

Kidney News

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Ongoing Research Links Bisphenol A with Negative Health Effects

By Tracy Hampton



disease in children. Still, the risks are far from clear.

In some of the most recent work, researchers found a link between BPA and low-grade urinary albumin excretion in children and adolescents (Trasande L, et al. *Kidney Int* 2013 Jan 9. doi: 10.1038/ki.2012.422). The findings suggest that youngsters who are exposed to BPA, which was once used widely in plastic bottles and is still found in aluminum cans and register receipts, may have an increased risk for the development of heart and kidney disease.

BPA may negatively affect health in a variety of other ways, according to published and ongoing studies. Animal research has linked BPA with early sexual maturation, altered behavior, hyperactivity, and effects on prostate and mammary glands. In humans, the chemical has been linked to cardiovascular disease, diabetes, and male sexual dysfunction (Schechter A, et al. *Environ*

Sci Technol 2010; 44:9425–9430. doi: 10.1021/es102785d).

BPA, disease, and obesity

The latest study by Trasande et al. involved an analysis of data from 710 children and adolescents who participated in the 2009–2010 National Health and Nutrition Examination Survey, which included measurements of urinary BPA and albumin. Compared with children with the lowest amount of BPA in their urine, children with the highest amount had an albumin-to-creatinine ratio that was 0.91 mg/g higher.

The findings may be particularly worrisome for children with poor kidney function.

“While we excluded children with pre-existing kidney disease from our analysis, I am concerned that BPA exposure may have even greater effects on children with kidney disease,” said co-lead author Howard

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Recent studies add growing evidence to the potential dangers of exposure to bisphenol A (BPA). The estrogen-like chemical may be linked to diabetes in adults and to heart and kidney

Ultrasound of Lung Congestion Could Signal ESRD Outcomes

By Eric Seaborg

Pulmonary congestion, even in patients without symptoms of heart failure, could be an important predictor of mortality and cardiovascular risks in hemodialysis patients, a new study shows.

In the multicenter study reported in the *Journal of the American Society of Nephrology*, researchers who used ultra-

sound (US) to categorize patients’ levels of extravascular lung water found that patients with very severe congestion had a four times greater risk of death and a three times greater of cardiac events than patients with mild or no congestion.

“This article is very significant because it points out the relationship

between volume overload and mortality and cardiovascular events,” said Rajiv Agarwal, MD, professor of medicine at the Indiana University School of Medicine, noting that the study did not address causality. “They are simply describing an association between a finding of lung congestion and important outcomes for the patients.”

Led by Carmine Zoccali, MD, of Riuniti Hospitals in Reggio Calabria, Italy, a research team studied 392 Caucasian patients from 11 dialysis units in southern Italy. They classified the subjects according to the New York

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Bisphenol A

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Trachtman, MD, of New York University School of Medicine. “Because their kidneys are already working harder to compensate and have limited functional reserve, they may be more susceptible to the adverse effects of environmental toxins. We clearly need further study of BPA exposure and its effects on the kidney both in healthy children and in children who have preexisting kidney disease.”

Trachtman and his colleagues noted that the link they found between BPA and low-grade albuminuria is consistent with previous results found in Chinese adults. They said the link supports efforts to prevent harmful exposure to the chemical.

“While our cross-sectional study cannot definitively confirm that BPA contributes to heart disease or kidney dysfunction in children, together with our previous study of BPA and obesity, this new data adds to already existing concerns about BPA as a contributor to cardiovascular risk in children and adolescents,” said co-lead author Leonardo Trasande, MD, MPP, also of New York University School of Medicine.

Trasande is referring to a study published last year in the *Journal of the American Medical Association* that included almost 3000 children and adolescents aged 6 to 19 years (Trasande L, et al. *JAMA* 2012; 308:1113–1121). The study found that 22.3 percent of children and adolescents with the highest levels of BPA in their urine were obese, compared with slightly more than 10 percent of children and adolescents with the lowest levels of BPA. That translates to 2.6 higher odds of obesity in the highest BPA group compared with the lowest BPA group. Previous research has also shown that elevated urinary BPA concentrations are associated with obesity and incident coronary artery disease in adults.

