BPA: Ubiquitous, Controversial, and Scary as Hell

Sascha Zubryd

Writer's Comment: I wrote this article hoping to interest the reader in the scientific debate about bisphenol A and to present him or her with detailed scientific information in an understandable way. It was a research-driven project. The hardest part was deciding what to leave out. There was no room for any description of how large proteins like oxytocin might interact with the endocrine system or for specific descriptions of cool experimental designs. I had to leave discussion of sex hormones other than estrogen behind in early drafts. After agonizing for a while, I decided to sacrifice some of my favorite intricate (and long) explanations of the science in favor of more varied and generally interesting content. I hope that after reading this article readers will feel competent to evaluate media coverage of BPA research and to make informed decisions about whether or not to use products containing BPA. I want to thank Lecturer John Boe for all his help and encouragement.

—Sascha Zubryd

Instructor's Comment: Sascha Zubryd has a rare journalistic talent: the ability to make scientific material not just intelligible but fascinating. Her article about bisphenol A (BPA) was not just a paper, but a real article, one I made copies of to give my friends to read. The first line of her piece, "The first time I heard of bisphenol A was when my housemate threw out her plastic Nalgene bottle," was not only a great lead; it was prophetic, for Sascha's piece led me to throw out my plastic Nalgene bottle, too. While humanizing and personalizing the story, Sascha never skipped over the important scientific facts and controversies, writing science so that nonscientists can understand it.

With her special gifts, I expect Sascha Zubryd to continue to produce superb scientific journalism.

—John Boe, University Writing Program

The first time I heard of bisphenol A was when my housemate threw out her plastic Nalgene bottle. When she told me why, I threw mine out, too. I started using an old glass apricot juice bottle. From the buzz I was hearing in the news and by word-of-mouth, I wanted nothing to do with this mysterious bisphenol A (BPA) that mimicked steroid hormones in my body, having who knows what kinds of effects. The question "Are plastic water bottles safe?" was popping up all over the news, but the answer depended entirely on who was asked. That made me wonder: what exactly *is* BPA, and who *does* know what effects it can have?

BPA is an endocrine disruptor—a chemical that mimics or interferes with the normal actions of any endocrine hormone (think sex hormones and steroids). More specifically, BPA is estrogenic, meaning it mimics estrogen's effects in the body.

Over two billion pounds of BPA are produced each year. It's used in polycarbonate food and beverage containers like clear, hard Tupperware and baby bottles. It's a component in lacquers that coat cans, fermentation drums for some beers and wines, and water supply pipes. Some dental sealants contain BPA. It's in adhesives, epoxy resins, polyester, CDs, DVDs, eyeglasses, and bicycle helmets. I was dismayed to learn that there's even BPA in the lid of my glass bottle!

Most of us are exposed to multiple sources of BPA on a daily basis. The Center for Disease Control found evidence of BPA in over 95% of American adults tested at random. But scientists estimate that average daily exposure to BPA is less than a millionth of an ounce per pound of body weight (1µg/kg/day). Such a low human exposure level may sound like good news, but there's a heated debate among BPA experts right now over whether very low levels of BPA are dangerous to humans—maybe even more dangerous than moderate levels.

The official story, currently endorsed by the EPA and the plastics industry, is that BPA is harmless to humans at current exposures. In 1988, the EPA declared that BPA was safe after running animal tests typically used to assess the levels of potentially harmful chemicals that

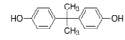
are actually dangerous: in vivo acute/chronic toxicity tests, carcinogenicity tests, and reproductive toxicity tests. They found that at high doses, BPA was toxic to rodents. The lowest dose the EPA tested, about eight ten-thousandths of an ounce per pound of rodent (50mg/kg/day), had no deleterious effects. This is the EPA's "no observable adverse effects level," or "safe" daily dose. It's many times higher than what humans are exposed to now. Based on the EPA's findings, the FDA approved the use of BPA-based plastics in food and beverage containers.

The trouble with the EPA's research and subsequent industry-funded studies is that they tested BPA as if it were a toxic substance like mercury or lead—they established a maximum safe dose and assumed that lower doses were safe. But for BPA it's not that simple. First, BPA is acutely toxic to aquatic creatures when only a tiny fraction of the EPA's "safe" dose is present in the water (10μg/mL). That toxicity raises a red flag. Aquatic animals are particularly sensitive to noxious chemicals and have served as early warning systems in the past about the dangerous properties of toxins like DDT. Second, as an estrogenic endocrine disruptor, BPA acts like a hormone. And hormones in the body don't always conform to typical "dose-response" patterns where higher doses mean bigger effects. With hormones, sometimes less is more. Tiny doses of BPA can have effects similar to those of very high doses, while intermediate doses have only minimal or no impact.

