but this association was strongest in female children (β for each 10-fold increase in mean BPA concentrations: 6.0; 95% CI: 0.1, 12.0). The magnitude of the observed associations were similar to those seen for other environmental toxicants and neurodevelopment (~0.5 standard deviation), but the clinical relevance of this association and its persistence into later childhood needs to be determined.

Conclusions

There is a growing body of literature examining the health effects of BPA exposure in humans. To date, most human studies have utilized cross-sectional designs that offer suggestive results, but cannot address the temporality of exposure and disease. For many childhood diseases (e.g. asthma, attention-deficit/hyperactivity disorder, and obesity), early childhood or fetal exposure to BPA may be more relevant to the development of disease than concurrent measures of BPA exposures. Concurrent urinary BPA concentrations may not accurately reflect prenatal exposure because of BPA's short half-life and high temporal variability. Despite these limitations, results from cross-sectional results should not be dismissed because they provide useful information that can be used to guide the design of stronger and more powerful studies.

Conclusions regarding the toxicity of BPA are based primarily on the results of animal studies and only six epidemiological studies have examined infant or childhood health outcomes. Given the unique susceptibility of the fetus and child to environmental exposures, additional studies are needed to examine the relationship between early life BPA exposure and childhood health outcomes including neurodevelopment, somatic growth, and pubertal development. Additional studies are also needed to further identify modifiable sources of BPA exposure among pregnant women and children.

Based on our current understanding of the adverse health effects of BPA, primarily from experimental studies in rodents and limited human studies, both health care providers and patients may request guidance and recommendations for reducing exposure to BPA. Health care providers can practice primary prevention by learning about BPA exposure sources and potential health impacts through a variety of resources listed in Table 2, including handouts created by university based Pediatric Environmental Health Specialty Units (http://www.aoec.org/PEHSU/facts.html). Providers can counsel patients to avoid BPA exposure by avoiding canned foods when possible, using plastic products with a 1, 2, 4, or 5 in their recycling symbol or glassware, and avoiding plastic products with a 3, 6, or 7 in their recycling symbol. They can also consult physicians professionally trained in environmental health to help address specific medical conditions that may be related to BPA and other endocrine disrupting chemical exposures.

Acknowledgments

None

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Key Points

1. Biomonitoring studies suggest that human exposure to BPA is ubiquitous in industrialized countries.
2. Few studies have examined the relationship between pre- and postnatal BPA exposures and childhood health outcomes, but results from animal studies suggest some cause for concern.
3. Additional high-quality prospective cohort studies with multiple pre- and postnatal BPA measurements are needed to address current research gaps.
4. Clinicians can counsel concerned patients to reduce or avoid potential source of BPA exposure.

Table 1

Study and Year	Study Type	N	Median Urinary BPA Concentration and Proportion Detected	Outcome and Participants	Results
Meeker et al. 2010 (26)	Cross-sectional	190	1.7 μg/L, 89%	Semen quality and sperm DNA damage in males seeking treatment for subfertility	Increasing urinary BPA concentrations were associated with decreased sperm concentration, motility, morphology, and DNA damage.
Galloway et al. 2010 (27)	Cross-sectional	715	3.6 μg/g	Serum testosterone, estradiol, and sex hormone binding globulin in Italian adults.	Positive association between urinary BPA concentrations and total testosterone in men
Li et al. 2010 (28)	Cross-sectional	427	Unexposed: 1.2 μg/g[†] Exposed: 53.7 μg/g[†]	Self-reported sexual dysfunction in BPA exposed male workers and non-exposed controls	Urinary BPA concentrations were associated with decreased male sexual function.
Li et al. 2010 (24)	Cross-sectional	550	Unexposed: 1.2 μg/g[†] Exposed: 57.9 μg/g[†]	Self-reported sexual dysfunction in BPA exposed male workers and non-exposed controls	Occupational BPA exposure associated with increased odds of erectile dysfunction, ejaculation difficulty, and reduced sexual desire.
Meeker et al. 2010 (29)	Cross-sectional	167	1.3 μg/L, 89%	Serum reproductive and thyroid hormones in males seeking treatment for subfertility.	Urinary BPA concentrations associated with altered hormone profiles in men.
Melzer et al. 2010 (30)	Cross-sectional	2,948	2003-04: 2.5 μg/L 2005-06: 1.8 μg/L	Self-reported diabetes/CVD and liver enzymes concentrations in US adults	Urinary BPA concentrations positively associated with increased odds of diabetes and elevated liver enzymes.
Mendiola et al. 2010 (31)	Cross-sectional	302	1.7 μg/L	Semen quality and reproductive hormones in males	Altered androgen profiles among more exposed men. Suggestion of association between BPA and seminal volume and semen parameters.
Wolff et al. 2010 (32)	Prospective Cohort	1,151	2.0 μg/L	Pubertal development in 7-10 year old females	No association between urinary BPA concentrations at 6-8 years of age and breast or pubic hair development 1 year later.
Braun et al. 2009 (14)	Prospective Cohort	249	1.3-1.8 ng/mL [†]	Externalizing and internalizing behaviors in 2-year old children	Prenatal BPA concentrations associated with externalizing behaviors in female children.
Cobellis et al. 2009 (33)	Case-control	69	52%	Endometriosis in Italian women	BPA was detected in the serum of 52% of women with endometriosis, while none of the 11 control women had detectable serum BPA.
Yang et al. 2009 (34)	Case-control	152	1.7 μg/L[‡]	Women with breast cancer and age matched controls	Median serum BPA concentrations were higher among cases compared to controls.
Mok-Lin et al. 2009 (35)	Prospective Cohort	84	2.6 μg/L, 85%	Estradiol and oocyte count in adult women undergoing IVF	BPA concentrations inversely associated with number of retrieved oocytes and estradiol concentrations
Lang et al. 2008 (36)	Cross-sectional	1,455	1.8 μg/L	Diabetes and liver enzymes in US adults	Higher BPA levels associated with increased odds of diabetes and elevated liver enzymes.
Padmanabhan et al. 2008 (37)	Cross-sectional	40	5.9 μg/L[‡]	Birth weight and gestational length at birth	No association between BPA and birth outcomes. Suggestive inverse association between BPA and birth weight.

