

GLASS PACKAGING INSTITUTE – SCIENTIFIC ADVISORY BOARD

# Report on the Study of Health Impacts of Bisphenol-A (BPA)

---

2013 Highlights

**Csaba Leranth, M.D., Ph.D., Heather B. Patisaul, Ph.D., Wade V. Welshons, Ph.D.**

**10/18/2013**



### **About the Glass Packaging Institute**

Founded in 1919 as the Glass Container Association of America, GPI is the trade association representing the North American glass container industry. On behalf of glass container manufacturers, GPI promotes glass as the optimal packaging choice, advances environmental and recycling policies, advocates industry standards, and educates packaging professionals. Through GPI, glass container manufacturers speak with one voice to advocate industry standards, promote sound environmental and recycling policies, and educate packaging professionals.

### **About the Science Advisory Board**

The Science Advisory Board of the Glass Packaging Institute is composed of three academic scientists, who provide independent, science-based, interpretations and assessments of current scientific issues and research relevant to the packaging industry. The members of the Science Advisory Board critically review data, publications, and government reports with respect to the safety and health consequences of the use of food and beverage packaging materials, upon request by GPI, and advise GPI and its members with respect to these issues. The SAB or one or more of its members may also issue, upon request by GPI, public statements or analyses of these issues. Any public statements or reports by the SAB or any individual members are independently determined by the SAB and its members.

## **Introduction**

The number and diversity of clinical efforts involved in the study of the effects of Bisphenol-A (BPA) is both wide and deep and has grown considerably over the past few years. In fact, the span of studies being conducted globally is of such a high volume that tracking the directions and outcomes of the research is quite challenging.

The use of BPA in making plastics and epoxies that are then used as a component of packaging in food is so common that it has resulted in ubiquitous human exposure to the chemical – a known endocrine disruptor. If a medicine were to be introduced for use in the population, it would be studied thoroughly in phased and progressive clinical studies to assess its safety before being used to treat patients. As a component of use in packaging food and beverages, however, the routine has been reversed - BPA was first introduced into the population and is now being closely studied for its effects and safety given its now widespread use and recent concerns regarding health effects.

There have been key questions about BPA exposure and its effect on human health that are in need of answer to build an empirical understanding for researchers, manufacturers, policy-makers and consumers. It is well known that when BPA is used in food and beverage packaging, there are circumstances where the chemical can become part of the material that will be consumed. This was perhaps most dramatically made clear in a well-publicized from a 2010 Harvard School of Public Health study that was published in the Journal of the American Medical Association (JAMA) in late 2011. In that study, “Canned Soup Consumption and Urinary Bisphenol A: A Randomized Crossover Trial,” study subjects consumed either fresh soup or canned soup for five days, after which urine samples demonstrated that among the group consuming the canned product, BPA levels were 1,221 percent higher than those who consumed fresh soup. That, along with many other studies, has now repeatedly and convincingly demonstrated that exposure to BPA used in a host of every day products and packaging results in increased levels measured in urine.

Because BPA is a known endocrine disruptor with a potential to interfere with many human functions, it is important to understand the effects of exposure in both animals and humans. A plethora of animal studies conducted around the world have effectively established a link between BPA exposure and interference with the reproductive systems of animals as well as showing links with many other conditions, including cardiovascular problems, diabetes, and obesity. However, there is a need for greater human exposure data to more definitively answer the many questions that exist regarding endocrine disrupting chemicals like BPA.

Key questions related to human exposure:

- How do effects seen in animal studies relate to human conditions?
- What dose or rate of exposure in animals causes concern?
- What are the current human exposures that cause concern – particularly the impact of early exposure (fetal development) versus childhood and adult exposure?

- What adverse effects in specific human systems have been associated with exposure to BPA in epidemiological studies?

### **Overview of Studies for 2013**

During 2013, there were a compelling number of epidemiological studies, and an ever-widening set of published effects in experimental animals, suggestive of low-dose, human relevant, BPA-related effects on a variety of endpoints.. In addition, there are at least 50 epidemiological studies in humans associating adverse effects in human populations with elevated exposure to BPA – in the general population, and not in a subset of exposed individuals. While BPA associations with the various parts of metabolic disease are standouts, they are not the only effects being observed.