Many independent and government-funded researchers have demonstrated detrimental effects of BPA in rodents at lower doses than the EPA's "no observable adverse effects level." But studies funded by the plastics industry tend to support the EPA's conclusion. According to eminent BPA expert Frederick vom Saal, the disagreement between these two groups of studies doesn't mean there's any uncertainty about the danger of BPA. His paper in the August 2005 issue of *Environmental Health Perspectives*, a peer-reviewed news and research journal, discussed the dramatically different results of studies with different sources of funding. In the paper, vom Saal said "94 of 98 (96%) government-funded studies report significant effects of low doses of BPA, whereas 0 of 8 (0%) industry-funded studies reports significant effects with the same low doses."

The findings are skewed on both sides. It's easy for industries not to publish a study if, say, the results don't support their interests. But academia isn't totally objective either. UC Davis professor Dr. Karen Bales, expert in the molecular components of social bonding in rodents and pri-

mates, addressed the issue during our interview. She said, "In academia it's very hard to publish without [significant] findings. That I know for sure." Dr. Bales' statistical analysis of vom Saal's figures revealed that the probability of the studies panning out the way they did just by chance (that is, without funding or some other non–research-related factor having played a role), is less than 0.0001. That's very, very unlikely. Funding or some other factor must have been involved, so it's reasonable to assume that industry studies are more likely to find that the chemical they sell is safe, and academic studies are more likely to get published if they find some significant impact of BPA.



Scientists study BPA in rodents because they're easily available as test subjects, and we know a lot about their anatomy and how their biological systems function. Rodents also have some striking similarities to humans, so many research findings from rodent studies can apply to humans, too. For example, Dr. Bales said that sexual differentiation during development (the process of becoming male or female while in the womb) follows a similar course in rodents and humans.

Vom Saal's and other scientists' research has repeatedly shown that low doses of BPA can have harmful and irreversible effects on sexual differentiation in rodents. For example, in 1998 vom Saal found adverse effects in male mice whose mothers had been exposed during pregnancy to BPA doses lower than the average human exposure level. Very small amounts of hormones are responsible for coordinating many different processes during development, so it makes sense that an endocrine disruptor like BPA, a sort of hormone impersonator, would influence the course of development. When pregnant mice got just twenty nanograms of BPA for each gram of their own body weight, sperm production efficiency in their male offspring decreased by 20% compared to normal mice. Twenty nanograms is less BPA than there is in the saliva of a person who had a plastic dental seal done an hour ago. But it's important to keep in mind that the animals affected by exposure to that tiny dose were still developing in the uterus. At that time, hormones have "organizational effects" that permanently shape how the developing organism's body functions. In fully developed adults, hormones generally have more transient "activating effects," so vom Saal's study is more relevant to effects of BPA in human fetuses than in adults.

The plastics industry has funded studies that refute vom Saal's findings. One of these studies, published in 1998, attempted to replicate one of vom Saal's experiments that showed enlarged prostate glands in adult mice exposed prenatally to doses of BPA that were comparable to human exposure levels. The replication study found no significant effects of BPA. But as vom Saal and other researchers have pointed out, the study had a serious flaw.

In addition to testing BPA like vom Saal had done, the 1998 study used a "positive control" chemical too. Diethylstilbestrol (DES), another endocrine disruptor, is known to increase prostate size in rodents. The idea of a positive control is this: showing results consistent with what we know should happen will confirm that an experimental set-up is working. That kind of confirmation gives a study's other findings more credibility. But the replication study didn't find any impact of DES on prostate size in mice, as it should have if no other factors were influencing the results. Instead of strengthening its findings, the replication study shot itself in the foot by clearly demonstrating a flaw in its own methods.

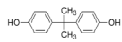
Dr. Bales was doubly surprised by the industry replication study's lack of results because that study kept its mice in separate cages, whereas vom Saal's mice were housed in groups. Bales, an expert in rodent social behavior, would have expected the individually housed mice to be more susceptible to DES than those housed together because mice get stressed out when they're isolated. It's curious that the industry study's mice weren't affected by DES or BPA, even though they should have been more sensitive than vom Saal's mice. The take-home message here is that it's important to be aware of how a study was done before deciding what to make of its results.

Studies done by other researchers have replicated vom Saal's findings just fine, and have also found that early exposure to low doses of BPA directly interferes with adult testicular function and reduces testicular size in males. In 2001, Japanese researchers found that female rodents exposed to BPA as fetuses had faster sexual development, an earlier first vaginal estrus (the mouse equivalent of human menstruation), and heavier body weight than normal mice.