Study and Year	Study Type	N	Median Urinary BPA Concentration and Proportion Detected	Outcome and Participants	Results
Wolff et al. 2008 (15)	Prospective Cohort	367	1.3 μg/L †	Birth size and gestational age in infants	No association between BPA and most birth outcomes. Modest positive association between BPA and birth weight.
Wolff et al. 2008 (38)	Cross-Sectional	192	1.1-2.4 μg/g	Pubertal development in 9 year old girls	No association between BPA and pubertal development
Itoh et al. 2007 (39)	Cross-sectional	140	1.6 μg/L, 93%	Endometriosis in Japanese women	Mildly elevated urinary BPA concentrations among women with endometriosis. Results were attenuated after adjustment for urine dilution.
Wolff et al. 2007 (40)	Cross-sectional	90	2.0 μg/L	BMI in 6–8 year old girls	Urinary BPA concentrations lower in girls ≥ 85th BMI percentile compared to girls < 85th percentile.
Sugiura-Ogasawara et al. 2005 (41)	Case-control	87	0.8-2.6 μg/L‡	Recurrent miscarriage in adult females	Higher serum BPA levels among women with recurrent miscarriage compared to controls.
Hiroi et al. 2004 (43)	Cross-sectional	37	1.4-2.9 μg/L‡	Endometrial hyperplasia in adult women	Mean serum BPA concentrations were lower among patients with complex endometrial hyperplasia and endometrial cancer compared to controls.
Takeuchi et al. 2004 (42)	Case-control	45	0.7-1.2 μg/L‡	Polycystic ovarian syndrome in adult females	Higher serum BPA concentrations in women with polycystic ovarian syndrome compared to controls.
Hanaoka et al. 2002 (44)	Cross-sectional	84	Unexposed: 1.0 μg/g Exposed: 4.2 μg/g	Testostereone, lutenizing hormone, and follicle stimulating hormone among adult male expoxy workers and non-exposed controls	Inverse association between urinary BPA concentrations and testostereone, lutenizing hormone, and follicle stimulating hormone.

*Units of μg/g are micrograms of BPA per gram of creatinine

†Median

‡Serum BPA concentrations in μg/L

Table 2

Evidence Based Pediatric Environmental Health Resources for Health Care Practitioners

Name of Organization	Description	Link
Pediatric Environmental Health Specialty Units	Made up of professionally trained environmental health experts. Provides evidence based education and consultations to health care providers, state and local governments, and individual families	http://www.aoec.org/PEHSU.htm
American Academy of Pediatrics Pediatric Environmental Health Handbook (Green Book)	Provides description and guidelines for common pediatric environmental health topics	https://www.nfaap.org/netforum/eweb/dynamicpage.aspx?site=nf.aap.org&webcode=aapbks_productdetail&key=17837ee5-f0fd-4486-9bcc-64f986b0f703
National Environmental Education Foundation	Provides numerous resources on environmental education including handouts on taking a pediatric environmental health history	http://www.neefusa.org http://www.neefusa.org/health/PEHI/index.htm
Physicians for Social Responsibility	Provides evidence based environmental health toolkits for health care providers to use. Can get CME credit for taking the toolkit course	http://www.psr.org/resources/pediatric-toolkit.html#what