

GLASS PACKAGING INSTITUTE – SCIENCE ADVISORY BOARD

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

2014 1st Quarter Highlights

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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 (SAB) 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.

Why This Report

It is highly unlikely that any single study is one day going to demonstrate that there is an adverse effect related to every day exposure to Bisphenol-A. Rather, it is the accumulation of evidence over time that will result in a growing understanding that as a society, we may want to lessen our exposure due to the ill effects and consequential health and financial costs. Given the intense interest in this topic and the growing and dedicated effort to examine this important issue, there are a plethora of studies that are published on a regular basis. The volume is so high, and sometimes very confusing, that it can be overwhelming. Our effort here is to focus on a few studies each quarter that may have gained public attention and to provide some context and understanding for their importance in helping the public make their own decisions about BPA exposure, for it is when consumers vote with their preferences that true change can occur.

Introduction

In our report looking back at 2013, we highlighted studies looking at the effects of Bisphenol-A (BPA) as they impacted a number of human conditions – asthma, cancer, central nervous system effects (anxiety/mood/brain development), diabetes, obesity, and fertility. During the first quarter of 2014 we continued to see more studies related to specific conditions, most notably perhaps in breast and prostate cancer.

However, possibly the most important study that was published and covered in mainstream media came out of FDA-sponsored studies through the National Center for Toxicological Research published in the journal *Toxicological Sciences* stating that BPA appeared to have no ill effects in low doses and that only in very high doses could an effect be perceived. The study generated headlines such as “[Maybe That BPA In Your Canned Food Isn't So Bad After All](#)” on the NPR dietary blog and in the trades with “[New BPA experiment finds no low-dose effects, FDA says](#)” in *Environmental Health News*. At the same time, a recent study out of the University of Missouri published in *Reproductive Toxicology* reported that numerous adverse effects were seen on rhesus monkeys exposed to low doses of BPA.

The emergence of a study that has FDA participation and sanction that states results contrary to many other high profile studies demonstrating adverse effects of BPA can lead to confusion and skepticism by the public, even prompting BPA proponents to label contrary studies as “advocacy” science. We hope to provide some clarity on the matter of looking at these studies for those concerned about BPA effects.

Finally, while most of the studies reviewed by the Glass Packaging Institute (GPI) Scientific Advisory Board (SAB) involve the role of BPA related to potential causality of adverse conditions, there was a study released this quarter that was a non-clinical publication regarding the economic impact of BPA exposure assessing the costs to society, also reviewed below. It opens up an important new area for examination.

Overview of Studies for First Quarter 2014

During the first quarter of 2014, there were reports of studies in key new areas that are of note, including several related to the effects of BPA on various types of cancer. While last year’s report overviewed the role of BPA related to specific conditions and while there are also studies about specific conditions for this quarter, perhaps most notable were two opposing studies regarding the extremely important issue of the level at which BPA exposure may cause harm.

First, we will overview those studies related to specific human conditions.

- **Cancer**

- **Men's Prostate** – There were two studies of note this quarter related to prostate cancer – both involving human study subjects. This is important because to date, most of the data related to prostate cancer has been in animal studies.

The first was [published in January in the journal *Endocrinology*](#) and was research conducted at the University of Illinois by noted researcher Gail S. Prins, Ph.D. This study looked at the effects of early life exposure to levels of BPA found in every day human exposure and provided the first direct evidence that such exposure increases cancer susceptibility in the human prostate epithelium (cells that cover the prostate gland) in living organism cells. While previous studies in rodent models showed a link between exposure and an enhanced susceptibility to the potential for prostate cancer in aging rodents, this study used human prostate stem-like cells that were derived from donors who were young and cancer-free. The cells were then grown in mice to develop the human cell membrane and the mice were then exposed by oral administration to low BPA doses and an increase in the incidence of cancer was found.

The second interesting prostate cancer study, also conducted with human subjects, was published in March in the online journal PLOS ONE from research conducted at the University of Cincinnati - [Exposure to Bisphenol A Correlates with Early-Onset Prostate Cancer and Promotes Centrosome Amplification and Anchorage-Independent Growth In Vitro](#). In this study, the BPA levels of men with prostate cancer were measured and compared to levels in men without prostate cancer and found that a 2-4 times higher urinary BPA level is an independent prognostic marker in prostate cancer and that BPA exposure may lower serum PSA levels in prostate cancer patients.

The first of these studies demonstrates that early life exposure can predispose individuals to an adult disease (prostate cancer) while the second shows a possible correlation, but not definitive causation, between adult exposure and the outcome of interest. Collectively, they serve as an example of how scientific studies are building blocks toward predicting when in life exposure is most consequential and how exposure contributes to disease. These studies highlight the importance of conducting research on many fronts from humans to cell based systems.

- **Liver Tumors** – In another study looking at the effects of BPA exposure during the gestation period, the University of Michigan, School of Public Health released findings that suggested a link between such exposure and liver tumors. In this study, 27 percent of mice exposed to one of three different doses were found to have either tumors or pre-cancerous lesions. The tumor effect increased with dose

exposure. The study is to be published in the journal [Environmental Health Perspectives](#).