American researchers have found evidence that exposure to BPA during development leads to abnormal weight changes in male and female rodents. Because obesity is a major health concern, scientists are intensely studying what they call "obesogens"—molecules that abnormally regu-

late how the body digests and stores fats. BPA is probably an obesogen, at least at certain doses. Researchers at the University of Tokyo directly exposed fertilized mouse eggs to the lowest dose of BPA ever tested as of 2001 (1 nM), then implanted the eggs in surrogate mothers and let them develop. When the mice grew up, they were 39% heavier than normal mice. Mice from eggs exposed to a BPA dose twice the EPA's "no observable adverse effects level" were 34% heavier than normal mice. But it's unclear what implications findings like these have for human obesity.

Yokohama City University scientists didn't find any weight gain in the offspring of pregnant mice injected with moderate doses of BPA. In fact in some cases the mice were lighter. It's possible that the different ways the mouse eggs were exposed to BPA, directly and by injecting the mother, could account for the different results of these studies. But the different effects on body weight of different doses of BPA could also be an example of how hormone-like substances have bigger effects at low and high levels than at levels in between.



No one fully understands the specific mechanism for how BPA has different effects at different levels. Some scientists, vom Saal included, suggest that the interactions between hormones and cells in the body evolved to amplify the presence of a tiny amount of hormone into a big cellular response. Like a chain letter, the hormone's original message gets sent to more and more cellular addresses as the cell's internal addressees communicate with each other.

Which cells get the message and how may also help explain BPA's dose-dependent effects. When BPA floats along in the blood stream, it gets snagged by certain types of receptors. Receptor molecules tell their cells that BPA is around, usually by changing shape in some way or activating another molecule inside the cell, triggering a chain letter effect called a second messenger cascade. We know that estrogen receptors—so named because they really like to grab estrogen molecules—respond to BPA. But there are multiple kinds of estrogen receptors, and other types of receptors also respond to BPA. Membrane estrogen receptors, which are located on a cell's surface, may change membrane permeability, regulating what substances can enter or leave the cell. They may also have other effects like activating second messengers. Nuclear receptors, estrogen and other, snag BPA once it has moved deep inside a cell, and once

they do, these receptors affect a process called transcription. Alterations in transcription turn genes on or off in a cell and can have effects ranging from a small increase in cellular metabolism to immediate cell death.

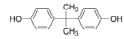
According to Dr. Bales, it's possible that different effects of BPA at different doses depend on which receptors the chemical is binding to the most at a given dose. Nuclear receptors have a higher affinity for BPA than estrogen receptors do, which essentially means that they're greedier. So if there's only a little bit of BPA around, nuclear receptor types gets almost all of it while other receptor types remain quiet. Dr. Bales surmised that when BPA is present at higher levels, greedy receptors may get "saturated," or filled up, which allows other receptors to get hold of BPA and have their own effects on cell function.

Receptors could also explain how the same dose of BPA can affect males and females differently. Males and females have different reproductive systems, so BPA obviously affects those systems differently in the two sexes. But BPA causes sex-dependent changes in other systems, too. For instance, Japanese medical researchers found that prenatal BPA doses 33 times lower than the EPA's "no observable adverse effects level" led to opposite changes in the size of a brain region called the locus coeruleus (ser-OO-lee-us) in male and female rats. The locus coeruleus, which makes noradrenaline, is involved in the body's automatic responses to stress. Normally the locus coeruleus is larger in female rats. But when the researchers exposed rats of both sexes to BPA, that difference disappeared. The area shrank in females and grew in males.

The Japanese medical researchers expected that BPA would affect behavior in male and female rats differently, too. They used an "open field test" where they observed rats running around in an enclosure the size of a playpen. Normal females ran around and reared up on their hind legs more than normal males did. The researchers also tested the rats' memories for bad experiences by repeatedly giving them electric shocks in a certain area of a cage, and then seeing whether they avoided that area when put back in the same cage 24 hours later. Male rats normally avoided the area more than females. In both the open field test and the memory test, females that had been exposed to BPA acted more masculine, and males acted more feminine. These animals ran around, reared, and avoided the shock area at rates in between those of normal males and females. Scientists have suggested numerous possible explanations

for this unisex behavior, like differences in metabolism or receptor availability between the sexes, but no one knows for sure.

The medical researchers' study suggests that human males and females might also respond in different ways to the same BPA exposure. But when we draw conclusions about humans from rodent studies, Dr. Bales said, "We have to take things individually. We're just starting to look at these things in non-human primates, let alone humans." So rodents can help us understand BPA, but they can't tell us everything we need to know.



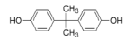
The main source of human exposure to BPA is food. Most of the BPA in food comes from containers made of BPA-based materials, like cans and hard plastics. The transfer of BPA from containers to the food they contain is called "migration." In cans, migration is affected by how hot the can got during manufacturing, and for how long. Studies looking at migration have measured BPA levels in cans off supermarket shelves, and they have also measured BPA migration rate in their own controlled heating environments. In general, cans that were hotter for longer had more migration. But even if a can wasn't subjected to particularly high temperatures during manufacturing, BPA can leach into the food during storage, especially when the food contains salt or vegetable oil.