In terms of studies dealing specifically with humans, particularly of note is the emerging evidence for neurobehavioral effects in children. Such findings are consistent with what is being reported in animal models. Although we do not yet understand the mechanisms underlying these effects, they have now been documented in a wide variety of species, which makes them compelling.

What follows is an overview of some of the study areas published this year in both animals and humans. These studies stand out as meaningful indicators of the broad effects of BPA exposure in humans categorized by the condition or effect.

#### **Asthma**

- In March, a study conducted at **Columbia University** and published in the [\*Journal of Allergy and Clinical Immunology\*](#) that reported an association – though did not establish causation - between BPA exposure and a heightened risk of asthma in children. In this study, investigators followed 568 women who were part of a study on mothers, newborns and environmental exposures. BPA levels in urine were measured during the third trimester of pregnancy and again when the children were 3, 5 and 7 years of age, finding at each measurement that 90 percent of the children had BPA exposure and that these children had an increased risk of wheezing and asthma.
- In August, the **National Primate Research Center (NPRC)** at **University of California - Davis** [announced results of ongoing research on BPA effects](#) on the endocrine system of macaque monkeys. As part of that study, NPRC found that after the fetuses of pregnant rhesus macaque monkeys were exposed to levels of BPA designed to replicate human exposure, there were changes observed in the lungs that increased the potential for the development of asthma. This research is distinct because most of the previous research done regarding the impact of BPA on lung tissue has been conducted on rodents, while the macaque monkey fetal development is closely associated with human fetal development.

## Cancer

- [A rat study from Tufts University](#), and published in EHP, provided reinforcing evidence that exposure to BPA, at human-relevant levels across gestation and lactation, elevates breast cancer risk. Effects included increases in intraductal hyperplasias and ductal carcinomas, meaning that BPA may act as a mammary gland carcinogen.
- Building on research in rodents published in 2007 that found low dose brief exposure of BPA had an effect on the prostate gland that enhanced carcinogenic potential, **University of Illinois** researchers [presented data at ENDO13](#) regarding BPA effects in vivo with a chimeric prostate model of human prostate epithelial stem-progenitor cells cultured from the primary prostate cells of healthy donors. Their data showed either of two doses having an adenocarcinoma effect.

## CNS - Anxiety/Mood/Brain Development

[Duke University researchers published a study](#) in the *Proceedings of the National Academy of Sciences* in February that found that BPA may impair the development of the central nervous system by suppressing a gene that is vital to nerve cell function. The study is significant because the findings were observed in cortical neurons of mice, rats and humans in a cell culture (not in vivo). It was found that exposing neurons to minute amounts of BPA altered the chloride levels inside the cells by shutting down a particular gene which would in turn delay the removal of the chloride from the gene. This paper is significant because it reveals a new mechanism by which BPA can impact brain development. It's further evidence that BPA is not simply a "weak estrogen" but may also have other modes of action, particularly in the developing brain.

- Research related to potential effects of BPA on the way genes work in the brains of laboratory rats [was published in May by Columbia University](#) in the *Proceeding of the National Academy of Sciences*. While past studies demonstrating a link between BPA exposure and alteration to genetic structures in brain tissue have been criticized for using high doses of BPA that were injected into the study animals, this study used "environmentally relevant" doses of BPA fed to the rats through their diet. The importance of this study is that the observed epigenetic changes were associated with observed changes in behavior while in prior studies, such a link was only surmised. Additionally, this is one of the only studies to date that took maternal care into consideration. The lead researcher was instrumental in the discovery that the quality of maternal care can impact the brain and behavior. Here, they controlled for that effect, so that they could specifically focus BPA-related outcomes.

- [In July in \*Environmental Research\*](#) carried results from a study from the **University of California – Berkeley** that showed that boys who were exposed to higher BPA levels as a fetus or during their early childhood were more likely to be suffering from anxiety, aggression, depression and hyperactivity by age 7, though this association was not present with girls. Previous studies had reported associations with BPA and anxiety-related behavior in girls. This study now provides evidence in both genders.
- A study out of **Seoul National University School of Medicine** published in August in the [Journal of Child Psychology and Psychiatry](#) found the suggestion of a relationship between BPA and child neurobehavior. While past studies shown to have an impact on behavior and on the brain have been in rodents and non-human primates, this study examined the urinary BPA concentrations of children age 8-11 and then assessed behavior and learning disability factors and found that an association may exist.