Evidence from animal studies

As these and other studies continue to find correlations between BPA and negative health outcomes or increased risks of disease, studies in animals are generating a wealth of additional, sometimes conflicting, data.

For example, mouse studies by Randy Jirtle, PhD, of the University of Wisconsin-Madison, have revealed that exposure to BPA in the womb results in the *agouti* gene being inappropriately expressed, leading to offspring that have a yellow coat color and that are more susceptible to obesity and type 2 diabetes than are mice with darker fur. The researchers found that BPA did so by affecting the methylation of DNA, an epigenetic change that does not involve alterations in the DNA sequence.

A recent 3-year study using more than 2800 mice did not find that BPA results in more offspring with yellow coat color and a corresponding risk for adult diseases (Rosenfeld CS, et al. *Proc Natl Acad Sci USA* 2013; 110:537–542). Senior author Cheryl Rosenfeld, PhD, of the University

of Missouri, noted that her team’s findings say nothing about the positive or negative effects of BPA. (Previous studies in her laboratory indicated that developmental exposure to BPA can disrupt adult behaviors and compromise cognitive abilities in mice.)

According to Jirtle, Rosenfeld’s group classified offspring into fewer categories of coat color and bred the females multiple times, which could have decreased the sensitivity of the assay and masked the hypomethylating effects of BPA.

“Also, the mechanism by which coat color changes is epigenetics, which they did not measure,” Jirtle said. “Coat color isn’t

the real issue here—it’s epigenetics. They said they could not replicate our findings, but they also did not replicate our studies.”

The effects of high-dose BPA seen in Jirtle’s studies have been reproduced in another study from the laboratory of Dana Dolinoy, PhD, of the University of Michigan School of Public Health, which also found that there seems to be a clear dose-response curve for BPA, with low doses being less effective at hypomethylating, and possibly leading to an opposite, hypermethylation effect (Anderson OS, et al. *Environ Mol Mutagen* 2012; 53:334–342).

Dolinoy and her team are currently

investigating environmental epigenetics and gene-environment interactions using animal models, human clinical samples, and human population studies. One recent study of human fetal liver samples showed that there was considerable exposure to BPA during pregnancy (Nahar MS, et al. *J Biochem Mol Toxicol* 2012 Dec 3. doi: 10.1002/jbt.21459) and that BPA in fetuses was in a form not eliminated from the body, unlike previous studies showing that adult humans can metabolize the chemical and rid their bodies of it. The researchers recently found that female mice exposed to BPA through their mother’s

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- Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning
- Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma and other neoplasms. Only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should prescribe *myfortic*® (mycophenolic acid) delayed-release tablet. Patients receiving *myfortic* should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient

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diet during gestation and lactation became hyperactive as adults, also exhibiting spontaneous activity and having leaner body mass than mice not exposed to the chemical (Anderson OS, et al. *FASEB J* 2013 Jan 23. [Epub ahead of print]).

Dolinoy's laboratory is conducting ongoing research that builds on epidemiologic and exposure studies in the United States, Mexico, and Egypt. The aim is to characterize perinatal and peripubertal exposure to BPA and to determine how such exposure affects the epigenome.

"There are several things we need to look at in evaluating studies that look at

BPA's effects on health, such as timing of exposure, levels of exposure, and toxicant-diet interactions," Dolinoy said. "In combining animal studies with human cohorts and focusing on developmental exposures and later-in-life health risks, such as obesity, we are evaluating epigenetics as the mechanism linking these two disparate periods of life."

Extent of BPA exposure

Experts agree that it is important to continue to study the effects of exposure to BPA and to monitor the extent of exposure to humans and the environment.

A 2010 study investigated the levels of BPA in fresh food, canned food, and food in plastic packaging in the United States (Schechter A, et al. *Environ Sci Technol* 2010; 44:9425–9423). The researchers detected BPA in 63 of 105 samples, including fresh turkey, canned green beans, and canned infant formula. BPA levels were higher in foods with a pH of 5 than in more acidic and alkaline foods.

Another source of BPA exposure lies in the thermal receipts generated at stores and automatic teller machines, for which it is used as a color developer. One study found that the estrogenic proper-

ties of thermal paper could be effectively removed through incubation with partially purified laccase from newly isolated ascomycete fungi (Divya LM, et al. *Appl Biochem Biotechnol* 2013 Jan 10. [Epub ahead of print]). Such treatment could potentially lower public exposure to BPA if it is adopted by industry.