- **Breast Cancer** – A molecule called RNA HOTAIR that exists in the human body does not, on its own, act to cause cancer. However, when HOTAIR begins to function in a particular way at high levels, it has been linked to tumor formation in pancreas, colon, and breast. Researchers at the University of Texas at Arlington exposed mammary gland cells to BPA and found that it combined with naturally present hormones in the body to induce a high level of HOTAIR expression. This does not lead to the direct conclusion that BPA causes cancer as a result of this study, but it does indicate that it disrupts genes in a way that could be a contributing factor. The results of the UT researchers were published in the [Journal of Steroid Biochemistry and Molecular Biology](#).
- **Dose – Related Studies**
 - **Lack of Low Dose Effect** - [A study published in February in the journal Toxicological Sciences](#) that involved FDA scientists sought to establish the dosage levels at which adverse events might be seen from exposure to BPA. The BPA was administered orally to a particular breed (Sprague-Dawley) of female rats who were dosed daily with BPA while pregnant. The pups born to the rats were directly dosed from one day after birth to termination, testing a range of seven different doses. Two very high doses were tested that were expected to show adverse events. The study also had two control groups (a group with which to compare the study subjects), both of which were not exposed to the BPA dosing, and one which was not gavaged (which is the process of force-feeding an animal by tube) and thus did not experience that stress. While the high dose group showed clear adverse effects of BPA that included low weight for the pups and effects on ovary and serum hormones, researchers associated with the study concluded that in the low-dose range, there really were no biologically significant changes observed at all.

Because this study involved the topic of dosing, reported findings of adverse events only at high level BPA doses, and is associated with FDA scientists, the GPI Scientific Advisory Board feels it important to provide some observations regarding this study that are cause for concern regarding the way this study was conducted, and important limitations of this study that were not sufficiently addressed in the media.

In order to obtain the clearest picture of the effect of a compound when undertaking a study, it is the gold standard to have a “control group” which is a set of study subjects who are not exposed to the compound in order to compare them to those that are exposed and to allow the measurement of the effect.

The study authors concluded that both control groups used in the FDA study were actually exposed to low doses of BPA (although it is unclear how that happened), a

finding explored more thoroughly in a companion paper to this study in which the contamination was documented. Ultimately, this means that the control groups were contaminated – a factor which significantly affects what can be concluded from the study. This could be a factor in why low dose effects were not detected. Because the control animals were exposed to similar levels of BPA as the “low dose” BPA groups, it is likely not possible to detect differences between them.

BPA is hypothesized to act like estrogen in the body. Related to an estrogen effect, there is another factor possibly affecting the outcome of this study. The animals in this study were fed a diet that was soy-based. Soy contains estrogen-like compounds produced by plants which could serve to mask some of the estrogen effects that one might expect to see from BPA exposure, making the control group not a control at all.

In addition, there were several other points of concern related to this study on the more technical side ranging from statistical methods that varied, to a minimization of limitations and weaknesses of the study on which profound conclusions were being based, and overall study design. Finally, a key area not addressed in the study is effects on brain development – an important omission given the sensitive nature of brain tissue.

The bottom line on this study – the fact that the control groups were exposed to BPA and that their diet contained soy-based foods are both factors that cast the results in a highly questionable light.

- **Low Dose Effect** – A study out of the [University of Missouri and published in the journal Reproductive Toxicology](#) is one of many studies that had findings contrary to the FDA-sponsored study noted above. This study is of interest on many levels, including the fact that while most BPA-exposure studies have been on rodents, this study was conducted using pregnant rhesus monkeys to assess daily low-dose exposure to BPA and the effects on a developing fetus. Researchers exposed the study subjects to a daily dose that was below the levels to which humans are exposed on a daily basis and found evidence of effects on multiple systems in the developing fetus, including to mammary gland, brain, ovaries, uterus, lung and heart tissues. Contrary to the FDA-sponsored study on dosing, the dosing and effects seen in this research suggest that the impact on humans has been under-estimated by past studies; made all the more relevant given it is a primate study.

Note, GPI SAB member Wade Welshons was a co-author of the publication of this study.

- **Economics**

- **Health and Economic Benefits of BPA Limitation** – A paper published in January in *Health Affairs* (payment required) entitled “[Further Limiting Bisphenol A in Food Uses Could Provide Health and Economic Benefits](#)” attempted to quantify the economic impact of BPA exposure as expressed through costs associated with treating some of the potential adverse effects of BPA on health. The evaluation focused on social costs of childhood obesity and adult coronary heart disease attributable to BPA exposure in the United States. This paper assessed BPA exposure to be associated with 12,404 cases of childhood obesity and 33,863 cases of newly incident coronary heart disease, with estimated social costs of \$2.98 billion in the year 2008. The authors concluded that removal of BPA from food could prevent thousands of cases of childhood obesity and coronary heart disease per year and stated that this could yield annual economic benefits of a very large scale. While by no means a definitive economic study on the impact of BPA, any attempt to estimate economic costs is laudable. It is also a difficult undertaking and the study certainly suggests a need to look at this issue further by gathering even greater amounts of data in increasingly rigorous studies.

Conclusion

Understanding the role of BPA and the potential adverse impacts of exposure is a long process, not an event. That said, the publications from this quarter are examples of definite progress. Work is advancing on many fronts and progressing from observations seen in the test tube to those being observed in living cells and, in many instances, moving from rodent studies to primate studies. New data is also providing information about when in life exposure is most likely to produce harmful effects - in particular to observe the long term effects of BPA during gestation. A key criticism of the FDA study was the exclusion of examining the effects of BPA on the brain, but it is expected that there may be some study results along those lines in the coming months.

In addition, the issue of dosing levels will continue to be a critical one, particularly in the wake of the FDA study.

We will continue to monitor for and note studies that are of particular interest given their ability to advance the public discourse about this important issue.