### Diabetes/Obesity

- [A study performed by the West Virginia University School of Medicine](#) published in May examined National Health and Nutrition Examination Survey (NHANES) data from 2003-2008 of 3,516 people to assess BPA levels and any association with diabetes. A comparison was made between urinary BPA levels with fasting glucose levels. Researchers found that the subjects with the highest BPA urinary levels saw a 34 percent increase in the rate of the pre-diabetic condition related to glucose levels.
- A 2012 [study out of the University of Missouri at Columbia](#) and published in July 2013 in *Reproductive Toxicology* examined the impact of low dose exposure to BPA on the offspring of pregnant mice exposed to BPA through diet. The study found that for a variety of endpoints suggestive of metabolic disorder including post-natal body weight and overall amount of abdominal fat, gonadal and renal fat pad weights, impaired glucose tolerance and serum concentrations of adiponectin – these were long-term effects due to maternal oral exposure to low doses of BPA.
- In another NHANES-related study – this time focused on children – in August the [American Academy of Pediatrics](#) published a **University of Michigan** report on the potential link between BPA and chronic diseases among children. Using data from 2003-2010, researchers evaluated associations between BPA and various measures of chronic illness. While there were no significant associations between BPA and most chronic diseases, higher levels of urinary BPA were associated with a higher likelihood of obesity and abnormal waist circumference-to-height ratio.

### Fertility

- The journal [\*Human Reproduction\*](#) in July carried publication of a **Harvard University** study that exposed 352 human eggs from 121 patients to varied levels of BPA in the laboratory. It was observed that the exposed eggs underwent spontaneous activation, causing the egg to act as if it had been fertilized when it had not. In addition, several eggs matured abnormally following exposure. Those eggs that were exposed the highest doses were more likely to show negative effects. These effects were observed in the laboratory, but when considered with prior work in rodents, this data reveals a key mechanism by which decreased fertility may occur. It's also one of the only studies showing direct effects on human tissue other than cultured cell lines. The findings make an association between BPA and these results, but are not a cause-and-effect link. According to the authors, "This is the first study investigating the effect of BPA on oocyte meiotic maturation, spindle morphology and chromosome alignment in human oocytes."

### **Conclusion – Future Trends**

These highlighted papers were selected from published studies of BPA exposures in the following areas: 21 human epidemiological studies; 3 studies of exposure and heart disease; 9 in obesity and diabetes; 12 in reproduction and fertility; 9 in neurobiology and behavior; 3 on thyroid effects; 3 in asthma and the immune system and 3 in cancer; 6 in environmental exposures and ecotoxicity; and 15 in areas of epigenetic and other mechanisms of action, pharmacokinetics, new screening, detection and amelioration methods. While BPA is not the only endocrine disrupting chemical, it is currently the most active in research, due to the extensive documentation of effects at levels of reported current human exposure.

In the coming year, we will be on the lookout for an increased focus on human data across a span of potential issues related to BPA. Recent studies have repeatedly revealed new potential effects that had not been heretofore considered, which could indicate additional new areas that will come to light in the coming year. In turn, that would likely open up the number of research pathways undertaken to assess the effects of BPA with relation to multiple outcomes.

In addition, there is likely to be an increased amount of data related to effects on children. This year, it was announced that the University of Illinois would be expanding a federally funded project launched in 2010 with an additional five year, \$8 million grant from the U.S. Environmental Protection Agency and the National Institute of Environmental Health Sciences to study environmental toxicology, including BPA.

In fact, as the cohorts under study age, we will know more about behavioral impacts in older children, but also we will get information on pubertal timing and development. This may possibly uncover some evidence that exposure to BPA and other endocrine disrupting chemicals (EDCs) are contributing the advancement of female puberty.

We are also likely to see a great deal more evidence for epigenetic effects in the brain and trans-generational effects on the brain and behavior. We will also be watching for further evidence that plastic containers leach endocrine active compounds other than BPA. As alternatives come on the market, people are looking into whether or not these products also leach EDCs.

In the near future, an exhaustive review of human BPA exposure studies - 91 cited in the paper - is currently in press at Reproductive Toxicology. The author notes that 53 of the 91 studies were published in the last year alone. The reference is:

Rochester JR, Bisphenol A and Human Health: A review of the literature, Reproductive Toxicology (2013), <http://dx.doi.org/10.1016/j.reprotox.2013.08.008>