With such a widespread presence of BPA, however, it may be difficult to avoid the chemical. Only increased attention and investigation can help reveal the true health effects of BPA and ultimately spur efforts and policies to reduce exposure. ●

Important Safety Information: (cont)

- *myfortic* is contraindicated in patients with hypersensitivity to mycophenolate sodium, mycophenolic acid (MPA), mycophenolate mofetil (MMF), or to any of its excipients
- **Embryofetal Toxicity:** *myfortic* can cause fetal harm when administered to a pregnant female. Use of *myfortic* during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations
- **Pregnancy Exposure Prevention and Planning:** FRP must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations, and must be counseled regarding pregnancy prevention and planning. (See additional important Pregnancy Testing, Contraception, and Pregnancy Planning information below)
- **Lymphoma and Other Malignancies:** Patients receiving immunosuppressive regimens involving combinations of drugs, including *myfortic*, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin
- **Infections:** Oversuppression of the immune system can also increase susceptibility to infection, fatal infections, and sepsis
- **Polyomavirus Infections:** Immunosuppressed patients are at increased risk for opportunistic infections, including Polyomavirus infections. Polyomavirus infections in transplant patients may have serious and sometimes fatal outcomes. These include cases of JC virus-associated progressive multifocal leukoencephalopathy (PML) and Polyomavirus-associated nephropathy (PVAN), especially due to BK virus infections, which have been observed in patients receiving *myfortic*. PVAN, especially due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for PVAN
- Cases of PML have been reported in patients treated with MPA derivatives including MMF and mycophenolate sodium. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms, and consultation with a neurologist should be considered as clinically indicated. Reduction in immunosuppression should be considered for patients who develop evidence of PML or PVAN. Physicians should also consider the risk that reduced immunosuppression represents to the graft
- **Blood Dyscrasias Including Pure Red Cell Aplasia:** Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA in combination with other immunosuppressive agents. In some cases, PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivatives. In transplant patients, however, reduced immunosuppression may place the graft at risk. Patients receiving *myfortic* should be monitored for blood dyscrasias (eg, neutropenia or anemia). If blood dyscrasias occur (eg, neutropenia develops [ANC <1.3 x 10³/μL or anemia]), dosing with *myfortic* should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately
- **Pregnancy Testing:** To prevent unplanned exposure during pregnancy, FRP should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL immediately before starting *myfortic*. Another pregnancy test with the same sensitivity should be done 8 to 10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. In the event of a positive pregnancy test, females should be counseled with regard to whether the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations
- **Contraception:** FRP taking *myfortic* must receive contraceptive counseling and use acceptable contraception during the entire *myfortic* therapy, and for 6 weeks after stopping *myfortic*, unless the patient chooses abstinence. Patients should be aware that *myfortic* reduces blood levels of the hormones in the oral contraceptive pill, and could theoretically reduce its effectiveness. (Please see package insert for acceptable contraceptive methods for females)
- **Pregnancy Planning:** For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of *myfortic* should be discussed with the patient
- **Gastrointestinal Disorders:** Gastrointestinal bleeding (requiring hospitalization) has been reported in *de novo* renal transplant patients (1.0%) and maintenance patients (1.3%) treated with *myfortic* (up to 12 months)
- **Patients with Renal Impairment:** Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m²) may present higher plasma MPA and MPAG AUC relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG
- **Concomitant Medications:** Caution should be used with drugs that interfere with enterohepatic recirculation because of the potential to reduce efficacy
- **Hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) Deficiency:** *myfortic* should be avoided in patients with HGPRT deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome
- **Immunizations:** Use of live attenuated vaccines should be avoided
- The principal adverse reactions associated with the administration of *myfortic* include constipation, nausea, and urinary tract infection in *de novo* patients and nausea, diarrhea, and nasopharyngitis in maintenance patients

References: 1. FDA/Center for Drug Evaluation and Research. FDA approved drug products: mycophenolate mofetil. Drugs@FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_drug_name. Updated January 13, 2012. Accessed January 13, 2012. 2. Data on file. IMS Health, National Prescription Audit TRx Data: December 2011 to November 2012.

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