BPA also leaches out from polycarbonate plastic containers like baby bottles and Nalgenes. It migrates more from old bottles than from new ones because as the plastic gets scratched up it starts to degrade, releasing more BPA. Washing plastics in alkaline solutions (like dish soap) and hot water or steam speeds degradation and can lead to more BPA migration.

It turns out that the most important time to worry about your BPA exposure level is when you're pregnant. Dr. Bales said, "I wouldn't expect a huge effect on something like testicular size [in an adult]." But when it comes to exposure in the womb, Bales said, "The long term developmental problems are pretty scary."

In 2002, researchers at Freie Universität in Berlin studied pregnant women to see whether their fetuses were exposed to BPA. Human fetuses may be particularly sensitive to the effects of BPA because they don't have the enzyme that adult bodies use to detoxify BPA in the liver. The researchers took blood samples from the mothers, and also tested placenta, umbilical chords, and the fetuses' blood. They found BPA levels in

both mothers and fetuses that were comparable to doses used in animal studies that show toxic effects on male and female reproductive organs.



In 2007, 38 BPA experts drew upon 700 different human and animal studies published in peer-reviewed scientific journals to produce an unprecedented consensus statement about the dangers of BPA. Following a National Institute of Environmental Health Sciences funded toxicogenomics research consortium in Chapel Hill, NC, this international group of scientists concluded that the deleterious effects observed in rodents given very low doses of BPA—doses comparable to those that humans are exposed to—are cause for concern because there is "potential for similar adverse effects in humans." These adverse effects include changes in the speed of prenatal development, obesity, changes in brain development and adult behavior, abnormal hormone levels, and poor immune function. In male rodents, effects of low doses of BPA also include decreased testosterone concentrations in the blood, smaller testicles, less sperm production, and higher risk for prostate cancer. Female rodents exposed to low doses of BPA show increased risk for breast cancer, abnormal estrus cycles, and early sexual development. It's a scary thought that these same effects might occur in humans.

The 38 experts' consensus statement admits that scientists haven't shown any direct link between human ailments and BPA exposure, and the chief BPA scientist for the American Chemistry Council, Steven Henges, has refuted its conclusion. In an October 2007 interview for The News Hour with Jim Lehrer, Henges said, "The position of the 38 scientists is distinctly at odds with the views of every other review of bisphenol A that has been conducted in recent years. . . . [I]n every case the conclusion from those reviews is that bisphenol A is not a concern for human health." In keeping with this view, a California bill that would have banned the use of BPA in children's toys failed in January 2006.

But the Canadian government is taking steps to ban BPA from use in all consumer products, based on research done in rodents and in humans. The European Union re-evaluated BPA as a harmful substance in 2002 and now endorses a "tolerable daily dose" 5000 times lower than the EPA's "safe" level (10μg/kg of body weight). The US National Toxicology Program (NTP) is also officially concerned about BPA. In its April 2008 Draft Brief on BPA (scheduled for peer review June 11), the

NTP says, "There is *some concern* for neural and behavioral effects in fetuses, infants, and children at current human exposures. The NTP also has *some concern* for bisphenol A exposure in these populations based on effects in the prostate gland, mammary gland, and an earlier age for puberty in females."

The NTP Brief is largely based on a 2007 report by a BPA expert panel for the Center for the Evaluation of Risks to Human Reproduction, which looked at both industry and government funded research. The Brief also considers the most recent scientific literature on BPA. John Bucher, head of the NTP, said, "Emerging trends in the literature do support the level of concern that our folks have indicated in their draft documents."

Many consumers are concerned about BPA, and manufacturing companies are adjusting their sales tactics accordingly. Nalgene, like most companies, officially insists that BPA is safe and refers worried customers to the EPA's information. But in response to consumer demand, Nalgene recently committed to phasing out the use of BPA in its products. Similarly, "Born Free Natural Baby Products" assures customers that its baby bottles are already BPA-free. Instead, they contain polysulfone (PES), which is more expensive to manufacture than BPA but is more stable at high temperatures. "Born Free" products are available at Whole Foods Market and CVS/Pharmacy stores.

More and more alternatives to BPA-based products are coming on the market. But products containing BPA aren't labeled as such, so it can be hard to tell what contains BPA and what doesn't. A good rule of thumb is if it's clear, hard, and plastic, it's probably made with BPA. Unlike Canada and the EU, the U.S. government hasn't expressed any intention of restricting the use of BPA in consumer products. For now, consumers must decide for themselves what to make of the research on BPA, and come to their own conclusions about the danger.